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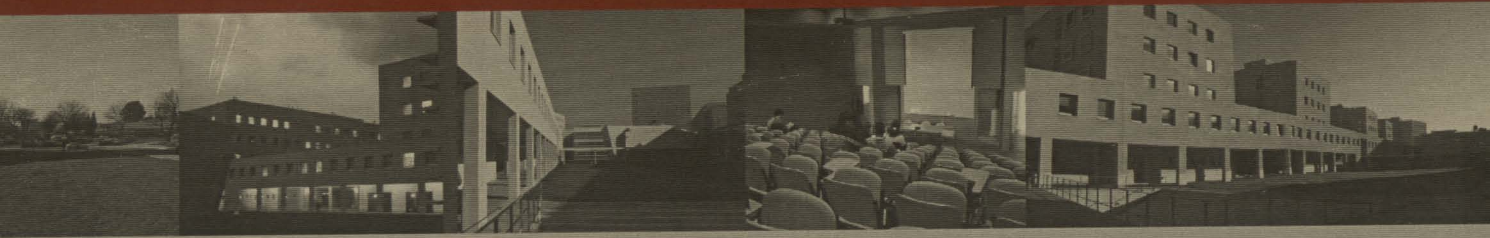

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Epidemiological Descriptive Study of Osteoporosis in Portugal, Using Geographical Information System

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To Miguel,
To Mum and Dad

To Doctor Maria de Fátima de Pina, for the patience, the incentive, for guiding me through the first steps of investigation, for the upbeat, well, for the friendship.

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Abstract

Osteoporosis is a disease characterized by compromised bone strength predisposing to an increased risk of fracture. It affects million of people around the world, with a tendency of increasing the incidence rates, due to the aging of the population and to the increase of risk factors. The most visible and dramatic consequences of osteoporosis are osteoporotic fractures that can occur manly on three skeleton sites: proximal femur (hip), vertebrae and distal forearm (wrist). From those, the hip fractures are considered the most serious because almost invariably lead the patient to hospital admission for chirurgical intervention and expose him to high mortality and morbidity risk. Because the majority of hip fractures are treated in public hospitals they are highly documented and can be considered a barometer of osteoporosis.

The objective of this study is to identify spatial patterns of proximal femur fractures incidence in Continental Portugal, through the use of Geographical Information Systems – GIS and Spatial Statistical Analysis.

The health data used in this study is from the National Hospital Inpatients Data Register managed by the Health Informatics and Financial Management Institute (Instituto de Gestão Informática e Financeira da Saúde – IGIF). This database contains all the admissions with a diagnosis related to proximal femur fracture that occurred between the period 2000 - 2002 and variables such as sex, age and provenience. It were selected the registers that occurred in individuals with more than 50 years of age, with diagnosis classified as International Classifications of Diseases 9th Revision - Clinical Modification (ICD9-CM) codes: 820.x and cause of admission with ICD9-CM codes: E880, E881, E884, E885, E886, E887 and E888. The demographic data used was a result of the 2001 Portuguese Census.

It was computed the number of patients with 50 years or more for each municipality according to sex and age, and calculate the age and sex direct standardized rates. The incidence rates were adjusted by the local empirical Bayesian estimator. The results showed that the incidence of osteoporotic proximal femur fractures increased with age and was higher in women than in men. Clusters of high rates were identified in the south and northeast of Continental Portugal, as well as in the littoral between Lisbon and Aveiro city; were also identified clusters of low rates northwest and central inland.

In conclusion the incidence of osteoporotic proximal femur fractures has different spatial pattern within the Portugal mainland territory.

Sumário

A osteoporose é uma doença caracterizada por comprometer a força da massa óssea, elevando o risco de fractura. Esta doença afecta milhões de pessoas em todo o mundo, com uma tendência para aumentar devido ao envelhecimento da população e ao aumento dos factores de risco. As fracturas osteoporóticas são a consequência mais visível e dramática da osteoporose e ocorrem essencialmente em três partes do esqueleto: o fémur proximal (anca), as vértebras e a extremidade distal do antebraço (punho). Destas, as da anca são consideradas as mais sérias, uma vez que quase invariavelmente obrigam o doente a uma hospitalização para intervenção cirúrgica e aumentam o risco de mortalidade e morbilidade. Devido ao facto de na sua maioria as fracturas de anca serem tratadas em hospitais públicos são as mais bem documentadas e são por isso consideradas o barómetro da osteoporose.

O objectivo deste estudo é identificar o padrão espacial da incidência das fracturas do fémur proximal em Portugal Continental, utilizando os Sistemas de Informação Geográfica – SIG e Análise Estatística Espacial.

Os dados de saúde foram fornecidos pelo Instituto de Gestão Informática e Financeira da Saúde – IGIF, da responsabilidade do Ministério Saúde Português. Esta base de dados contém todas as admissões em hospitais do Serviço Nacional de Saúde relacionadas com facturas do fémur proximal no período 2000 - 2002, assim como variáveis como sexo, idade e proveniência. Foram seleccionados todos os doentes com mais de 50 anos, com diagnósticos classificados com Código Internacional de Doenças 9ª Revisão - Modificação Clínica (CID9-MC) códigos: 820.x e causas de admissões codificadas com CID9-MC: E880, E881, E884, E885, E886, E887 e E888. Os dados demográficos usados foram o resultado do Censo Português de 2001.

Foi calculado o número de doentes com idade igual ou superior a 50 anos em cada município, de acordo com o sexo e idade e foram calculadas as taxas de incidência directas, padronizadas pela idade e sexo. As taxas de incidência foram ajustadas pelo método Bayesiano empírico. Os resultados mostraram que a incidência das fracturas osteoporóticas de fémur proximal aumenta com a idade e é maior nas mulheres do que nos homens. Foram identificados *clusters* de taxas altas no sul e nordeste de Portugal Continental, assim como no litoral entre Lisboa e a cidade de Aveiro. Foram também identificados *clusters* de taxas baixas no noroeste e interior centro.

Em conclusão a incidência das fracturas do fémur proximal apresenta padrões espaciais distintos no território continental português.

Contents

Index of Figures

Index of Tables

Abbreviation List

BMD - Bone Mineral Density

DBMS - Database Management System

DRG - Diagnosis Related Group

EB - Empirical Bayesian

ESDA - Exploratory Spatial Data Analysis

GIS - Geographical Information Systems

ICD9-CM - International Classifications of Diseases 9th Revision - Clinical Modification

IGIF (Instituto de Gestão Informática e Financeira da Saúde) - Health Informatics and Financial Management Institute

INE (Instituto Nacional de Estatística) - National Institute of Statistics

LISA - Local Index of Spatial Autocorrelation

MDCs - Major Diagnostic Categories

NIH - National Institutes of Health

NUTS - Nomenclature of Territorial Units for Statistics

SD - Standard Deviation

SNS (Serviço Nacional de Saúde)- National Health Service

WHO - World Health Organization

1. Introduction

Osteoporosis is a disease characterized by the loss of bone strength (Kanis 2002), whose most visible and dramatic consequences are the fractures (Cooper and Melton III 1996). The fractures that can be considered a consequence of osteoporosis occur manly on three different skeleton parts: proximal femur, vertebrae and distal forearm, and occur due to low trauma (fractures that would not be expected in young healthy adults (Center and Eisman 1997)). Due to the need of surgery the great majority of femur fractures require hospitalization (Cummings and Melton III 2002; Trombetti, Herrmann et al. 2002; O'Neill and Roy 2003), therefore these kind are the most documented and have become considered the international barometer of osteoporosis (Cummings and Melton III 2002). The incidence of these fractures is higher in women than in men and increases sharply after the age of 50 (Dennison and Cooper 2000).

The burdens of osteoporotic fractures due to its high morbidity and mortality rates (Riggs and Melton III 1995; Cooper and Melton III 1996; Walker-Bone, Reid et al. 1998; Jordan and Cooper 2002) can incur at two levels the economical and social costs.

The economical costs, also considered direct costs (those associated with goods and services), attributable to osteoporotic fractures are not easy to determine, because the recovery does not take place only during hospitalization, it extends for long periods, with physical therapies sections, with medication, with home medical care, with ambulance encounters, etc (Tosteson 1999). In spite of the difficulty, there are studies that report that medical costs just for initial stabilization of proximal femur range from US$ 1 900 (about 1 460 €) in Portugal to US$ 9 000 (about 7 000 €) in Greece (Dennison and Cooper 2000). However, since it is unknown the methodology used to calculate such costs, these values may not be comparable.

However, economical costs can also include indirect cots, those associated to the social components, and that are even more difficult to identify and measure (Tosteson 1999). It is documented that about eight per cent of men and three per cent of women die while hospitalized (Walker-Bone, Dennison et al. 2001), but the mortality does not occur only during the period of hospitalization, the 1-year mortality rate is estimated in 31 per cent in men and to 17 per cent in women (Amin and Felson 2001). However, and to illustrated that the consequences of morbidity are also severe, about 80 per cent of women aged 75 and older affirmed prefer death over the loss of independence after fracture (O'Neill and Roy 2003). In fact, the loss of independence is a major consequence of proximal femur fracture, with up to a third of hip fracture patients becoming totally dependent (Cooper and Melton III 1996), and only 70 % of the patients being able to return to their original residence (Center and Eisman 1997). Depending on the health conditions prior to the fracture, some authors affirm that incomplete recovery at one year pos fracture, varies from 20 to 90% (Center and Eisman 1997) and 40% of the patients are unable to walk independently while 80% or more are unable to carry out independently one activity of daily living like shopping (Dennison and Cooper 2000). The consequences are not only related to physical components, the psychological impact of osteoporosis is not to be diminish, with patients experiencing the loss of their social roles, social isolation leading to anxiety and depression (Gold 2001).

Several habits of modern life are considered propitious to the occurrence of bone loss leading to osteoporosis. Risk factors like low practice of physical activity, smoking, drinking, low calcium intake and other nutritional issues have been identified (NIH 2000, Scott 1990).

The problem of aging populations it is well known, as well as the change in population habits in all countries, Portugal is no exception. This combination is causing the number of osteoporotic fractures to increase, increasing with it, the social problems subjacent to high morbidity and mortality.

In Portugal, the conditions are propitious to the expansion of osteoporosis. The number of population over fifty years represents about 30 percent of the Portuguese population and according to National Institute of Statistics (INE – Instituto Nacional de Estatística) the population projections to 2050 show that the aging index, translated as the number of elderly people for each 100 young people, will suffer an increase in regions (North, Center, Lisboa and Tejo Valley, Alentejo, Algarve, Madeira and Azores), passing from a range of 61 to 173 in 2000 (minimum value presented in Azores and a maximum in Alentejo), to a range of 209 to 380 in 2050 (minimum value presented in Lisboa and Tejo Valley and a maximum value in Alentejo). The index of old people dependency, translated as the number of old people for each 100 active individuals will go from a value of 24, in the year 2000, to a value within the range of 54 to 67 over the years until 2050. In addition, the youth is changing their habits and trading the physical activity for hours in front of computers, the healthy alimentation for the "junk" food, a change that will bring consequences in their health in the future.

The studies conducted in Portugal so far have not been populations studies, in a country where the costs with health are in the daily news and being osteoporotic fractures a costly condition (Tosteson 1999) it is needed to have information in order to prevent future costs.

The diseases are no longer considered only a result of biochemistry, it is needed to develop a social and environmental perspective in the etiology of diseases (Nossa, 2001 cited by Pina, 2001). As it is easily understandable, the social and environmental conditions in the study of diseases, can be considered geographical entities, presenting a variation within the space, therefore the possibility of geographical variation in the diseases is to be assessed. The use of Geographical Information Systems (GIS) in the spatial study of diseases is helpful because it allows the integration of different types of data and processes the visualization and analysis in maps of geographical patterns, in order to understand the disease process. It may also be helpful in the allocation of resources or in the planning of interventions in the population, in order to change their habits and prevent a certain disease.

The epidemiological studies concerning osteoporosis are, in its majority, analytical, assessing the association of the incidence and some kind of risk factors. The studies that report some kind of geographical variation, only do so in a descriptive way, and seldom present maps.

The aims of this study are to describe the occurrence of proximal femur fractures, its spatial pattern and determine the existence of spatial clusters, in Portugal.

The work is structured in five chapters.

The first chapter is the introduction, and focuses the problem of the osteoporosis, the importance of the study, the existent studies as well as the objectives of the work.

The second chapter focuses on the theory existent in the major areas in which this work may be classified: Epidemiology, Osteoporosis as well as Epidemiology of Osteoporosis, Geographical Information Systems and Spatial Statistics.

The third chapter is dedicated to the description of the Materials and Methods.

In the fourth chapter the Results are presented.

Finally, in the last chapter, the fifth, the Discussion of the results and the Conclusions are displayed.

Bibliography

Amin, S and D T Felson (2001). "Osteoporosis in Men." Rheumatic Disease Clinics of North American **27**(1): 19-47.

Center, J and J Eisman (1997). "The epidemiology and pathogenesis of osteoporosis." Bailliéres Clinical Endocrinology and metabolism **11**(1): 23-62.

Cooper, C and L J Melton III (1996). Magnitude and Impact of Osteoporosis and Fractures. Osteoporosis. D. F. R Marcus, J Kelsey, Academic Press: 419-434.

Cummings, S R and L J Melton III (2002). "Epidemiology and Outcomes of Osteoporotic Fractures." The Lancet **359**: 1761-67.

Dennison, E and C Cooper (2000). "Epidemiology of Osteoporotic Fractures." Hormone Research **54**: 58-63.

Gold, D T (2001). "The Nonskeletal Consequences of Osteoporotic Fractures - Psycologic and Social Outcomes." Rheumatic Disease Clinics of North American **27**(1): 255-262.

INE – Instituto Nacional de Estatística. URL: http://www.ine.pt.

Jordan, K M and C Cooper (2002). "Epidemiology of osteoporosis." Best Practice & Research Clinical Rheumatology **16**: 795-806.

Kanis, J A (2002). "Diagnosis of osteoporosis and assessment of fracture risk." The Lancet **359**: 1929-1936.

NIH – National Institutes of Health Consensus Statement Online (2000). "Osteoporosis, Prevention, Diagnosis, and Therapy. URL: http://consensus.nih.gov.

Nossa, P (2001). Geografia da Saúde: o caso da Sida. Oeiras, Celta Editora.

O'Neill, T W and D K Roy (2003). "The epidemiology and scale of the problem." Hospital Medicine **64**(9): 517-520.

Pina, M F (2001). Aplicação e Avaliação de Técnica de Interpolação Espacial para geração de superfícies de densidade a partir de dados populacionais em uma região do município do Rio de Janeiro. COPPE. Rio de Janeiro, Universidade Federal do Rio de Janeiro.

Riggs, B L and L J Melton III (1995). "The Worldwide Problem of Osteoporosis: Insights Afforded by Epidemiology." Bone **17**(5): 505S-511S.

Scott, J C (1990). "Osteoporosis and Hip Fractures." Rheumatic Disease Clinics of North American **16**(3): 717-740.

Tosteson, A N A (1999). Economic Impact of Fractures. Osteoporosis in Men. E. S. Orwoll, Academic Press: 15-27.

Trombetti, A, F Herrmann, et al. (2002). "Survival and potential years of life lost after hip fracture in men and age-matched women." Osteoporosis International **13**(9): 731-737.

Walker-Bone, K, E Dennison, et al. (2001). "Epidemiology of Osteoporosis." Rheumatic Disease Clinics of North American **27**: 1-18.

Walker-Bone, K, D M Reid, et al. (1998). "Is screening for osteoporosis worthwhile?" British Medical Bulletin **54**(4): 915-927.

2. State of Art

2.1. Epidemiology

2.1.1. History and Definition

The word Epidemiology, if analysed etymologically, results from the combination of the word *"epi"* that means on, upon, befall, the word *"demo"* that means people, population and the word *"ology"* that means the study of. Thus, if taken literally, the term Epidemiology means "the study of that which befalls people." (Timmreck 1994; Stone, Armstrong et al. 1999).

The basis of epidemiologic studies evolved from the scientific revolution in the 1600's which suggested that orderly behaviour of the physical universe could be expressed, i.e. described, analyzed and understood, in terms of mathematical relationships. So, if these relationships existed for the physical universe, then similar relationships should exist to express the biological world. These became known as the "laws of mortality". John Graunt, a tradesman, who was one of the founders of the Royal Society of London, constructed the first knowned lifetable; when he summarized the mortality experience in terms of numbers, percents and probabilities. Through the analysis of the table he thought possible to formulate a law of mortality and he propose that each country should built similar tables, so that a general law of mortality would be built (Lilienfeld 1994).

With the development of the mathematical principles during the late 1600's and 1700's Graunt's idea was improved, and it was also during this period that the idea of using several groups for comparison appeared (Lilienfeld 1994).

Until the 19th century, epidemiologic studies were the result of isolated work of some individuals, such as James Lind (1747), who developed hypothesis from epidemiologic observations of the treatment and etiology of scurvy, and carried an experiment to evaluate the hypothesis, and, Daniel Bernoulli (1760), a member of a knowned family of European mathematicians, that using a lifetable determined that inoculation at birth of smallpox conferred lifelong immunity and increase life expectancy (Lilienfeld 1994).

With the French Revolution, in the 19th century, an interest in public heath and preventive medicine stimulated the epidemiologic approach to disease and brought to light its importance in the efficacy of medical practices. Pierre Charles-Alexander Louis is considered the major figure of epidemiology in this period, with his creation of the "numerical method" to apply in epidemiologic investigations, and his contribution in teaching, not only French students but also foreign ones. William Farr, one of Louis's English students, was the first director of the Registrar-General's Office, the national centre for health statistics in England. He was also a member of the London Epidemiological society, where the members discussed their epidemiological activities (Lilienfeld 1994).

In the late 19^{th} century, with the development of bacteriology, the agents of the diseases where identified and the need for epidemiology, as recognised in that period was lessened. It was during the fist half of the 20^{th} century that through the work of statisticians and demographer-sociologists (some of which worked in the life insurance industry, and had an interest in determining which individuals were at great risk of morbidity and mortality) that epidemiology refleurish and gain new guide lines. In our days, Epidemiology can be defined as the study of the occurrence and distribution of diseases and other health-related conditions in populations (Pereira 1995; Kelsey and Sowers 1996). The objectives of Epidemiologic researches, usually, are: understand the causes of disease, plan treatment and contribute to the development of public health policies (Lilienfeld 1994; Essex-Sorlie 1995). Taking in consideration these objectives, more extensive definitions of Epidemiology can be found, one of those definitions is: Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems (Last 2001).

In order to achieve the objectives, epidemiologists study various factors such as demographic, biological, genetic, social and economical characteristics and personal habits and then reasoning them, by first: determinate a statistical association between characteristics and diseases, and second: derivate biological inferences from such associations (Lilienfeld 1994). For these reasons Epidemiology is considered an integrative and eclectic discipline which combines knowlegments from other disciplines such as statistics, sociology and biology (Lilienfeld 1994; Pereira 1995).

2.1.2. Types of Epidemiological Studies

Epidemiological studies can be classified by the use of different criteria. The more usual classifications are descriptive epidemiology versus analytic epidemiology and the classification in observational epidemiology versus experimental epidemiology.

The classification that divides epidemiologic studies in descriptive and analytic is based on the objectives of the studies (Pereira 1995), although objectives are not always easy to separate. The objective of the descriptive studies is, like the name says, to describe the data, while the objective of analytic studies is to investigate hypothesis that can be formed by descriptive or other analytic study preformed for other purposes. Descriptive studies, according to Last (2001) are used only to describe the existing distribution of the variables without regard to casual or other hypothesis whereas analytical studies are used when insights or information about various aspects of a disease are available to form an hypothesis (Timmreck 1994). Descriptive epidemiology tries to describe *how* a disease is distributed in a population, whereas analytic epidemiology tries to explain *why* (Kelsey and Sowers 1996).

Descriptive epidemiology studies the occurrence of disease or other health related characteristics in human populations. Usually observations concerning the relationships of disease to basic characteristics such as age, sex, race, occupation, social class and geographical location are the main concern of this kind of studies (Last 2001). The data are compiled and analysed by the major characteristics, frequently called epidemiologic variables which are time (*when*), place (*where*) and people (*who*) (Stone, Armstrong et al. 1999; Last 2001). Time, can provide important patterns and can be divided in several units, such as minutes, hours, days, weeks, months, years, decades, depending on the objective of the investigation. Place refer to a geographical unit and can be a point defined by latitude and longitude, an address, a political unit such as country, municipality, district, neighbourhood, a operational unit such as enumeration districts, census tracts, health districts or a physical unit such as water basins. Finally, note that people can be analysed in an individual level where the value of each variable is given for each individual (Medronho 2003) or in a ecological level where the units of analysis are populations or groups of people (Last 2001). The variables of interest can integrate factors such as age, sex, race, social economical, occupation, and others both for individual or population level.

Descriptive epidemiology, normally, uses data collected for other purposes, frequently denominated secondary data, like data from national health systems (Barker and Hall 1972). This kind of researches using data that have already been collected has two main advantages: speed and economy (Hearst, Grady et al. 2001) because it will not be necessary to dispend the resources (time, people, financial costs) to gather the information, at least in a theoretical point of view. Despite the advantages, the use of existing data also as limitations: the investigator as little or no control over the data and the selection of which data to collect, the quality of data gathered, and how data is recorded are all predetermined. Also, the data may be gathered with several missing or incorrect information and that may compromised the result of the investigation. One of the other disadvantages may be the difficulty on the access and integration of data, that often is accessible in different organisms and that may have different methodologies of data managing.

Secondary data sets, are of two types: individual and aggregate (Hearst, Grady et al. 2001). In individual data sets information for each subject is available; the source for this kind of data set may be from medical records, health care billing files, death certificates, from other research study, from large regional or national data sets. The major drawback of this kind of data is the problem of confidentiality concerning a particular subject. In aggregate data the information is only available for a group of subjects; the advantage of this data it is availability because the problem of confidentiality do not apply, the major disadvantage is that the fact that individuals in a group may differ from each other in a very precise way and may form subgroups that the investigator can not access, or otherwise groups may tend to have associations that may not hold for the individual (Hearst, Grady et al. 2001), this last is the so called ecological fallacy (Last 2001).

Analytic epidemiology is used to examine associations formalized by causal hypothesis (Kelsey and Sowers 1996; Last 2001). Any analytic study starts with questions or logical propositions carefully defined that usually are the result of solid theoretical researches, and that constitute the hypothesis that is taken under testing. An analytic study is usually concerned with identifying or measuring the effects of risk factors or is concerned with the health effects of specific exposure(s) (Last 2001).

The data often used by analytic epidemiology is specially collected for the effect, this may increase the costs, financially and timing, of this type of study (Kelsey and Sowers 1996).

The classification that divides epidemiologic studies in observational or experimental is based on whether patients are merely observed or whether some kind of intervention is performed (Essex-Sorlie 1995).

Experimental studies can be defined as studies in which the conditions involved are under the direct control of the investigator (Lilienfeld 1994; Rothman and Greenland 1998a; Last 2001). The typical experimental study is one in which there is a number of groups of subjects, each exposed to a particular experimental condition. The objective of the experiment is determine whether the various experimental conditions differ in their influence on the subjects (Hassard 1991). In this kind of study, the subjects are exposed to the agent or putative cause because the investigator intended them to be. This assignment, can only be influenced by the protocol and never by the needs of the subjects, this fact, brings ethical constrains, such as, any exposure should be limited to preventive measures, subjects shouldn't be deprived of some preferable form of treatment that is not included in the study and all treatment alternatives should be equally acceptable under present knowledge. Therefore an experiment occurs only when it is feasible (Timmreck 1994; Rothman and Greenland 1998a).

The prevention of bias and confounding, that if present might affect and compromise the validity of the trial, is one of the main concerns when designing an experimental study. Bias can be defined according to Last (2001) as a "deviation of results or inferences from the truth, or a process leading to such deviation", and confounding can be defined as "a situation in which the effects of two processes are not separated. The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome". Some of the principles used to avoid bias and confounding are: assign the exposure in a random way, and blinding. One of the most obvious sources of bias is when subjects are allocated to exposure groups, because the investigator although in a subconsciously way may tend to expose the subjects in a more suitable way to get positive results (Hassard 1991; Timmreck 1994; Malim and Birch 1997; Cummings, Grady et al. 2001). Chance should be the only determining factor to determine which group each subject is assign to, therefore random assignment provides that baseline prognosis characteristics, like sex and age, will be distributed equally (Hassard 1991; Timmreck 1994; Cummings, Grady et al. 2001). The importance of blinding is equal to the importance of randomise allocation. The influence of psychological factors in the response to a treatment is well knowned, therefore patients should be completely ignorant to all methods and assignments and if possible also the investigators should be ignorant to the same information to prevent the subject to realize the differences. A study that the subjects are blind to the treatment they are receiving is called a single-blind study. A double-blind study occurs when both subjects and investigators (who apply the treatment) are blind to the methods and treatments or group's assignments. A triple-blind study is when not only the subjects and investigators (who apply the treatment) but also the investigators responsible for the evaluation are blind (Hassard 1991; Timmreck 1994; Cummings, Grady et al. 2001; Escosteguy 2003). Randomisation eliminates confounding by baseline variables and blinding eliminates confounding by co-interventions (Cummings, Grady et al. 2001).

Experimental studies include clinical trials and field/community trials. In a clinical trial the subjects are patients and the goal is to evaluate a potential cure or find a preventive of a disease or a disease squeal (Rothman and Greenland 1998a). Usually, this term is used when a controlled experiment is made involving two or more groups of patients (Last 2001). Beside of the random assignment of the exposure, clinical trials should try to employ blinding to prevent certain biases that might affect the conclusions. Ideally, all the people involved, such as the patient and who makes the assignment, should be ignorant to the assignment. In this kind of study it is very important that most of the participants adhere to the protocol and will not be lost at follow-up period in order to maintain the validity of the trial (Grady, Cummings et al. 2001).

The field and community trials differ only on whether the intervention is made in a community instead of an individual. In a community trial the unit of allocation is an entire community or political subdivision (Stone, Armstrong et al. 1999; Last 2001). In both the studies the subjects, in oppose to what happens in the clinical trial, are "not yet" hill. Because of this fact, field and community trials require a great number of people, and therefore the costs are higher. These kinds of experiments are normally used only in the case of the study of preventive of either extremely common or extremely serious diseases (Rothman and Greenland 1998a). Community trials are useful to discover regional differences in such things as the cultural and behavioural factors, furthermore this research process has more benefits for a community than studies made with a unit of allocation of individuals (Hearst and Hulley 2001).

Observational studies can be defined as studies that do not involve any intervention, experimental or otherwise (Last 2001), i.e. studies in which the investigator does not manipulates the conditions involved in the study (Essex-Sorlie 1995). In this kind of study the epidemiologist observes the associations between exposure and outcome and has no power in assigning the exposure, the only intervention by the investigator is record, classify, count, and statistically analyse results (Last 2001). This kind of study is very frequent because it does not have the costs restrictions and ethical restrictions of the experimental study (Rothman and Greenland 1998a) since people often expose themselves to many potential harmful factors, such as cigarette smoke or birth control pills.

One of the most renowned observational study is the one conducted by John Snow (1913-1858) about cholera in London. During the mid nineteenth century there was a cholera epidemic in London; Snow's investigation consisted in comparing the cholera mortality cases with the source of the water supply, which was supplied by several water companies that piped drinking- water from different parts of the Thames. This allowed Snow to have groups exposed to different levels of exposure without intervene directly with the exposure. Therefore by merely observation he discovered the association between contaminated river water and cholera risk as well as the latency time of the disease (Timmreck 1994; Rothman and Greenland 1998a; Järup 2000; Last 2001).

There are two main designs of observational studies: cohort and case-control (Rothman and Greenland 1998a). The term cohort comes from the Latin *cohors*, the tenth part of a legion, and has broadened to described any designated group of persons who are followed or traced over a period of time (Last 2001). Therefore a cohort study involve following groups of subjects over time (Cummings, Newman et al. 2001). The definition of the group of subjects to be followed is the main concern of this kind of study, they should be appropriate to the research question and available for the follow-up period (Cummings, Newman et al. 2001). A cohort study can be used to estimate average risks, rates, or occurrence times of specific events (Rothman and Greenland 1998b).

Two basic variation of this design are possible: prospective studies and retrospective studies. In the prospective studies, the subjects are not yet hill, they are divided into groups: exposed and unexposed, or different rates of exposure, and then followed to see if they develop the disease (Pereira 1995; Kelsey and Sowers 1996). The study sets from what might be the causes to get to the effects. The basic steps for performing a prospective cohort study are: the investigator assembles a cohort, measures predictor variables and potential confounders and then follows the cohort and measures outcomes (Cummings, Newman et al. 2001). As an advantage of this variation is the fact that because potential factors are measure before the outcome occurs, the inference that the factor may be the cause of the outcome is strengthened. As a disadvantage is the fact that is an expensive design and inefficient to study rare outcomes (Rothman and Greenland 1998a; Cummings, Newman et al. 2001). In the retrospective study the investigation is initiated at a point in time after the exposure occurred, just like in a prospective study, the difference is that the assembly of the cohort, baseline measurements, follow-up and outcomes all happened in the past (Cummings, Newman et al. 2001). This causes a disadvantage because this study can only occur if adequate data about risk factors and outcomes are available. As advantages this kind of study has the same as the prospective cohort study and they are less costly and time-consuming than the prospective studies, because the subjects are already assembled, baseline measures have already been made, and the follow-up period has already taken place (Cummings, Newman et al. 2001).

A case-control design studies persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease (Last 2001). Case-control studies are also called retrospective studies, because the subjects are chosen to be included in cases if they have the characteristics or disease of interest or are chosen to be included in controls if they are disease free, and then the epidemiologists investigate backward the experience and history of the patients. The study sets from the effect to get to the causes (Pereira 1995; Rothman and Greenland 1998a; Last 2001; Newman, Browner et al. 2001). The selection of cases, apart from random sampling, can be done from the source population who develop the disease of interest, as for the selection of controls it should be done from the same population and should be representative of the population in respect to exposure (Rothman and Greenland 1998c).

One of the major advantage of this kind of study is it efficiency with rare outcomes, another advantage is since it provides the ability to examine a large number of predictor variables it is useful in the generation of hypothesis, besides its relative small cost (Newman, Browner et al. 2001). But this kind of study design has limitations; most of them because the investigation is done backwards. As a consequence, information of potential risk factors and other relevant variables may not be available either from records or the participants' memories (Kelsey and Sowers 1996). Cases may search for a cause for their disease and thereby be more likely to report an exposure then controls (Kelsey and Sowers 1996; Newman, Browner et al. 2001). This kind of study is also susceptible to sampling bias that depends on both the disease and risk factors, to reduce this bias the investigator can sample cases and controls in the same way, match cases and controls or use several control groups, sampled in different ways (Newman, Browner et al. 2001). Because of these limitations this design is used to provide leads to be followed by other types of designs or to take preventive measures (Kelsey and Sowers 1996).

Both case-controls and cohort studies can be designated of longitudinal studies because they require a period of follow-up; they provide a "film" of the population. In a cross-sectional study, another possible classification, the cause and the effect are detected simultaneous, all variables are measured at a single point in time; therefore they provide a "snap-shot" of the population. This kind of study is especially useful for providing descriptive information about prevalence, estimating the frequency of a disease in a point in time (Essex-Sorlie 1995). It also has the advantages of avoiding the time, expense and dropout problems that may occur in the follow-up period (Newman, Browner et al. 2001). As disadvantages it can be point the fact that this design does not establish sequence of events (Newman, Browner et al. 2001).

Another way to classify the epidemiological studies is the division between spatial and non-spatial epidemiology. Spatial epidemiology is concerned in both describing and understanding the spatial variation in disease risk (Elliot, Wakefield et al. 2000). The non-spatial epidemiology is not, obviously concerned in the spatial variation, its focus is on other variables concerned with diseases.

The variable space as long been part of the epidemiological studies, and its importance as long been recognised, the Mankind needed to "understand" and "resolve" problems related to disease and therefore no variable susceptible to be important in the analyse should be underestimated. However was through the use of spatial statistics that spatial epidemiology gains the amplitude given to the concept of "epidemiology".

In spatial epidemiology four types of studies were identified by Elliot et al (2000): disease mapping, that are carried out to summarise spatial and spatio-temporal variation in risk; geographical correlation studies, that examine the geographical variation in exposure to environmental variables in relation to health outcomes measured on a geographical scale; the assessment of risk in relation to a point or line-source, that are appropriated when increased risk close to the source is suspected, or where the source is considered to present a potential hazard; and finally the detection of relatively uncommon events in space that are believed or perceived to be greater or smaller than what could be expected by chance.

These kinds of epidemiologic studies are also permeable to bias and confounding, some forms specific of spatial studies and some common to other studies (Elliot and Wakefield 2000). Bias can be the result of geographical choice, that is: the choice of an area rather than another can influence the analyse. Another source of bias can be the numerator and the denominator that are involved in the risk estimates, the migration of population between geographical location is a problem that can affect both the numerator as well as the denominator, and is difficult to model and therefore to eliminate. The disregarding of the fact that the outcomes of spatial units "close" are not independent can also lead to biased estimates.

2.1.3. Health Indicators

Health indicators are variables susceptible to direct measurement, which reflect the state of health of persons in a community (Last 2001). According to the World Health Organization (WHO 1999) indicators are needed for example to:

- Monitor trends in health;
- Compare areas or countries in terms of their environmental health status, so as to help target action where is most needed or to help allocate resources;
- Help investigate potential links between environment and health;
- To help raise awareness about environmental health issues across different stake-holder groups.

From the exposed, one can conclude the important role of the indicators; therefore it is needed that they are effective. According to the same font (WHO 1999), in order to achieve effectiveness the indicators should meet a number of different criteria. They should provide a relevant and meaningful summary of the conditions of interest, because usually their users are not experts in the subject of matter. They should be transparent, testable and scientifically sound in order to satisfy the wider community. They should be sensitive to real changes in the conditions they measure, yet robust enough not to be swamped by noise in data in order to detect variations or changes. They must be cost-effective to compile and apply in order to be used.

The health indicators can be divided in two groups: morbidity and mortality rates. Morbidity is considered any change, subjective or objective, from a state of physiological and psychological well-being (Last 2001), and can be measure though the incidence or prevalence rates. Mortality rates concern the mortality of the populations.

The term incidence is according with Last (2001), from a WHO font of 1966, " the number of instances of illness commencing, or of persons falling ill, during a given period in a specified population", i.e. the number of new cases of diseases within a specified period of time. According with the same author the term incidence is also used to denote incidence rate, i.e., the rate at which new events occur in a population, usually calculated by the following formula (Selvin 2001)

$$i = \frac{nd}{p} \times base$$

where:

nd - number of new cases of disease;

p - number of individuals at risk.

The incidence rate is given in the rate per 10^n person-period of time (base), if this period is a year than the rate is an annual rate. If the population concerning this rate is dynamic then the denominator of the formula, the number of persons exposed to risk is calculated by the average size of the population that usually is estimated at the middle period (Stone, Armstrong et al. 1999; Last 2001).

The term prevalence, is according with Last (2001), "the number of events, e.g., instances of a given disease or other condition, in a given population at a designated time", i.e. the number of existing cases in a given population, at a time, but is also used to denote the prevalence rate, that is usually calculated by the following formula:

$$p = \frac{ad}{p} \times base$$

where:

ad - total number of cases in a specified period;

p - number of individuals exposed to risk during a specified period.

Like in incidence rate, the prevalence rate is given in the rate per 10^n person-period of time (base) and if the population concerning this rate is dynamic then the denominator of the formula, the number of persons exposed to risk is calculated by the average size of the population and usually is estimated at the middle period (Stone, Armstrong et al. 1999; Last 2001).

Another important health indicators is the case fatality rate, that can be defined according to Last (2001), as the proportion deaths in the total of cases within a specified time. It is usually expressed as percentage and calculated through the following formula:

$$cfr = \frac{f}{nd} \times 100$$

where:

f – number of deaths from a disease (in a given period);

nd – number of diagnosed cases of that disease (in the same period);

Mortality rate also denominated death rate, is "an estimated of the proportion that dies during a specified period" (Last 2001). Is generally calculated by the following formula:

$$m = \frac{d}{p} \times base$$

where:

d – number of deaths in a specified period;

p – number of persons at risk of dying during a specified period.

The mortality rate gives an estimate per 10^n person-period of time (base), and the denominator is calculated by the average size of the population that usually is estimated at the middle period (Stone, Armstrong et al. 1999; Last 2001). This rate as well as morbidity rates can be calculated using specific criteria, like rates by age, by cause of death and so on.

Comparison of crude rates may be confounded by differences in the population structure that is being compared (Julious, Nicholl et al. 2001); In order to facilitate comparisons between two or more sets the rates should suffer a process of standardization (Julious, Nicholl et al. 2001; Bhopal 2002; Rothman 2002), usually the sets to be compared are defined by age or by sex and age (Julious, Nicholl et al. 2001). Standardization uses a defined set of weights to combine results across strata, and therefore provide for better comparability of stratified results from one study to another or within a study (Rothman 2002). The weights used to create the standardization, come from a standard population and their choice completely define the standard. However if all categories have similar rates, the choice of weights would matter little. In spite of the advantages of standardization, this process also has disadvantages: as they are not true population based rates, they do not accurately measure the health status of the population (Bhopal 2002).

There are two important methods of standardization of mortality or morbidity data: the direct and the indirect method. The methods will be exposed using the terms of mortality data but they can also be used with morbidity data.

The rates resulting from the direct method are applied to answer the question: how many cases would have occurred in the standard population if it had the same rates as the population under study? (Bhopal 2002)

The directly standardized rate: DSR, is the rate that results from the direct standardization method and it can be expressed as quotient of the expected number of deaths in the standard population, if that population had the age and sex specific rates as the population under study, by the total number of persons in the standard population, and it can be calculated by the following formula:

$$DSR = \frac{\sum_{i=1}^{k} N_i \frac{d_i}{n_i}}{\sum_{i=1}^{k} N_i}$$

where:

N_i – number of persons in the i[th] group of the standard population;

d_i – number of deaths in the i[th] group of the population in study;

n_i – number of persons in the i[th] group of the population in study;

k – number of groups.

From the result of the direct standardization, i.e., through the cases happening in the population under study calculating the expected cases in the standard population, is also possible to obtain a more easily understandable ratio, simply by dividing the expected number of deaths in the standard population, if it had the same the age and sex specific rates as the population under study, by the observed deaths in the standard population. This ratio can be calculated through the following formula and it can be designated by Comparative Mortality Figure: CMF (Julious, Nicholl et al. 2001).

$$CMF = \frac{\sum_{i=1}^{k} N_i \frac{d_i}{n_i}}{\sum_{i=1}^{k} D_i}$$

where:

N_i – number of persons in the i^{th} group of the standard population;

D_i – number of deaths in the i^{th} group of the standard population;

d_i – number of deaths in the i^{th} group of the population in study;

n_i – number of persons in the i^{th} group of the population in study;

k – number of groups.

The problem when using this ratio can be the problem in assessing the data for the deaths in the standard population (Julious, Nicholl et al. 2001). A CMF of 1 indicates that the study population has the same mortality experience as that of the reference population and a CMF over 1 represents an unfavourable mortality experience of the population under study.

The rates resulting from the indirect method are applied to answer the question: "How many cases would have occurred if the study population had the same rates as the standard population?"(Bhopal 2002).

The indirectly standardized rate: ISR, is the rate that results from the indirect standardization method and it can be calculated by the following formula:

$$ISR = \left[\frac{\sum_{i=1}^{k} d_i}{\sum_{i=1}^{k} n_i \frac{D_i}{N_i}} \right] \times \left[\frac{\sum_{i=1}^{k} D_i}{\sum_{i=1}^{k} N_i} \right]$$

where:

d_i – number of deaths in the i^{th} group of the population in study;

n_i – number of persons in the i^{th} group of the population in study;

D_i – number of deaths in the i^{th} group of the standard population;

N_i – number of persons in the i^{th} group of the standard population;

k – number of groups.

Note that the first factor can be designated standardized mortality rate – SMR, and is the ratio of the total number of deaths in the population of study by those expected in that population if it had the age and sex specific death rates as a "standard" population.

$$SMR = \frac{\sum_{i=1}^{k} d_i}{\sum_{i=1}^{k} n_i \frac{D_i}{N_i}}$$

where:

d_i – number of deaths in the ith group of the population in study;

n_i – number of persons in the ith group of the population in study;

D_i – number of deaths in the ith group of the standard population;

N_i – number of persons in the ith group of the standard population;

k – number of groups.

Like in CMF, a SMR of 1 indicates that the study population has the same mortality experience as that of the reference population (Goldman and Brender 2000) and a SMR over 1 represents an unfavourable mortality experience of the population under study (Julious, Nicholl et al. 2001).

This ratio is the most commonly used technique to compare mortality/morbidity experience of different geographical areas (Julious, Nicholl et al. 2001).

Some controversy has rose as for the use of indirectly in opposite of the use of directly standardized rates. According with some authors (Julious, Nicholl et al. 2001; Bhopal 2002) the indirectly standardized rates is inappropriate to do comparisons between different geographical areas because for different geographical areas it has different denominators (Julious, Nicholl et al. 2001). The standardization is weighted in relation to the structure of the population under study (Bhopal 2002) and if it differs from an area to another, the weights used are different. The only comparison valid is the one between the study population and the chosen standard (Julious, Nicholl et al. 2001; Bhopal 2002). The reasons pointed to the frequent use of SMR in comparisons of different geographical areas are: the fact that the direct standardization rate yields only a rate rather than a more easily interpreted ratio and that direct standardization may not be carried out when sub-group mortality data is not available or are based upon small numbers and are completely unreliable (Julious, Nicholl et al. 2001). However some authors agree that the reasons pointed are not a valid ones, because also the direct methods can produce a CMF, that provides an easily understandable ratio, as described previously, and according with other authors (Pickle and White 1995) the instability of directly adjusted rates due to small numbers can be lessened by aggregating the raw data over the geographical units or by smoothing them with Bayesian methods. Therefore some (Julious, Nicholl et al. 2001) conclude that the SMR should only be used to compare mortality from different causes within a single population and only when it is strictly necessary (when event data is not available by sets) should it be used to compare different geographical areas.

In spite of the differences, the direct and indirect method will produce numerically identical results if one of the conditions holds (Pickle and White 1995):

- if the proportional population distribution in each area is identical to that in the standard population;
- if the age-specific rates in each area are identical to those in the standard population;
- if the age-specific rates for each area are proportional to those in the standard population; in this case the SMR equals the crude rate in the standard population times the proportionality constant of each area.

In the absence of age-by-area interactions the direct method of age adjustment preserves the ordering and proportional differences of the underlying age-specific rates, whereas the indirect method preserves the ordering but does not necessary preserve the magnitude (Pickle and White 1995). According to Pickle et al., 1995, in the presence of age-by-area interactions any summary rate will mask the underlying age-specific patterns and the choice of the procedure interferes with such patterns.

Bibliography

Barker, D J P and A J Hall (1972). Introdução à Epidemiologia, Guanabara Koogan.

Bhopal, R S (2002). Concepts of Epidemiology: an integrated introduction to the ideas, theories, principles, and methods of epidemiology, Oxford University Press.

Cummings, S R, D Grady, et al. (2001). Designig an Experiment: Clinical Trials I. Designing Clinical Research. T. B. Newman, Lippincott Williams & Wilkins: 195-212.

Cummings, S R, T B Newman, et al. (2001). Designing an Observational Study: Cohort Studies. Designing Clinical Research. S. B. Hulley, S. R. Cummings, W. S. Browneret al, Lippincott Williams & Wilkins: 95-105.

Elliot, P and J C Wakefield (2000). Bias and confounding in spatial epidemiology. Spatial Epidemiology: Methods and Applications. D. J. Briggs, Oxford University Press.

Elliot, P, J C Wakefield, et al. (2000). Spatial epidemiology: methods and applications. Spatial epidemiology Methods and Applications. D. J. Briggs: 3-14.

Escosteguy, C C (2003). Estudos de Intervenção. Epidemiologia. R. d. A. Medronho, D. M. Carvalho, K. V. Bloch, R. R. Luiz and G. L. Werneck, Athneu: 151-160.

Essex-Sorlie, D (1995). Medical Biostatistics & Epidemiology, Prentice-Hall International Inc.

Goldman, D A and J D Brender (2000). "Are Standardized Mortality Ratios Valid for Public Health Data Analysis?" Statistics in Medicine **19**: 1081-1088.

Grady, D, S R Cummings, et al. (2001). Designig an Experiment: Clinical Trials II. Designing Clinical Research. T. B. Newman, Lippincott Williams & Wilkins: 195-212.

Hassard, T H (1991). Understanding Biostatistics, Mosby-Year Book.

Hearst, N, D Grady, et al. (2001). Research Using Existing Data: Secondary Data Analysis, Ancillary Studies, and Systematic Reviews. Designing Clinical Research. S. B. Hulley, S. R. Cummings, W. S. Browneret al, Lippincott Williams & Wilkins: 195-212.

Hearst, N and S B Hulley (2001). Community and International Studies. Designing Clinical Research. S. B. Hulley, S. R. Cummings, W. S. Browneret al, Lippincott Williams & Wilkins: 275-283.

Järup, L (2000). The role of geographical studies in risk assessment. Spatial Epidemiology: Methods and Applications. P. Elliot, J. C. Wakefield, N. G. Best and D. J. Briggs, Oxford University Press.

Julious, S A, J Nicholl, et al. (2001). "Why do we continue to use standardized mortality ratios for small area comparisons?" Journal of Public Health Medicine **23**(1): 40-46.

Kelsey, J L and M Sowers (1996). Introduction to Epidemiologic Methods. Osteoporosis. R. Marcus, D. Feldman and J. Kelsey, Academic Press: 397-418.

Last, J M (2001). A Dictionary of Epidemiology, Oxford University Press.

Lilienfeld, D E (1994). Foundations of Epidemiology, Oxford University Press, Inc.

Malim, T and A Birch (1997). Research Methods and Statistics, MacMillan Press.

Medronho, R A (2003). Estudos Ecológicos. Epidemiologia. R. d. A. Medronho, D. M. Carvalho, K. V. Bloch, R. R. Luiz and G. L. Werneck, Atheneu.

Newman, T B, W S Browner, et al. (2001). Designing an Observational Study: Cross-sectional and case-control Studies. Designing Clinical Research. S. B. Hulley, S. R. Cummings, W. S. Browneret al, Lippincott Williams & Wilkins: 107-123.

Pereira, M G (1995). Epidemiologia Teoria e Prática, Editora Guanabara Koogan, S A.

Pickle, L W and A A White (1995). "Effects of the Choice of Age-adjustment Method on Maps of Death Rates." Statistics in Medicine **14**: 615-627.

Rothman, K J (2002). Epidemiology: An Introduction, Oxford University Press.

Rothman, K J and S Greenland (1998a). Types of Epidemiologic Study. Modern Epidemiology. K. J. Rothman, Lippincott- Raven: 67-78.

Rothman, K J and S Greenland (1998b). Cohort Studies. Modern Epidemiology. K. J. Rothman, Lippincott-Raven: 79-91.

Rothman, K J and S Greenland (1998c). Case-Control Studies. Modern Epidemiology. K. J. Rothman, Lippincott- Raven: 93-114.

Selvin, S (2001). Epidemiologic Analysis: a Case-Oriented Approach, Oxford University Press.

Stone, D B, R W Armstrong, et al. (1999). Introdução À Epidemiologia, MacGraw-Hill.

Timmreck, T M (1994). An Introduction to Epidemiology, Jones and Bartlett Publishers.

WHO (1999). "Environmental Health Indicators: Framework and Methodologies."

2.2. Osteoporosis

2.2.1. Definition and other Issues

During many years, osteoporosis was considered an inevitable consequence of ageing. With the development of scientific techniques, evidences that allowed the problem to be seen from other points of view began to appear. As it is easily understandable the intrinsic process of ageing does not necessary lead to disease (Hunter and Sambrook 2000), as osteoporosis is considered today, by many authors (Uebelhant and Delmas 1991; Jonhston JR and Slemenda 1995; Pernadas and Coelho 1999; Gold 2001).

Osteoporosis can be defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (Kanis 2002). In figures 2.1 and 2.2 it can be seen the difference between a healthy bone and an osteoporotic one.

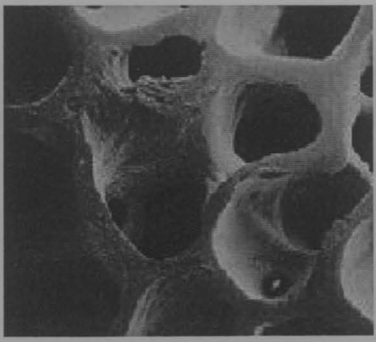

Figure 2.1 - Normal, healthy bone

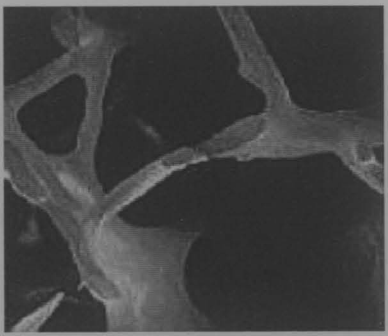

Figure 2.2 - Osteoporotic bone

Osteoporosis can be further characterized based on the etiology, in primary and secondary osteoporosis. Primary osteoporosis is the term used to designate the osteoporotic condition that is not associated with any disease or disorder known to produce bone mass loss in a quantity possible to determine osteoporosis. Secondary osteoporosis, in contrary, is the term used to designate the osteoporotic condition caused by a disease or condition that produce bone mass loss (Scott 1990) or a result of medications (NIH 2000). The National Institutes of Health, NIH, in its Consensus Development Conference Statement, in the year 2000, gave examples of such causes, it pointed out glucocorticoid-induced osteoporosis, hypogonadism and celiac disease.

Bone tissue is highly metabolic; it is constantly in a process of formation/resorption that can be designated by remodelling process (Hunter and Sambrook 2000). This process is, according to Dempster (2003) accomplished by the concerted action of teams of osteoblasts and osteoclasts, the osteoblasts are the cells responsible for the formation, whereas the osteoclasts are the cells responsible for the resorption. The balance of the remodelling process depends on age, sex and skeletal compartments (Dempster 2003). In the first decades of life the activity of formation is superior to the activity of resorption, leading to a progressive increase in bone mass. The way in which this process takes place, leads to the existence of a point in which the amount of bone mass reaches its peak. Then the activity of resorption takes the lead and as a consequence, the bone mass decrease making the bone more fragile (Hunter and Sambrook 2000; Nogueira 2002).

The process of bone remodelling is different for men and women. Men have higher peak bone mass than women at most sites, (Jonhston JR and Slemenda 1995) and in women the loss is substantially more significant than in men; Men lose, during their lifetime, approximately two thirds of the amount of bone that women lose after the middle of the third decade (Hunter and Sambrook 2000). Both sexes evolve in a similar way in the construction of the peak bone mass, this similarity maintains during the period that goes from the reach of the peak until the beginning of the menopause in women. After the menopause, women suffer an abrupt acceleration in the rate of bone loss (passing from a loss of 0.3% per year for a lost of 2% per year in the spine (Uebelhant and Delmas 1991)), that persists for about five to ten years (Dempster 2003), after which the rate of bone loss slows down again.

Bone tissue can be classified into trabecular and cortical (Silva 2002), which are present in different scales in the skeleton compartments. The remodelling processes differs in the trabecular and cortical tissues therefore it is clear that the peak bone mass is not reached simultaneous in all skeleton compartments; besides the trabecular bone loss is more accelerated than cortical bone loss therefore also the rate loss is not equal in all body sites (Hunter and Sambrook 2000; Dempster 2003).

The amount of bone mass, as it was described before, may be understood as having a peak, i.e., a point during the life of individuals in which the amount of bone mass reaches it is maximum value; It is with this maximum value that the individual has to face the progressive loss which will occur for the rest of his life from this point on (Heaney, Abrahms et al. 2000). From this information, one can conclude that an optimisation of this peak is essential so that the individual does not suffer with the loss that will occur, and that is inherent to the process of bone metabolism.

Supposing that a theoretical optimal point of bone mass exist (genetic potential), determined hereditarily. The hereditary factors are considered determinant in three-fourths of the variance in peak bone mass in a population (Heaney, Abrahms et al. 2000) and it would determine the maximum amount if they were not influenced by environmental factors. It is estimated that only 46% to 62% of BMD is attributable to genetic factors, the remain 38% to 54% is affected by lifestyle factors (Morgan 2001). A correct diet that include calcium and vitamin D, practice of physical exercise, long periods of immobilization, clinical conditions that influence the correct segregation of hormones (specially sexual ones) (Jonhston JR and Slemenda 1995), fractures during life, all this factors determine the bone quality and have reflections whether an individual reaches or not his genetical potential as well as reflections in bone quality (Heaney, Abrahms et al. 2000; Hunter and Sambrook 2000). In figure 2.3, a diagram representing the bone mass during life, for individuals that reach the peak bone mass and those who do not, it is also represented some environmental factors, such as exercise, vitamins and nutrients as well as possible fracture risk.

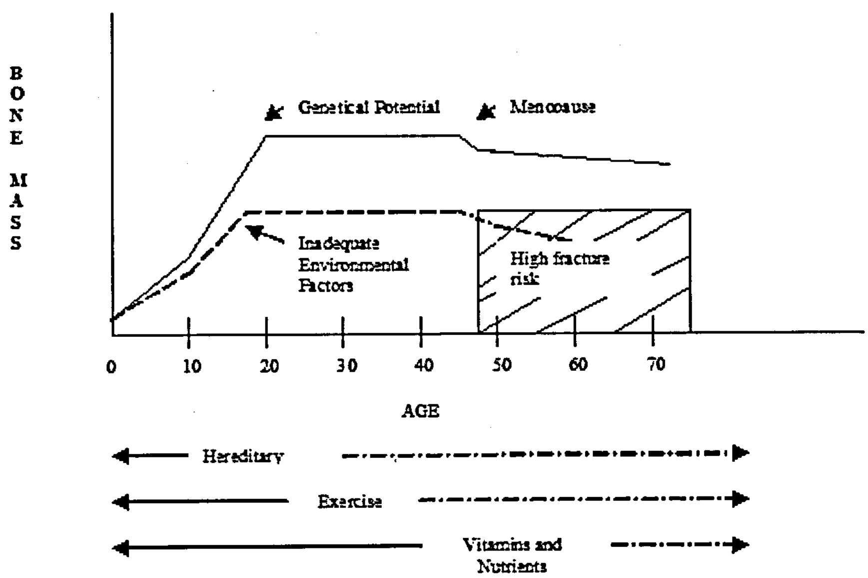

Figure 2.3 - Diagram of bone mass, during the lifetime, of individuals that reach the peak bone mass and those who don't, it's also represented some environmental factors as well as possible fracture risk. Adapted from Heaney R P 2000.

All the environmental factors referred in the last paragraph remain important in the prevention of osteoporotic condition, even after obtaining the BMD peak, because they also represent a preventional role in the loss of BMD (Marcus 2001; Morgan 2001; Nieves 2003; Sinaki 2003).

The definition of osteoporosis presented before, was of little or no help to the physicians, because it was not a quantitative and therefore it was difficult to diagnose someone with osteoporosis before the occurrence of low-trauma fractures (Walker-Bone, Dennison et al. 2001). A more operational definition was needed in order to prevent instead of treating, i.e., in order to have a osteoporosis diagnose before the first fracture occur (Miller 2003).

The alterations in bone tissue that occur in the level of measurable characteristics can be classified as quantitative alterations, but in bone tissue also occur qualitative alterations. The quantitative alterations refer to the bone mineral density (BMD), a unit that is expressed as grams of mineral per area or volume (NIH 2000). The qualitative alterations refer, for example, to the alterations in the architecture, that can be the result of the accumulation of damages (like micro fractures that often are detected, only when fractures of higher impact take place) (NIH 2000). Both alterations contribute to bone strength and therefore to osteoporotic condition (Dias 1998).

The amount of bone mass was, during several time, evaluated by simple processes of radiology, but with the expansion of the problem of osteoporosis, the need of quantify it in an unequivocally an more efficient way led to the appearance of several non-invasion methods. The majority of these methods give the measure of BMD (Gomes 1990; Nogueira 2002), an objective measure of a bone dimension, that contributes to approximately 70 percent of bone strength (NIH 2000). The loss of BMD at virtually any skeletal site (Faulkner 2001) is highly correlated with the risk of fracture (Hans, Dargent-Molina et al. 1996; Nguyen, Center et al. 2001). The strength of such relation depends on the site measured and the type of fracture (Faulkner 2001), therefore it can act as a predictor of fracture; a study mentioned that a single BMD measurement at the forearm could predict the fracture on a 25-year perspective (Duppe, Gärdsell et al. 1997).

The fact that BMD is a measurable dimension of the bone strength, through which an objective comparison between individuals can be made, the WHO introduced a new definition of osteoporosis: a densitometric one. Faulkner, 2001, referred that this definition was intended to define populations rather than be used in individual diagnose, but the need led to a wide use of such definition in the diagnose. This definition is based on comparisons between the BMD of the patient and the BMD of a pattern population and allows the distinction between several osteoporotic degrees as well as normality. The distribution of BMD is approximately Gaussian, independently of the technique used, therefore the comparisons can be made in terms of standard deviations (Kanis 2002). The definition is made in terms of T-score, that gives the information of how BMD of the patient is related to mean BMD of young Caucasian female normal adults (NIH 2000) (age 20 to 30 years old) and is expressed in terms of standard deviations (SD) above or bellow the referred mean. So to predict the risk of fracture, quantify the degree of osteoporosis and evaluate the response of a treatment (Gomes 1990; Miller 2003), the BMD defines:

Table 2.1 - Densitometric definition of osteoporosis, WHO.

$score\ T > -1\ \ SD$	Normal
$-2.5\ \ SD < score\ T < -1\ \ SD$	Osteopenia
$score\ T < -2.5\ \ SD$	Osteoporosis
$score\ T < -2.5\ \ SD$ Plus at least one fracture	Established Osteoporosis

The cut point of -2,5 was used based on an association between the prevalence at this point and lifetime fracture risk. Based on the assumption that the increased fracture risk is a gradient and not a threshold some other cut points were used to define the osteopenia condition (Miller 2003).

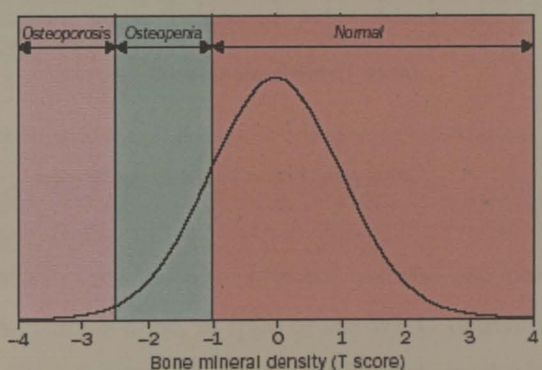

Figure 2.4 - Distribution of Bone Mineral Density in healthy young women, and the classification of several degrees of osteoporosis in terms of T score, reproduced from Kanis, 2002.

The advantage of using a T-score is that the prevalence of osteoporosis increases exponentially with age as the frequency of osteoporotic fractures does, in opposite the disadvantage of using such method is that it undervalues the age in the obtaining of the risk. Kanis et al (2000), illustrate such a fact through the use of an example: supposing that two women present the same BMD, one is 50, the other is 70 years old, the relative risk is higher in the younger woman although the absolute risk, at least in short term is higher in the older woman. In figure 2.5, it is illustrated the increase in the proportion of individuals that have the osteoporotic condition as age increases.

The definition can also be given in terms of Z-score; this score differs from the T-score because the "comparison" is made in terms of the BMD mean of individuals of the same age and gender, the disadvantage of such method is that the prevalence of osteoporosis does not increase exponentially with age because even though two individuals of different age present different BMD, they could fall in the same standard deviation for the mean, because the value of such means would be different (Kanis, Johnell et al. 2000).

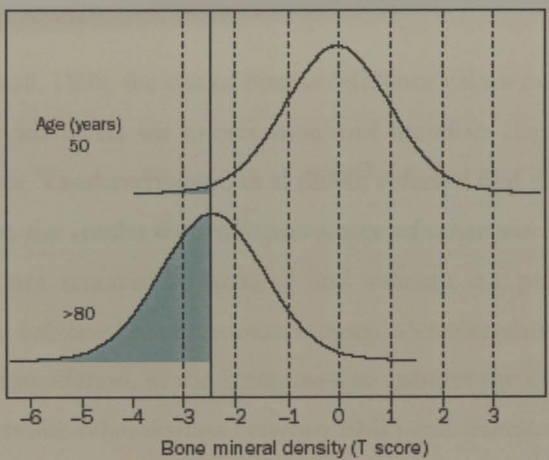

Figure 2.5 - The differences in the proportion of osteoporotic individuals at 50 and more than 80 years of age. Adapted from Kanis, 2002.

Another factor that can contribute to different osteoporosis prevalence is the site of the skeletal where the measure is done, in spite of the WHO definition was intended to be used in several skeletal sites, the definition as been currently used with measures of hip BMD. A study mentions that the prevalence of osteoporosis varies from 0 to 36% in men and from 2 to 45% in postmenopausal women, when using different skeletal compartments (Melton III 2001).

From what it was exposed in the previously paragraphs, the referenced used is of extreme importance. Kanis, 2002, comments that a "small difference between ranges have a large effect on the number of individuals with BMD below a diagnostic threshold". The International Osteoporosis Foundation and WHO recommend the use of the National Health and Nutrition Examination Survey (NHANES) reference database in US women aged 20-29 years as the reference (Kanis 2002).

The EPOS (European Prospective Study) performed in ten European centers, including Cambridge, Oslo, Zagreb, Athens, Prague and others, concluded that substantial BMD differences (even after data adjustment for age, height, weight and other significant interactions) were encountered (Crabtree, Cunt et al. 2000), suggesting that the concern should be in obtaining a database, to search the references, for each geographical location (Formica 1998).

However, through this definition it is not clear how to diagnose men, children and other ethnic group. In the diagnose of men through the definition given previously, there are two aspects to be considered: the use of the female reference and the use of the cut points referred.

According to Orwoll, 1999, the use of female reference values can limit the number of men that meet thresholds levels for intervention and therefore deprive some men of appropriate care. Moreover, Vanderschueren, et al (2000) referred that the use of female or male cut points influences the results for male prevalence of osteoporosis and considered that some more studies are required to achieve and validate cut points for men (the thresholds have only been validated for Caucasian women) (Vanderschueren, Boonen et al. 2000). In spite this recommendation, in the literature also appears the indication that some studies conducted show similar relationships between BMD and fractures, for men and for women, which may suggest that the same cut points can be applied (Pende and Francis 2001).

Concerning the diagnose of osteoporosis in other ethnic groups either than Caucasians, and children the same observations about different BMD measures can be made, because, for example, Blacks have more bone mineral density than Whites of comparable ages and body weights (Hui, Dimeglio et al. 2003), and children from what it was exposed previously do not present the same BMD as adults and therefore any comparison made is compromised.

Having expose the factors that influence the BMD and the definition of osteoporosis through these measures, the diagnosis of this condition should be done by a careful assessment of risk factors for low bone mass, a quantification of BMD and a thorough medical and physical examination (Becker 2003); This combination must be especially followed in the case of men, children and other ethnic groups since the diagnosis through the BMD measure may not be effective.

2.2.2. Epidemiology of Osteoporosis

The visible outcome of osteoporosis are fractures (Cooper and Melton III 1996), that serve as an alternative to assess the impact of the disease.

The incidence of fractures in human is bimodal, presenting a peak in youth and a peak in elderly (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001). However these peaks present different and important characteristics. The fractures that occur in the youth usually follow a substantial trauma and are more frequent in men. In oppose, the fractures that occur in the elderly usually are the consequence of a low trauma, and are more frequent in women. The fractures that are considered osteoporotic are the ones that follow low trauma (Cooper and Melton III 1996; Dias 1998; Walker-Bone, Dennison et al. 2001) and besides this characteristic, share other two proprieties: incidence rates are greater in women than in men and rates increase with age (Cooper and Melton III 1996; Silva 2002). At the age of 50, the overall lifetime risk, i.e., the risk during the remainder of life, of a Caucasian woman in the United States having a clinically identified fracture is 75% (Wehren 2003).

The osteoporotic fractures occur manly on three skeleton compartments: proximal femur, vertebrae and distal forearm, although the epidemiological characteristics of the fractures differ from site to site.

The cost of osteoporotic fractures is not easy to determine, because the costs are incurred at many different levels of healthcare (Walker-Bone, Reid et al. 1998). The majority of these costs can be attributable to proximal femur fracture (Tosteson 1999; Trombetti, Herrmann et al. 2002). In England and Wales, in 1994 this cost was estimated in about $1.4 million, but in 1998 the estimated rose to $1.7 million. In the USA the cost may be as high as $20 billion annually, with proximal femur fracture accounting for one third of this total (Walker-Bone, Reid et al. 1998; Melton III 2003).

in the period of 1992-1997, by Billsten et al (2000), came encounter with the same conclusion, urban incidence rates in hip fracture are higher than rural ones, however they concluded that this difference was decreasing compared with a study conducted in 1980 (Billsten, Sernbo et al. 2000).

Furthermore, the increase urbanization of several Asian countries led to an increase in proximal femur fractures (Center and Eisman 1997; Jordan and Cooper 2002); however these rates remain lower than in white populations (Center and Eisman 1997). In USA, the age-adjusted rate in white women increases with the socio-economic deprivation, decreasing water hardness, the proportion of the population drinking fluoridated water, the decrease in latitude and the percentage of land in agricultural use (Jordan and Cooper 2002).

Although, differences have been established between races, it is interesting that is also referred that the incidence of hip fractures varies between subjects that having the same origins live in different countries (Lau 2001) and some studies showed that the rates in hip fracture in Japanese women are lower than the rates in Japanese-American women (Melton III 1999), showing that the role of environment is not to be forsaken in face of genetic factors.

About 90% of all hip fractures result from a simple fall from standing height or less (Cummings and Melton III 2002; O'Neill and Roy 2003), however only about 1% of falls in elderly women result in proximal femur fracture (Cummings and Melton III 2002). The majority of the fractures occur in the winter and indoors (O'Neill and Roy 2003).

Proximal femur fracture is associated with high mortality and morbidity (Riggs and Melton III 1995; Walker-Bone, Reid et al. 1998; Gold 1999; Jordan and Cooper 2002; Lofman, Berglund et al. 2002; O'Neill and Roy 2003). Most of the deaths occur within the first 6 months after fracture (Riggs and Melton III 1995; Walker-Bone, Reid et al. 1998; Jordan and Cooper 2002; O'Neill and Roy 2003), and after the occurrence there is a reduction of 10 to 20% in survival (Scott 1990; Walker-Bone, Reid et al. 1998; Melton III 2003; O'Neill and Roy 2003). Some deaths are the result of acute complications of the fracture or its cirurgical managements, although some can also be attributable to complications related from co-existing illness (O'Neill and Roy 2003). However, these mortality rates differ, by age and sex, with older male patients having the lowest survival (Walker-Bone, Reid et al. 1998), and in the same age, mortality rates after proximal femur are higher in men than in women (Trombetti, Herrmann et al. 2002; Melton III 2003). The 1-year mortality rate is estimated in 31% in men compared to 17% in women (Amin and

Felson 2001). This fact may also be the result of longer permanence in hospitals by men; there are studies that reveal that the mean length of stay in orthopaedic ward was significantly longer in men (Trombetti, Herrmann et al. 2002). These kind of fractures have a high impact on the quality of life of the individuals: one in five individuals require long-term nursing care, up to 50% who where mobile before fracture require some assistance (Scott 1990; O'Neill and Roy 2003) and about 80% of women aged 75 years and older preferred death over the loss of independence after the fracture (O'Neill and Roy 2003). One year after proximal femur fracture, 40% of patients could not walk independently, 60% require assistance with at least one essential activity of daily living, and 80% could not perform at least one other activity of daily living, such as shopping (Walker-Bone, Reid et al. 1998).

Progressive aging of population may cause the problems to rise; using only demographic data the number of proximal femur fractures in USA could triple by the year 2040 (Riggs and Melton III 1995; Dennison and C 2000), and the number of this kind of fractures worldwide will increase from 1.66 million in 1990 to 6.26 million by the year 2050 (Riggs and Melton III 1995; Dennison and C 2000). Besides, during the next years there will be an inversion in the pattern of occurrence of proximal femur fractures; by the year 2050, the large majority of these fractures will occur in Asia and Latin America (which can affect the already poor health care systems), in oppose to what happens nowadays with about half of all proximal femur fractures occurring in Europe and North America (Riggs and Melton III 1995; Dennison and C 2000).

In spite of this increase in the number of proximal femur fractures, the study of Lofman et all (Lofman, Berglund et al. 2002), concluded, using a Poisson model, that the total age and sex adjusted number of proximal femur fractures will decrease by 11% up to the year 2010 compared with 1996. When considering sexes in separate, they concluded a decrease in 19% in women but an increase in 7% in men (Lofman, Berglund et al. 2002), facts that they could not explain, but that could be the result of therapeutic and/or preventive measures in women.

As it was said before, the proximal femur fracture accounts for the higher peace of costs; reported medical costs just for initial stabilization of proximal femur range from US$ 1.900 in Portugal to US$ 9.000 in Greece (Dennison and C 2000).

2.2.2.2. Vertebral Fractures

The vertebral fractures are the most common and yet the least well-investigated (Van der Klift, de Laet et al. 2002). The epidemiology of vertebral fractures is difficult for two reasons: a significant part of vertebral fractures are asymptomatic, with an estimated of only one third of vertebral fractures coming to clinical attention (Lips 1997) and about 10% necessitate admission to hospital (Cummings and Melton III 2002), and therefore radiographic surveys of the general population are required to generate valid information of the prevalence of such fractures (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001). Furthermore there is not a consensus on a definition of vertebral deformities from lateral thoracolumbar radiographs (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001), in fact the prevalence of vertebral fractures could vary by up to three-fold depending on the criteria used (Cummings and Melton III 2002). Nevertheless, a fourth of white women aged 50 years or more have one or more vertebral fracture by some definitions (Cooper and Melton III 1996) and vertebral fractures in patients aged 45 years and older account for 52 000 hospital admissions in USA and 2188 in England and Wales every year (Cooper and Melton III 1996). Estimates point that the incidence is about three times that in proximal femur fracture in post-menopausal women (Dennison and C 2000).

The effect of increased age shows that the incidence rises rapidly in both sexes (Cummings and Melton III 2002; Van der Klift, de Laet et al. 2002), but with a more linear pattern in women than in men (Cooper and Melton III 1996; Dennison and C 2000).

The effects on gender, on vertebral fracture, are not as clear as in the proximal femur fracture; studies show that prevalence rates of vertebral fractures are more similar in women and men than proximal femur fractures, with female-to-male ratio of age-adjusted in the order of 2:1 (Cooper and Melton III 1996; Dennison and C 2000). There are results that indicate that the female-male ratio varies through life: in middle age men have nearly twice as many vertebral deformities as women, whereas in the eighth decade men have only two-thirds of the ones presented in women (Anderson and Cooper 1999). The risk of vertebral deformities among men was significantly elevated in those with high levels of physical activities and in women the risk was higher for those with a late menarche or early menopause (Dennison and C 2000). Moreover previous vertebral deformities have been shown to increase the risk of subsequent vertebral deformities by 7 to 10 times, in both sexes and was more marked in individuals with deformities caused by moderate or minimal trauma than with severe trauma (Dennison and C 2000).

The lifetime risk of a clinically diagnosed vertebral fracture is about 16 % in white women compared with just 5 % in white men, in part because women live longer than men (Cummings and Melton III 2002).

The patterns of geography between countries are not as marked as the ones in proximal femur (Cummings and Melton III 2002). However between European countries the differences found can be comparable to the ones present in proximal femur fractures (Melton III 1999; Dennison and C 2000).

The European Vertebral Osteoporosis Study (EVOS), studied a sample of men and women of 36 centers of 19 European countries including Portugal, Spain and UK. This study encountered an overall prevalence of vertebral deformities of 12% in Portugal, data obtained in Oporto, showed a vertebral prevalence in women of 13,5% and 16,6% in men (Dias 1998). The prevalence increased in both sexes with age but more defined in women (Dennison and C 2000; Walker-Bone, Dennison et al. 2001), the incidence begins to be higher in men but with the increase of age this pattern turns (Lips 1997). The highest rates were found in Scandinavian countries (Dennison and C 2000; Walker-Bone, Dennison et al. 2001) where 20 % of women and 16 % of men presented vertebral deformities, whereas the lower rates where found in Eastern Europe, where 11 % of women and men were affected (Lips 1997; Dennison and C 2000; Walker-Bone, Dennison et al. 2001). The differences between centers for each sex were greater than the differences between the sexes at any given center (Lips 1997).

Studies show that only a third of new vertebral fractures result from falls, the majority were the result of compressive loading associated with lifting, changing positions (Cooper and Melton III 1996). Results from EPOS, showed that modification of lifestyle risk factors such as milk intake, smoking, alcohol drinking, or physical activity was unlikely to have a major impact on the population occurrence of vertebral fractures, concluding that the biological mechanisms should be further explored (Roy, O'Neill et al. 2003).

The impact of one vertebral fracture may be easily recovered but the effects of several vertebral fractures are cumulative and lead to acute and chronic back pain, limitation of physical activity and progressive height loss (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001). This loss in participating in physical activities may lead to poor self esteem and even depression; on the other hand the fear of having another fracture may cause a decrease of physical activity which can be considered a factor of fracture risk (Walker-Bone, Dennison et al. 2001). A study in United Kingdom, which preformed a questionnaire in men at least six months after a symptomatic vertebral fracture, showed that three-quarters reported sleep disturbance by pain and half were still using analgesics every day (Anderson and Cooper 1999).

Survival rates 5 years after vertebral fractures were found in some studies to be around 80% of those expected for men and women of similar age with no fracture (Walker-Bone, Dennison et al. 2001). A study conducted during a 5-year period in Australia, found that the increased mortality associated with vertebral fractures was comparable to the one found for mortality in men after hip fracture and greater than that seen in women (Center, Nguyen et al. 1999). Excess mortality seems to increase after diagnosis of the fracture (Walker-Bone, Dennison et al. 2001), and there are differences between sexes: survival at 5 years is worse in men than in women (Walker-Bone, Dennison et al. 2001). The causes of the excess mortality rate after vertebral fracture are not clear (Cooper and Melton III 1996).

2.2.2.3. Distal Forearm Fracture

The fact that less than 20 % of forearm fracture patients require hospitalisation (Cooper and Melton III 1996; O'Neill and Roy 2003) can explain the small number of population-based studies, and therefore there are some aspects of the epidemiology that are still poorly explained (Cooper and Melton III 1996). However despite the low hospitalisation rates, distal forearm are responsible for 50 000 hospital admissions and over 400 000 physician visits in the USA each year (Cooper and Melton III 1996).

The effect of age in the incidence of distal forearm fractures display a different pattern of the one presented by proximal fractures or vertebral fractures. In white women, there are studies indicating that the incidence increases steadily from a baseline of 100 per 100 000 per year at the age of 50 to 1200 per 100 000 at the age of 85, however others report that the rates reach a plateau at approximately 800 per 100 000 (Thompson, Taylor et al. 2004). In men the incidence rates remains more or less constant (Cooper and Melton III 1996; Dennison and C 2000; Walker-Bône, Dennison et al. 2001; Cummings and Melton III 2002). Women, still present the higher incidence, with 85% of fractures occurring in female sex (Jordan and Cooper 2002), and with an age-adjusted ratio, female-to-male of 4:1 (Center and Eisman 1997; Cummings and Melton III 2002). About half occur in women aged 65 years and older (Cooper and Melton III 1996; Dennison and C 2000; Walker-Bone, Dennison et al. 2001). The lifetime risk, of a woman 50 years of age having a distal forearm fracture is 16%, whereas the lifetime risk of a man of the same age is 2.5% (Lips 1997).

However, the geographic pattern presented by forearm fracture is comparable to the one presented by the proximal femur fracture. Particularly elevated in Scandinavian countries and reduced in black populations (Dias 1998). Some data shows that forearm fracture rates in the United Kingdom are around 30% lower than those in the United States (Melton III 1999).

When considering the differences seen within the same country, the USA pattern of the fracture is higher in East and lower in Western United States (Melton III 1999).

Distal forearm fracture almost always follow a fall on the outstretch arm (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001), and there is a winter peak, because the incidence of this fractures relates to falls outdoor during periods of icy weather (Walker-Bone, Dennison et al. 2001; Cummings and Melton III 2002; Jordan and Cooper 2002).

The morbidity caused by forearm fractures is significant; one study showed that, after one year of the occurrence of the fracture, only 50% of patients reported a good functional recovery and 1% become dependent (Walker-Bone, Dennison et al. 2001; Jordan and Cooper 2002). Up to 30% of individuals who experience this kind of fracture will experience some long-term complication, such as secondary osteoarthritis (O'Neill and Roy 2003), consequently 39% of all physical therapy sessions attributable to Osteoporotic fractures in the USA (Melton III 2003). However this fracture are not associated to increased mortality (Walker-Bone, Dennison et al. 2001; Jordan and Cooper 2002), but the experience of this kind of fracture was showed to increased the risk of having a proximal femur or vertebral fracture (Dennison and C 2000).

Bibliography

Amin, S and D T Felson (2001). "Osteoporosis in Men." Rheumatic Disease Clinics of North American **27**(1): 19-47.

Anderson, F H and C Cooper (1999). Hip and Vertebral Fractures. Osteoporosis in Men. E. S. Orwoll, Academic Press: 29-49.

Becker, C (2003). "Clinical evaluation for osteoporosis." Clinics in Geriatric Medicine **19**: 299-320.

Billsten, M, I Sernbo, et al. (2000). "The incidence and mortality of hip fractures in two regions of southern Sweden: 1992-1997." Current Ortopheadics **14**: 182-188.

Center, J and J Eisman (1997). "The epidemiology and pathogenesis of osteoporosis." Bailliéres Clinical Endocrinology and metabolism **11**(1): 23-62.

Center, J, T V Nguyen, et al. (1999). "Mortality after all the major osteoporotic fracture in men and women: an observational study." The Lancet **353**: 878-882.

Chevalley, T, F Herrmann, et al. (2002). "Evaluation of Age-adjusted Incidence of Hip Fractures Between Urban and Rural Areas: The Difference is not Related to the Prevalence of Istitutions for the Elderly." Osteoporosis International **13**: 113-118.

Cooper, C and L J Melton III (1996). Magnitude and Impact of Osteoporosis and Fractures. Osteoporosis. D. F. R Marcus, J Kelsey, Academic Press: 419-434.

Crabtree, N, M Cunt, et al. (2000). "Hip Geometry, Bone Mineral Distribution, and Bone Strenght in Men and Women: The EPOS Study." Bone **27**(1): 151-159.

Cummings, S R and L J Melton III (2002). "Epidemiology and Outcomes of Osteoporotic Fractures." The Lancet **359**: 1761-67.

de Laet, C and H A P Pols (2000). "Fractures in the elderly: epidemiology and demography." Bailliéres Clinical Endocrinology and metabolism **14**(2): 171-179.

Dempster, D W (2003). "The pathophysiology of bone loss." Clinics in Geriatric Medicine **19**: 259-270.

Dennison, E and C Cooper (2000). "Epidemiology of Osteoporotic Fractures." Hormone Research **54**: 58-63.

Dias, A A (1998). Epidemiologia da Osteoporose. Osteoporose. M. V. Queiroz, Edições Técnicas: 25-39.

Duppe, H, P Gärdsell, et al. (1997). "A Single Bone Density Measurement can Predict Fractures over 25 years." Calcified Tissue International **60**: 171-174.

Faulkner, K G (2001). "Update on Bone Density Measurement." Rheumatic Disease Clinics of North American **27**(1): 81-99.

Formica, C A (1998). "Standardization of BMD Measurements." Osteoporosis International **8**: 1-3.

Gold, D T (1999). Outcomes and the Personal Impact of Osteoporosis. Osteoporosis in Men. E. S. Orwoll, Academic Press: 51-63.

Gold, D T (2001). "The Nonskeletal Consequences of Osteoporotic Fractures - Psycologic and Social Outcomes." Rheumatic Disease Clinics of North American **27**(1): 255-262.

Gomes, J A M (1990). "Métodos não invasivos de medição da massa óssea." Arq Reumatol **12**: 337-354.

Hans, D, P Dargent-Molina, et al. (1996). "Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study." The Lancet **348**: 511-514.

Heaney, R P, S Abrahms, et al. (2000). "Peak Bone Mass." Osteoporosis Int **11**: 985-1009.

Hui, S L, L A Dimeglio, et al. (2003). "Difference in Bone Mass between Black and White American Children: Attributable to Body Build, Sex, Hormone Levels, or Bone Turnover?" The Journal of Clinical Endocrinology & Metabolism 88(2): 642-649.

Hunter, D J and P N Sambrook (2000). "Bone Loss, Epidemiology of bone loss." Arthritis Res **2**: 441-445.

Jonhston JR, C C and C W Slemenda (1995). "Pathogenisis of Osteoporosis." Bone **17**(2): 19S-22S.

Jordan, K M and C Cooper (2002). "Epidemiology of osteoporosis." Best Practice & Research Clinical Rheumatology **16**: 795-806.

Kanis, J A (2002). "Diagnosis of osteoporosis and assessment of fracture risk." The Lancet **359**: 1929-1936.

Kanis, J A, O Johnell, et al. (2000). "Risk of Hip Fracture According to the World Health Organization Criteria for Osteopenia and Osteoporosis." Bone **27**(5): 585-590.

Karagas, M R, G L LuYao, et al. (1996). "Heterogeneity of hip fracture: Age, race, sex, and geographic patterns of femoral neck and trochanteric fractures among the US elderly." American Journal of Epidemiology **143**(7): 677-682.

Lau, E M C (2001). "Epidemiology of Osteoporosis." Best Practice & Research Clinical Rheumatology **15**(3): 335-344.

Lips, P (1997). "Epidemiology and Predictors of Fractures Associated with Osteoporosis." The American Journal of Medicine **103**: 3S-8S.

Lofman, O, K Berglund, et al. (2002). "Changes in Hip fracture Epidemiology: Redistribution Between Ages, Genders and Fractures Types." Osteoporosis International **13**: 18-25.

Marcus, R (2001). "Role of Exercise in Preventing and Treating Osteoporosis." Rheumatic Disease Clinics of North American **27**(1): 131-141.

Melton III, L J (1999). Epidemiology of Fractures. Osteoporosis in Men. E. S. Orwoll, Academic Press: 1-13.

Melton III, L J (2001). "The Prevalence of Osteoporosis: Gender and Racial Comparison." Calcified Tissue International **69**: 179-181.

Melton III, L J (2003). "Adverse Outcomes of Osteoporotic Fractures in the general Population." Journal of Bone and Mineral Research **18**: 1139-1141.

Miller, P (2003). "Bone mass measurement." Clinics in Geriatric Medicine **16**: 281-297.

Morgan, S L (2001). "Calcium and Vitamin D in Osteoporosis." Rheumatic Disease Clinics of North American **27**(1): 101-129.

Nguyen, T V, J Center, et al. (2001). "Risk Factors for Proximal Hemerus, Forearm, and Wrist Fractures in Elderly Men and Women." American Journal of Epidemiology **153**(6): 587-595.

Nieves, J W (2003). "Calcium, vitamin D, and nutrition in elderly adults." Clinics in Geriatric Medicine **19**: 321-335.

NIH – National Institutes of Health Consensus Statement Online (2000). "Osteoporosis, Prevention, Diagnosis, and Therapy. URL: http://consensus.nih.gov.

Nogueira, M L G (2002). Padrões Osteodensitométricos de Referência em Mulheres [dissertação]. Porto, Universidade do Porto.

O'Neill, T W and D K Roy (2003). "The epidemiology and scale of the problem." Hospital Medicine **64**(9): 517-520.

Orwoll, E S (1999). The Clinical Evaluation of Osteoporosis in Men. Osteoporosis in Men The effects of gender on skeletal health. E. S. Orwoll, Academic Press: 527-552.

Pende, I and R M Francis (2001). "Osteoporosis in men." Best Practice & Research Clinical Rheumatology **15**(3): 415-427.

Pernadas, C M and J M S Coelho (1999). "Utilização Adequada da Densitometria Óssea - Tomografia Computorizada Quantitativa / Outras Técnicas de Medição." Acta Radiológica Portuguesa **XI**(42): 45-55.

Riggs, B L and L J Melton III (1995). "The Worldwide Problem of Osteoporosis: Insights Afforded by Epidemiology." Bone **17**(5): 505S-511S.

Roy, D K, T W O'Neill, et al. (2003). "Determinants of Incidence Vertebral Fractures in Men and Women: results from the European Prospective Osteoporosis Study (EPOS)." Osteoporosis International **14**: 19-26.

Scott, J C (1990). "Osteoporosis and Hip Fractures." Rheumatic Disease Clinics of North American **16**(3): 717-740.

Silva, C S A G (2002). Fracturas, Massa Óssea e Diabetes, Estudo Epidemiológico em Mulheres Peri e Pós-Menopáusicas. Faculdade de Medicina. Porto, Porto.

Sinaki, M (2003). "Nonpharmacologic interventions Exercise, fall prevention, and role of physical medicine." Clinics in Geriatric Medicine **19**: 337-359.

Thompson, P W, J Taylor, et al. (2004). "The annual incidence and seasonal variation of fractures of the distal radius in men and women over 25 years in Dorset, UK." Injury, Int J Care Injured **35**: 462-466.

Tosteson, A N A (1999). Economic Impact of Fractures. Osteoporosis in Men. E. S. Orwoll, Academic Press: 15-27.

Trombetti, A, F Herrmann, et al. (2002). "Survival and potential years of life lost after hip fracture in men and age-matched women." Osteoporosis International **13**(9): 731-737.

Uebelhant, D and P D Delmas (1991). "A determinação da densidade óssea na mulher menopaúsica." Mom Obst Gin **91**: 197-200.

Van der Klift, M, C de Laet, et al. (2002). "The Incidence of Vertebral Fractures in Men and Women: The Roterdam Study." Journal of Bone and Mineral Research **17**: 1051-1056.

Vanderschueren, D, S Boonen, et al. (2000). "Osteoporosis and osteoporotic fractures in men: a clinical perspective." Bailliéres Clinical Endocrinology and Metabolism **12**(2): 299-315.

Walker-Bone, K, E Dennison, et al. (2001). "Epidemiology of Osteoporosis." Rheumatic Disease Clinics of North American **27**: 1-18.

Walker-Bone, K, D M Reid, et al. (1998). "Is screening for osteoporosis worthwhile?" British Medical Bulletin **54**(4): 915-927.

Wehren, L E (2003). "The epidemiology of osteoporosis and fractures in geriatric medicine." Clinics in Geriatric Medicine **19**: 245-258.

2.3. Geographic Information Systems

The Geographic Information Systems (GIS) can be defined, etymologically, as a special class of information systems that handle geographic data. However, this definition leads to at least two other terms that remain undefined: information systems and geographic data. In order to understand the term GIS it is useful to go over the terms mentioned before, remark that the words data and information are both mentioned, perhaps implying different meanings. In fact, the difference between data and information, is widely spread and consensually accepted, data may consist of numbers, text or symbols, that are almost context free, information, however, implies some degree of selection, organization and preparation for particular purposes (Silva 1999; Longley, Goodchild et al. 2001). Information can be therefore understood as data that have been given some degree of interpretation (Longley, Goodchild et al. 2001). Information Systems can be defined as a set of interrelated components that gather, process, store and distribute information in order to support decision-making, coordination and control. Geographic data can be defined it, as the data which have a defined location in the geographic space (Martin 1996).

However, if the etymological definition does not present great variety, another kind of definition does, especially because the GIS are relatively young technology being used by a variety of heterogeneous groups that create their own definition. Therefore several definitions can be found in the literature, here a list of a few examples of how GIS can be defined:

"computational systems, used to the understanding of facts and phenomenon that occur in the geographical space." (Santos, Pina et al. 2000)

"computerized tools that allow the management, the processing and the analyze of information (...) allowing the integration of great amounts of data of different sources into maps, graphs and tables." (OPAS 2002)

"spatial decision support systems" (Longley, Goodchild et al. 2001)

"a tool for revealing what is otherwise invisible in geographic information" (Longley, Goodchild et al. 2001)

Computer based systems that are used to store, manipulate and analyze geographic information (Aronoff 1995).

The GIS technology is, as mentioned before, a recent one, however, the indication of a date to set a mark in the use of GIS is a difficult task, because it depends upon the definition accepted, and that, as exposed previously is not a simple matter. Therefore if considering a strict definition: GIS being a computer-based system for analyzing spatially referenced data, then the decade indicated as common use of these systems is the 80's; however if a more wide definition is considered: GIS being any system handling geographical data then the decade indicated is a more previous one (about 10 years earlier).

The motivation for such development, is not less controversial, some authors indicate that these systems were developed with military purposes (OPAS 2002) implicating a real interest in improving the speed and efficiency in the treatment of spatially referenced data. Others indicate that the motivation was only academic, impelled by curiosity or challenge (Coppock and Rhind 1994). What seems clear, in the opinion of Coppock et al. (1994) is that there were many initiatives, usually occurring independently and in ignorance of each other, concerning the different facets of these systems: in the 1960's the cartographers and mapping agencies started to introduce the computers in the creation of maps in a more efficient way, about a decade previously the first military satellites were developed and became an impulsive force in the development of GIS (Longley, Goodchild et al. 2001).

The first system to be recognize as a GIS, was the Canada Geographic Information System (CGIS) in the mid 60 (Coppock and Rhind 1994; Silva 1999; Longley, Goodchild et al. 2001). These systems besides a mapping tool, were also a powerful tool to identify the nation resources and their existing, and potential uses (Longley, Goodchild et al. 2001), in the way that it could store and recuperate the data in accord to the necessity of the users (Silva 1999).

The widespread of the GIS was during the 80's, manly because of the informatics rapid development, that allowed the hardware and software components, to become accessible (especially financially) to the majority of the industry (Longley, Goodchild et al. 2001), and in the opinion of Martin (1996) because of an explosion in the quantity of geographically referenced data collected and available to a wide range of organizations. Amongst the first customers were the forestry companies and natural resources agencies, driven by the necessity to track their resources (Longley, Goodchild et al. 2001).

The GIS, being an information system requires data, and as mentioned before, geographical one. The data used in these systems has, therefore, a clear geographical location that allows the event or geographical feature to be located in space. This kind of data is also designated spatial data, and is manly characterized by having two components: a graphic and a non-graphic one (Santos, Pina et al. 2000). The graphic component (map), according to Pina, 2000, is the "graphic description of the object symbolized in the map". This component can include coordinates (such as latitude or longitude), codes (such as geocodes), and symbols that will define the elements in the map (Pina 2000; OPAS 2002). The non-graphic component (tables) consist on the characteristics, qualities or attributes of the phenomenon or feature represented in the map (Pina 2000). These attributes can be of several natures, they can be classified into physical or environmental, but they can also be classified as social or economic (Longley, Goodchild et al. 2001), therefore examples of attributes can be atmospheric temperature or the number of patients attending an health unit.

The two components being parts of a single unit, need to be some how related between themselves. The more common way to make the connection between the graphic and non-graphic components of spatial data, is through the use of a common code, designated by geocode (Pina 2000). This geocode also serves the purpose of making the data a representation of a reality directly related to a geographic location. Therefore, the data suffer a process of georeferencing, that is nothing more than "the process of referencing the data to a system of terrestrial coordinates or terrestrial units (address, point, neighbourhood, municipality, etc.), using a geocode." (OPAS 2000). Is because of such a designation of this process that this data is also designated, beyond of geographical and spatial georeferenced data. In the opinion of Longley, et al (2001), the primary conditions of an efficient georeference, is that it be unique, i.e., each geocode must correspond to a unique location and that its meaning be shared among all of the people who wish to work with the information. The authors exemplify what they intended to say with an example: the georeference of locations by the address, the geocode must be unique that no other house is at that address, and that the meaning is shared sufficiently so that the mail is delivered. The same authors refer that to be useful the georeference must be persistent through time, because it would be very confusing and expensive if the geocodes changed constantly.

The implementation of a GIS project is a resource consuming process; the resources consumed may be classified, for example, in terms of financial and time resources; however these resources can be attributed to different levels. Longley, et al (2001), present six components, of what they designate GIS anatomy, and to which resources can be allocated:

Hardware – "the device that the user interacts with directly in carrying out GIS operations"; (page 17)

Software – "can range from a simple package designed for a PC (...) to a major industrial-strength workhouse designed to serve an entire enterprise of networked computers"; (page 18)

Data – "consists of a digital representation of selected aspects of some specific area of the Earth's surface (...), built to serve some problem solving"; (page 18)

People – "who design, program, and maintain it, supply it with data, and interpret its results"; (page 18)

Procedures – "an organization must establish procedures, lines of reporting, (...) for ensuring that the GIS activities stay within budgets, maintain high quality, and generally meet the needs of the organization"; (page 18)

Network – "GIS today relies heavily on the Internet", "there are many successful applications of GIS on the Internet (...). They range from using GIS to disseminate information (...) to selling goods and services (...) to helping members of the public to participate in important local, regional, and national debates" (page 15)

Therefore, a GIS project involving such different components must have clear definition of objectives and functions to meet. Santos et al. (2000), identify five objectives that can be encountered in the implementation of a GIS project: the visualization of information (GIS allows several forms of visualization), organization of data, integration of data of several fonts, data analysis and prediction of occurrences. However if five objectives can be defined, four functions can be identified. Fischer, et al (1996), define four basic functions of GIS, related to spatial data:

1. Data Input;
2. Data Storage;
3. Data Analysis;
4. Output.

The user of the GIS perceives the reality and feeds data to the GIS; the storage, management and integration of great amounts of spatial data is also considered an important function by Santos et al. (2000); to the GIS is also attributed the function of providing ways to analyze the data (Ficher, Scholten et al. 1996; Santos, Pina et al. 2000), finally they also provide different outputs to the users. The figure 2.6 summarizes the four functions, and their relations in a simplified way.

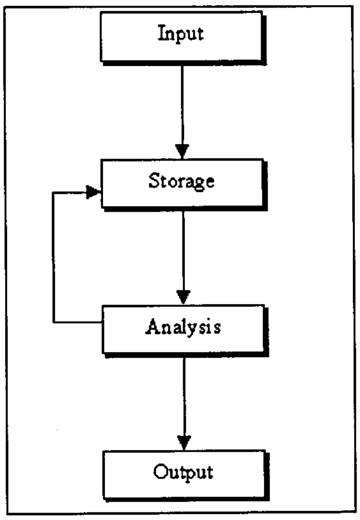

Figure 2.6 - Illustration of the four basic functions of GIS, adapted from Fisher, MM at al., (1996).

Having defined the GIS, as well as its objectives, a brief overview of the four functions will be presented, having in consideration the two components of spatial data, that present different processes in assessing the functions.

The process of feeding data to the GIS is described essential to georeference the data. The georeference process in the graphic component is usually done when of the digitalisation of the map (Santos, Pina et al. 2000) where each geographic figure (point, line or area) is associated to a coordinate of terrestrial reference, like latitude and longitude According to Santos et al. (2000) the fact that this process is done when of the digitalisation of the map, allows the possibility of associating different maps, more the authors advice this is a preoccupation to have in account whenever of an acquisition of bases is done, otherwise the use of information of different terrestrial references is not possible.

In the non-graphic component the georeferencing may be done by two ways: one is through the association of the coordinates to data, the other is through the association of the data to spatial units present in the map (like neighbourhoods, census tracks, etc.) (Santos, Pina et al. 2000). Some programs also allow the location of events on segments of streets by the interpolation of the initial and final numbers of the segment. Martin, 1996, refer that the socio-economic data (attribute data) is not usually collected with the purposes and methods required in GIS application, and therefore is sometimes a hard task to georeference it. In addition, the data may only be available at an aggregate level instead of at an individual level, and therefore sometimes it is impossible to avoid the ecological fallacy when analysing it. The same idea is expressed by Santos, et al. (2000) when they refer that the georeferencing of non-graphic data in small area is one of the limiting facts of the use of GIS in health related issues, because the health data is not often available with the address of the cases and even when this occur the filling of the addresses is usually of low quality, involving lack of information, errors, etc. If the number of events to georeference is little, then this process can be done manually with the help of a map or a GPS. However, when the number of events is great then the manual georeferencing is not viable, and therefore is advisable that the events have addresses associated and maps that allow the automatic georeference.

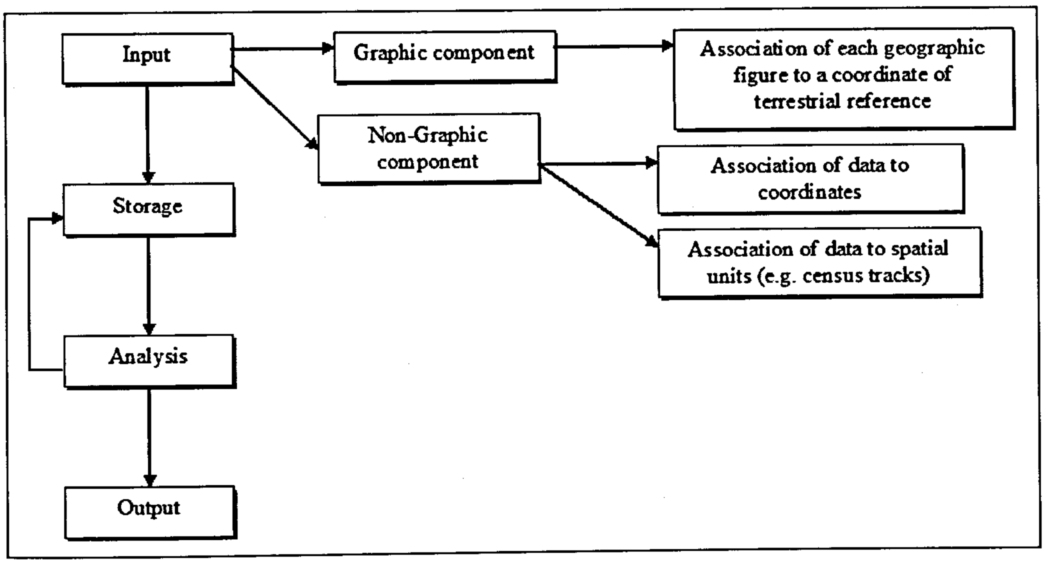

Figure 2.7 - Illustration of geoprocessing the different components of spatial data.

In the beginning of GIS, due to the different characteristics presented by the two components of the spatial data, the design of the databases used to store this data was the hybrid model. In this approach, the two components are stored in different databases; the graphical components is usually handled directly by the GIS, for speed of input/output, while the non-graphical component is usually stored in a standard database management system (DBMS) (Healey 1994; Pina 2000). The integration of both databases is done through the use of the geocode, like referenced earlier.

The graphical data can be represented digitally, manly, with the use of two models: the vector and the raster model (Pina 2001).

The vector model uses three types of geographical entities: points, lines and polygons represented in figure 2.8, truly the basic entity is the point, because a line and a polygon can be obtained by linking points with segments. All entities in the real world can be therefore represented through the use of such entities. For example, trees can be represented digitally in a map through the use of a point, and a line can represent rivers or streets, lakes can be represented by polygons.

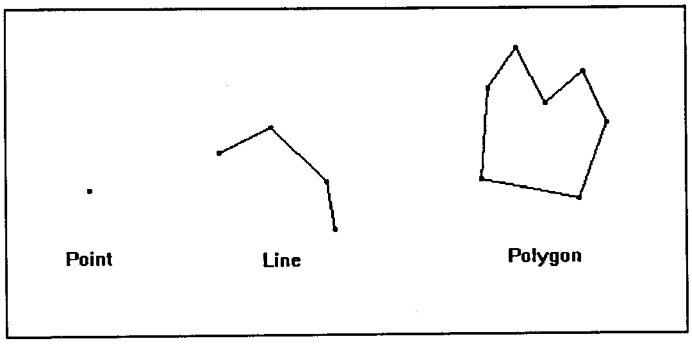

Figure 2.8 - Basic entities of the vector structure.

In the vector model to store digitally spatial data, there are two structures: the *spaguetti* structure and the topological structure (Pina 2001).

In the *spaguetti* structure; all entities in the map are stored line by line. Points are coded by their correspondent pair of coordinates, lines are coded using the list of coordinates that correspond to the successive points that compose it, polygons are coded by the coordinates that define its perimeter (Pina 2001). This is a simple way to store spatial data, however it also presents disadvantages, one of such disadvantages is that lines, that are common to more than one polygon, are stored twice: one to which they belong, creating therefore a lot of repeated information (Pina 2000). The great disadvantage of this model is the fact that it doesn't allow spatial analysis, because it doesn't store information of how the features relate between themselves it only stores coordinates.

In figure 2.9 and table 2.2 is presented an example of the storage using the *spaguetti* structure.

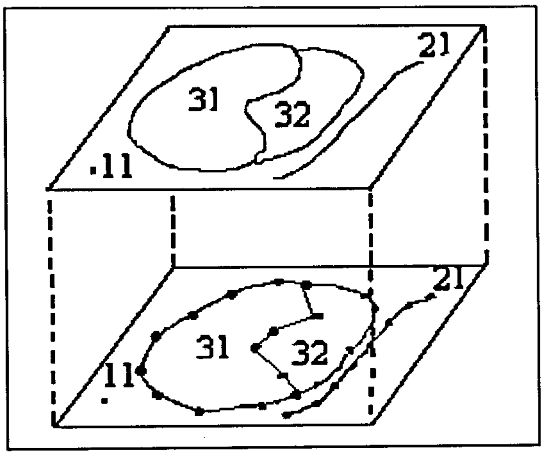

Figure 2.9 - "Spaguetti" model of the storage of the graphical component, reproduced by Aronoff, (1995).

Table 2.2- Storage of the coordinates in the "Spaguetti" model, reproduced from Pina (2001).

	Number of the entity	**Coordinates**
Point	11	$x_{11}1, y_{11}1$
Line	21	$x_{21}1, y_{21}1; x_{21}2, y_{21}2; x_{21}n, y_{21}n;$
Polygon	31	$x_{31}1, y_{31}1, ..., x_{31}n, y_{31}n, x_{31}1, y_{31}1$
Polygon	32	$x_{32}1, y_{32}1, ..., x_{32}n, y_{32}n, x_{32}1, y_{32}1$

The construction of the topological structure is obtained by transforming the points, lines and polygons on topological entities: nodes, arcs and polygons and constructing several tables containing information about these topological entities as well as a table containing the coordinates. The figure 2.10 exemplifies a map to be stored using the topological structure.

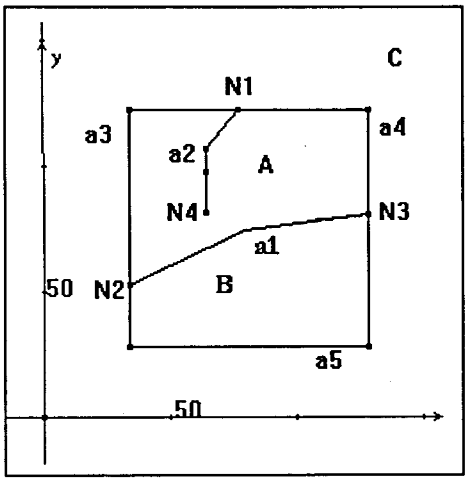

Figure 2.10 - Topological model of the storage of the graphical component.

A table of coordinates containing the coordinate information for each node that compose each arc is constructed, as exemplified in table 2.3. Having defined the "location" of the spatial entities, it is necessary to define the way they associate with each other, i.e., it is necessary to define a topology. The topological table of nodes contains the information of which arcs connect with each node, as exemplified in table 2.4. The topological table of arcs, contains the information relative to each arc, and involves the information about initial and final node, and polygon at right and left side, as exemplified in table 2.5. Finally the topological table for polygons contains, for each polygon, the information relative to which arcs compose it, as exemplified in table 2.6.

Table 2.3 - Coordinate table

Arcs	Initial x,y	Intermediate x,y	Final x,y
a1	40, 25	75, 75	125, 80
a2	...	...	...
a3	...	...	...
a4	...	...	...
a5	...	...	...

Table 2.4 - Topological table of nodes.

Nodes	Arcs
N1	a2, a3, a4
N2	a1, a5
N3	a1, a4, a5
N4	a2

Table 2.5 - Topological table of arcs.

Arcs	Initial Node	Final Node	Polygon at left	Polygon at right
a1	N2	N3	A	B
a2	N4	N1	A	A
a3	N2	N1	C	A
a4	N1	N3	C	A
a5	N3	N2	C	A

Table 2.6 - Topological table of polygons.

Polygon	Arc
A	a1, a3, a4
B	a1, a5
C	External area

Another way to store digitally the spatial data is with the use of raster structure, as mentioned before. Longley, et al. (2001) refer that in a raster representation, the space is divided into an array of cells. Cells are also designated pixels, each cells stores the type of object or the condition encountered in that position (Pina 2000). Therefore, each geographic entity, with location and attributes, is defined by the location of row and column of that array (Pina 2001). According to Pina (2000), in opposite to the vector structure, the entities of the raster structure do not correspond to the real world entities, for example a road does not exists in the raster structure as an entity but as a group of cells that compose it.

The organization of the graphical components is obtain through the use of layers, that can be defined according to Longley, et al. (2001) as a collection of geographic entities of the same geometric type. Each layer represents a theme or class of information and the definition of the themes that compose each layer depend upon the objectives of the project.

Figure 2.11 - Layers that contain homogeneous information and that can be composed to represent the real world reproduced from County of Sacramento geographic Information Systems webpage.

The non-graphical data is stored in a standard DBMS (Pina 2000), usually a commercial one, such as ORACLE, ACCESS or SQL (Healey 1994; OPAS 2002). There are several types of structures for DBMS, the inverted list, the hierarchical system, the network systems and the relational system (Healey 1994). The majority of GIS, uses the relational system for the database (Pina 2000; OPAS 2002), that is characterized, summarily and with simplicity, by the use of tables (relations) of rows and columns to represent the data (Healey 1994).

Each table represents an entity set, where each row or "tuple" represents an individual entity and each column contains information relative to one attribute of the entity set (Healey 1994; OPAS 2002). As an example, in table 2.7 is represented the entity hospitals, where each row represents a particular hospital and each column contains the attributes: the first column contains the code and the second column contains information about the name of the hospital.

Table 2.7 - Table of Hospitals.

Hospital Code	Hospital Name
1	São João
2	Santo António
3	Pedro Hispano

The relational approach is obtained by the use of the primary key, which is the value of a column or the combination of values of multiple columns used to identify uniquely each row (Healey 1994; Pina 2000; OPAS 2002). These relations are obtained by a mechanism of joining that can process in the following ways: the primary key in one table links to a column in a second table, where is called foreign key (Healey 1994) both tables join themselves in a third table. The way that this process occurs depends on the relationship between the lines of two tables, this relation ship can be *one-to-one*, where each line of table A is only related to one line of table B and each line of table B is only related to one line of table A *one-to-many*, where each line of table A can be related to any number of lines of table B and each line of the table B can only be related to one in table A, finally the relation *many-to-many*, where any number of lines in table A can be related to any number of lines in table B and any number of lines in table B can be related to any number of lines in table A. As an example, is presented a relational join between the table 2.7 of hospitals and the table 2.8 of patients, which is a one-to-many relation, because each patient is associate only with one hospital but each hospital can have more than one patient.

Table 2.8 - Table of Patients.

Patient Code	Name	Hospital Code
1	António	1
2	Maria	1
3	Manuel	3

The virtual table 2.9 created from the relation is one where the hospital code "migrates" to the table of patients. In its table the hospital code is considered a primary key, in opposite, in the virtual table it is called a foreign key.

Table 2.9 - Resulting table of the joining.

Patient Code	Name	Hospital Code	Hospital Name
1	António	1	São João
2	Maria	1	São João
3	Manuel	3	Pedro Hispano

In conclusion, the storage of spatial data can be synthesized in the following Figure 2.12, where both components are differentiated.

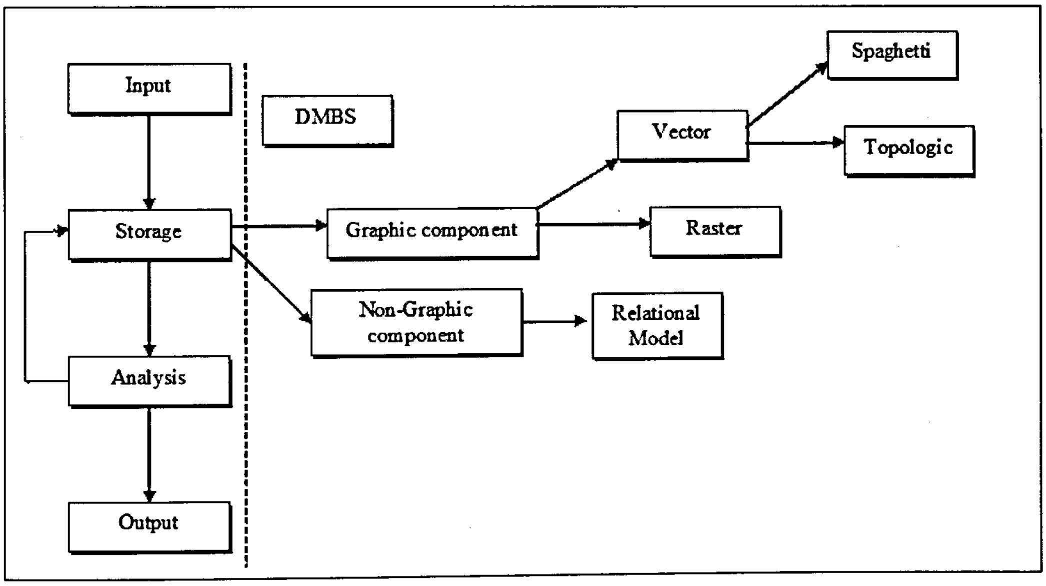

Figure 2.12 - Illustration of the storage of the different components of spatial data.

In our days, with the advances made in the databases, it is also possible to encounter some GIS in which the distinction between the graphic and the non-graphical component is no longer used. In this kind of software the geographic objects are, according to Longley, et al. (2001) an integrated package of geometry, proprieties and methods, and are stored in the same database (Pina 2000), using the object-oriented DBMS (Healey 1994; Longley, Goodchild et al. 2001). This fact is illustrated through the use of the intermittent line before the two components.

The capability of performing analysis, in both components, is an important characteristic that distinguish the GIS from other systems that use georeferenced data like CAD (Computer Aided Design and Drafting) (Santos, Pina et al. 2000). Openshaw and Clarke (1996), present some important aspects that GIS should be able to perform in a spatial analysis: GIS should be able to handle very large values, should provide the possibility to study regions independently and the results should be mappable.

The spatial analysis preformed by GIS is mostly descriptive and exploratory (Openshaw and Clarke 1996; O'Sullivan and Unwin 2003), making use of the manipulation of the data. Rarely the GIS present the capability of employing statistical methods, therefore there have been developed interfaces, to overcome these necessities that allow the user to perform his analysis in other software and then came back to the GIS (Pina 2003). However, the descriptive and exploratory analysis is as important as more sophisticated methods, and plays an important role, in the opinion of O'Sullivan and Unwin, (2003), in the generation of questions and formulation of hypothesis. Two major classes of spatial analysis processes will be described summarily: query and transformations (Longley, Goodchild et al. 2001), that are represented in the Figure 2.13.

The analysis preformed through the use of queries is considered the most basic of analysis operations (Longley, Goodchild et al. 2001). According to Longley et al. (2001), no transformations in the data occur and no new data is produce, the system only answers questions posed by the user. The queries may focus only on attributes (non-graphic components), only on geographic features (graphic components) or on both, for example: "Which municipalities have more than 25 000 residents?" focus only on the attributes, "Which are the cases within the municipality A?", focus only on the geographic features (cases-points, municipality-areas) and finally "Which are the cases with age superior to 50 within the municipality A?" that focus on both.

The class of processes classified in transformations include, according with Longley, Goodchild et al., 2001, processes that change datasets or combine them to create new ones, examples of these processes are: buffering, overlay and spatial interpolation. Buffering consists on identifying all areas that are within a certain distance of a an object (point, line or area), forming a new object with these areas (Longley, Goodchild et al. 2001). Examples of this buffering process can be the generation of exposition areas that surrounds certain pollution fonts (Santos, Pina et al. 2000). The overlay consist in laying the layers or maps on "top" of each other, to form new ones, where the information that compose this new map, is a combination of the information present in the maps or layers that compose it. For example, the combination of a map containing the pollution density and other the population density, form a new map with the information of the population expose (Santos, Pina et al. 2000). Finally the spatial interpolation, that allows the estimate of the conditions found in places where there was no information gather (Santos, Pina et al.

2000; Longley, Goodchild et al. 2001). The interpolation is used to transform a set of discrete data in continuous data (OPAS 2002), by a process of intelligent guesswork, i.e., using mathematical algorithms. This process is useful for example in estimating the rainfall, or temperature in places where there are no weather stations (Longley, Goodchild et al. 2001).

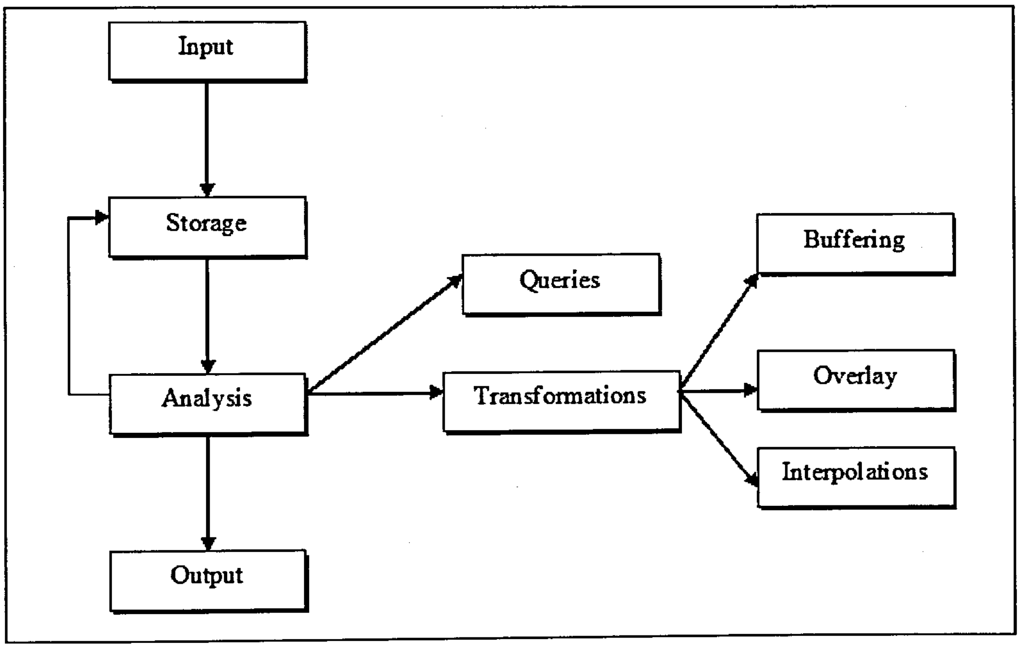

Figure 2.13 - Illustration of the analysis function in a GIS.

Finally the output, a GIS can produce maps, considered the most important output (OPAS 2002), but can also produce graphs and tables (Santos, Pina et al. 2000; OPAS 2002). This wide variety of choices provides the users the solution for the presentation of the right output for each case.

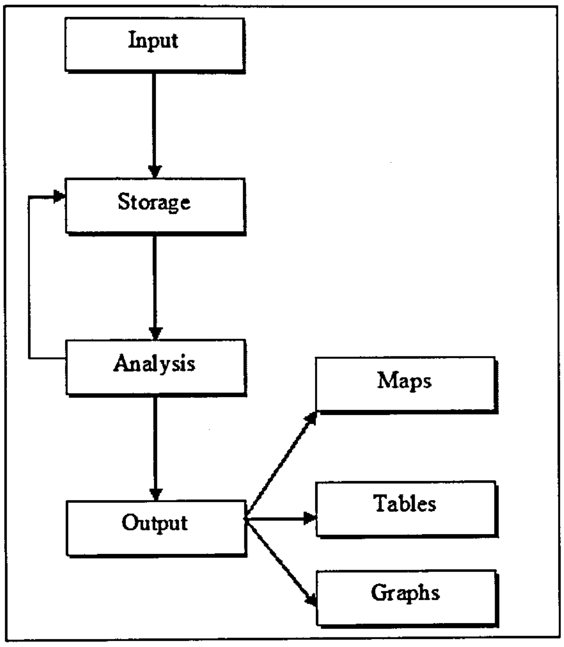

Figure 2.14 - Illustration of the output function in a GIS.

Having gone over all the objectives, the functions, the components, a more integrative definition of GIS, can be presented,

GIS is an organized set of hardware, software, geographic data and people trained, to capture, store, maintain, manipulate, analyze and present all the forms of georeferenced informations (page 115 (OPAS 2000))

The GIS have a wide variety of areas where it is used (e.g. traffic and transport planning, agricultural planning, environmental and natural resource management) and with the increasing awareness that whatever happens somewhere, i.e., almost all data may have a geographical component, the GIS will have an increased used (Scholten and Lepper 1991). The health issues are no exception; therefore GIS have been also used in health related issues, making use of health data.

The use of geography in health is consensually accepted as important. Every epidemiological study must take into consideration that all diseases, virtually, vary in their incidence across geographical areas (Bhopal 2002), and this variation must be analyzed systematically, in order to understand if this variation is real, i.e., caused by environmental or social factors, or just illusory, just an occurrence of a random process. The study of space in disease studies is considered by Medronho et al. (2003) as old as Medicine itself. However, the initial date of the use of maps seems to be more obscure. There is some controversy about the date of the first medical map; some are of the opinion that the first medical map is forever lost in time (Barret 2000), some others are of the opinion that the first medical map could only be constructed in the late eighteen century, because it was only then that the data become available (Walter 2000). However having in consideration that the ones producing disease maps were physicians not geographers, the question of obtaining data only had cense when considering larger geographical areas (Barret 2000). So it is possible that the first disease map was not a large area map but making use of a smaller area. When considering the disease that worked as a catalyst and the place were it started the controversy maintains, some considered that the mapping of diseases were impulsionated by the spreading of cholera from India to Europe, maybe because of the quantity of authors that published maps of cholera, in Europe between 1820-1840. However there are studies that show that in New York, 1798, a physician drew a "spot map" of the location of people with yellow fever (Barret 2000). Despite of this controversy, the most known disease map is the one produced by John Snow.

According to McLeod, 2000, Snow is considered a hero for several reasons: fist he demonstrated that cholera is transmitted by contaminated water, and then through spatial analysis he determined the source of the contamination and manage to close the water pump which resulted in a decrease number of deaths.

The results obtained by John Snow, are examples of the main applications of GIS in health, that according to Santos et al. (2000) can be divided into the following areas:

1. Epidemiological Surveillance;
2. Evaluation of the Health Services;
3. Urbanization and Environment;

In the epidemiological surveillance, applications that map health indicators allow the generation and analysis of hypothesis concerning, for example, the aetiology of the disease (Santos, Pina et al. 2000; Bhopal 2002). It is also possible to encounter applications that allow the planning of prevention and control programs, or the evaluation of risk.

The evaluation of the health services, according with the same authors can be divided into sub-areas such as: analysis of the spatial distribution of health services, planning and optimisation of health resources, accessibility studies and utilization of health services.

Finally, the urbanization and environmental area that contains applications related to urbanizations problems; it is consensual that the individuals living in cities live under different conditions, some of which related to the urbanization. Therefore the study of the so called urban diseases can take these factors in consideration. This area contains as well the problems that relate disease with environment. Both relations can be detected, for example, through applications that allow the identification of epidemiologic characteristics of areas close to contamination fonts.

The application of GIS in health as flourished, and the numbers of scientific papers using the GIS in health studies, as increased. Some examples, of each application area presented previously will be summarily described.

A study that focused on the assessment of health care provided to Kaingáng Indians, using GIS to correlate distribution of deaths and access to health services, conducted by Hökerberg, et al (2001), entitled "Organization and quality of health care for Kaingáng Indians in Rio Grande do Sul, Brazil". Amongst others variables, the investigators studied the distance that the Indians had to go in order to get medical attention, the resulting map containing this information as well as the characterization of the municipalities according to public health services (SUS – Sistema Único de Saúde) capacity, is reproduced in figure 2.15.

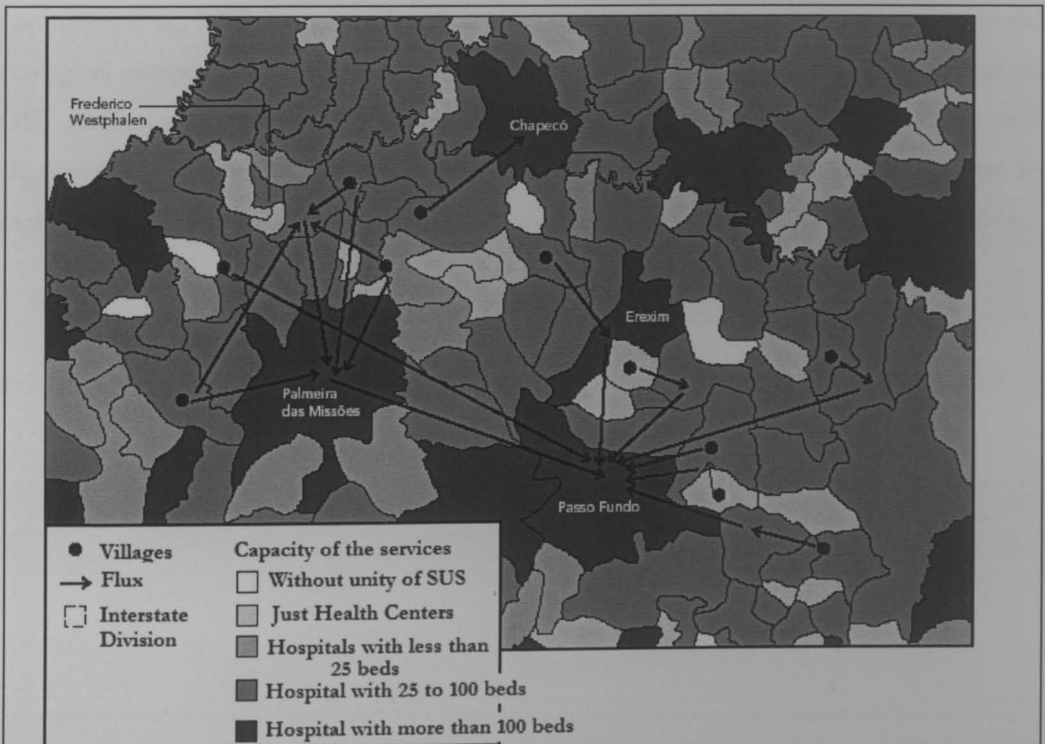

Figure 2.15 – Resulting map of the flux of patients according to the capacity of the services. Reproduced from Hokerberg et al. (2001).

The authors also refer in the conclusions that the GIS will assume a great importance in the implementation of a information system concerning the indigenous health, in order to obtain a service of better quality (Hökerberg, Duchiade et al. 2001).

Classified in the same area of Evaluation of the Health Services, can be the study entitled "Spatial access to health care in Costa Rica and its equity: a GIS-based study" conducted by Rosero-Bixby (2004). The author's objectives were the development of a methodology to access to health care and its equity and build a GIS of the demand and supply of health facilities in Costa Rica as a platform for data visualization and spatial analyses. In order to achieve his objectives the author mapped several national indicators of access such as the distance to the closest hospital care, and referred the importance of integrating the population data and the information about the indicators presented, with the help of GIS technology. The study concluded that the GIS platform developed allowed to pinpoint communities with inadequate access to health care, where interventions to improve access would have the greatest impact (Rosero-Bixby 2004).

Finally, a study designated "Spatial distribution of leptospirosis in Rio Grande do Sul, Brazil: recovering the ecology of ecological studies", performed by Barcellos, Lammerit, et al., 2003, with the objective of identifying the transmission areas and possible ecological components of leptospirosis transmission. In order to obtain the objectives the GIS technology was used to overlay the county maps on environmental units characterizing land use, altitude and river basins, and to calculate the incidence rates for each environmental class. The resulting map of such overlay, is reproduced in figure 2.16.

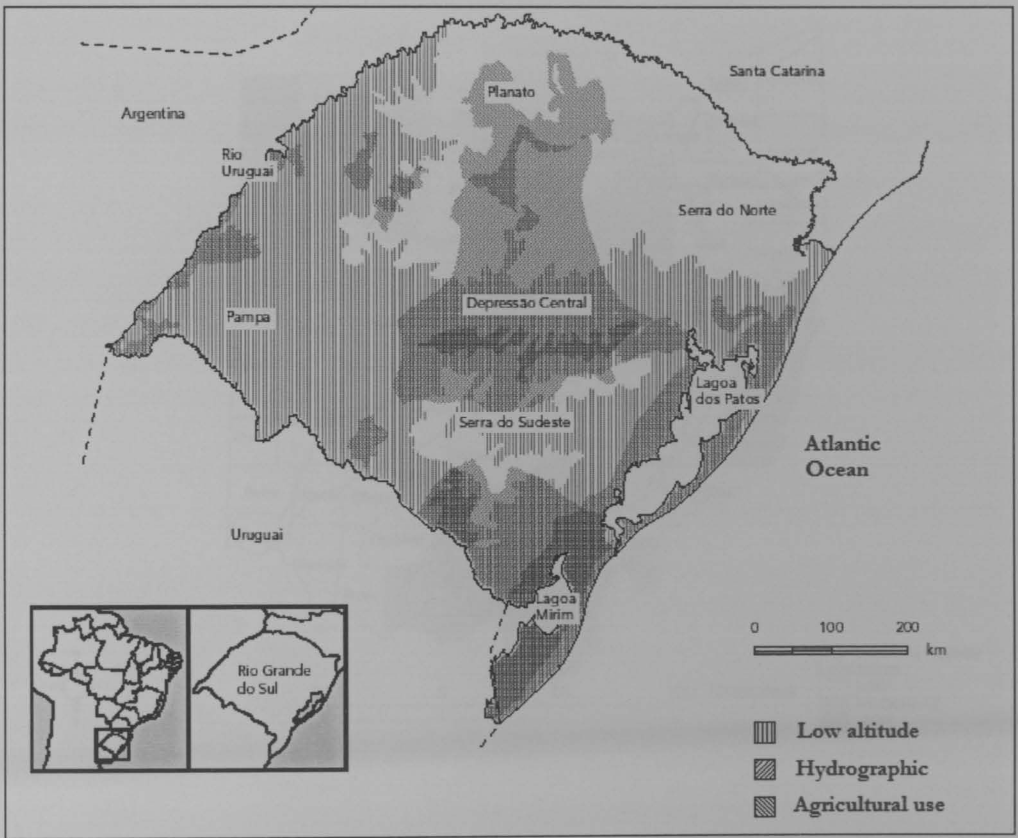

Figure 2.16 - Overlay of critical indidence of leptospirosis according to some environmental classes. Reproduced from Barcellos, et al. (2003).

The authors concluded the existence of favourable ecological characteristics for leptospirosis transmission in places involving intensive agricultural production (Barcellos, Lammerhirt et al. 2003).

A study concerning organ donor in the state of Ohio, USA, performed by Grubesic (2000), entitled "Driving donation: a geographic analysis of potential organ donors in the state of Ohio, USA", uses GIS in order to study the problem within a spatial analysis.

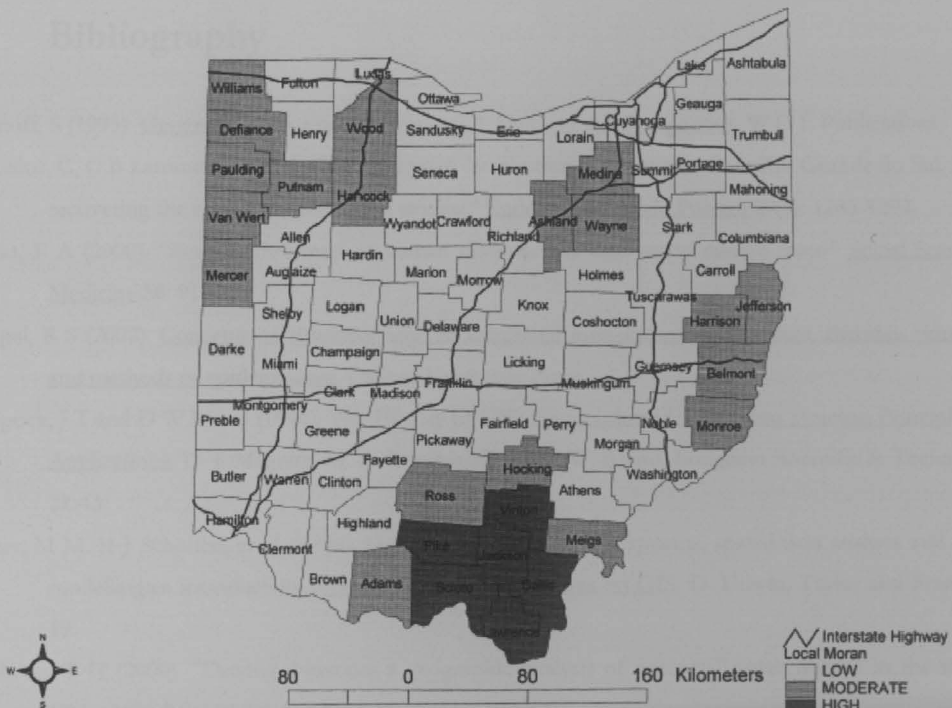

Figure 2.17 - Resulting map of Local statistic association. Reproduced from Grubesic (2000).

This map allowed a more extensive analysis with the creation of statistical models that concluded that the variables like income and education as well as race can affect the decision of potential donors (Grubesic 2000).

The examples presented display that the main reasons for the success of the application of GIS in health are: its capability of handling and integrating large amounts of different data and the possibility of performing analysis and the dynamic generation of maps in accord with the text of OPAS (2002).

Bibliography

Aronoff, S (1995). Geographic Information Systems: A Management Perspective, W D L Publications.

Barcellos, C, C B Lammerhirt, et al. (2003). "Spatial distribution of leptospirosis in Rio Grande do Sul, Brazil: recovering the ecology of ecological studies." Cadernos de Saúde Pública **19**(5): 1283-1292.

Barret, F A (2000). "Finke's 1792 map of human diseases: the first world disease map?" Social Science & Medicine **50**: 915-921.

Bhopal, R S (2002). Concepts of Epidemiology: an integrated introduction to the ideas, theories, principles, and methods of epidemiology, Oxford University Press.

Coppock, J T and D W Rhind (1994). The History of GIS. Geographical Information Systems, Principles and Applications. D. J. Maguire, M. F. Goodchild and D. W. Rhind, Longman Scientific & Technical. **1**: 21-43.

Ficher, M M, H J Scholten, et al. (1996). Geographical information systems, spatial data analysis and spatial modelling:an introduction. Spatial Analytical Perpectives on GIS. D. Unwin, Taylor and Francis: 3-19.

Grubesic, T H (2000). "Driving donation: a geographic analysis of potencial organ donors in the state of Ohio, USA." Social Science & Medicine **51**: 1197-1210.

Healey, R G (1994). Database Management Systems. Geographical Information Systems Principles and Applications. D. J. Maguire, M. F. Goodchild and D. W. Rhind, Longman Scientific & Tecnhical: 251, 267.

Hökerberg, Y H M, M P Duchiade, et al. (2001). "Organization and quality of health care for Kaingáng Indians in Rio Grande do Sul, Brazil." Cadernos de Saúde Pública **17**(2): 261-272.

Longley, P A, M F Goodchild, et al. (2001). Geographic Information Systems and Science, John Wiley & Sons, LTD.

Martin, D (1996). Geographic Information Systems Socioeconomic Applications, Routledge.

McLeod, K S (2000). "Our sense of Snow: the myth of Jonh Snow in medical geography." Social Science & Medicine **50**: 923-935.

OPAS (2000). Conceitos Básicos de Sistemas de Informação Geográfica e Cartografia Aplicados à Saúde, Organização Panamericana da Saúde - Representação no Brasil.

OPAS (2002). Sistemas de informação geográfica em saúde: conceitos básicos.

Openshaw, S and G Clarke (1996). Developing spatial analysis functions relevant to GIS environments. Spatial Analytical Perspectives on GIS. D. Unwin, Taylor & Francis: 21-37.

O'Sullivan, D and D Unwin (2003). Geographical Information Analysis, John Wiley & Sons, Inc.

Pina, M F (2000). Armazenamento de Dados em SIG. Conceitos Básicos de Sistemas de Informação Geográfica e Cartografia Aplicados à Saúde. M. S. Carvalho, M. F. Pina and S. M. Santos, Organização Panamericana de Saúde - Representação no Brasil.

Pina, M F (2001). Aplicação e Avaliação de Técnica de Interpolação Espacial para geração de superfícies de densidade a partir de dados populacionais em uma região do município do Rio de Janeiro. COPPE. Rio de Janeiro, Universidade Federal do Rio de Janeiro.

Pina, M F (2003). "O uso dos Sistemas de Informação Geográfica na Análise de Dados de Saúde." Arquivos de Medicina **14**(4): 183-186.

Rosero-Bixby, L (2004). "Spatial access to health care in Costa Rica and its equity: a GIS-based study." Social Science & Medicine **58**: 1271-1248.

Santos, S M, M F Pina, et al. (2000). Os Sistemas de Informações Geográficas. Conceitos Básicos de Sistemas de Informação Geográfica e Cartografia Aplicados à Saúde. M. S. Carvalho, M. F. Pina and S. M. Santos, Organização Panamericana de Saúde - Representação no Brasil.

Scholten, H J and M J C d Lepper (1991). "The benefits of the application of Geographical Information Systems in public and environmental health." **44**: 160-170.

Silva, A B (1999). Sistemas de Informações Geo-referenciadas: conceitos e fundamentos, Editora da Unicamp.

Walter, S D (2000). Disease mapping: a historical perspective. Spatial epidemiology Methods and Applications. P. Elliot, J. C. Wakefield, N. G. Best and D. J. Briggs: 223-239.

2.4. Spatial Statistics

Spatial statistics can be defined as the set of scientific methods that are used to collect, describe, visualize and analyse the data that can be considered a collection of random variables $\{X_t : t \in T\}$ where $T \in \Re^3$ (Assunção 2001), or as Bailey and Gatrell, (1995), defined it in broad terms, spatial analysis is the quantitative study of phenomena that are located in space. However, it is important to underline that if the data is spatially located but this feature does not intervenes in the analysis, then one is not in presence of spatial statistic; the main characteristic of this kind of analysis, and that makes the difference between this and the non-spatial analysis, is that the spatial arrangement is in a explicit way present in the analysis (Assunção 2001).

Data used for this kind of analysis has undoubtedly, a geographical coordinate and it can be divided into four categories: point process data, spatially continuous data, area data, and spatial interaction data.

The point process data is a data set consisting of a series of point locations $(s_1, s_2, \ldots)$ in a study region $\Re$ (Bailey and Gatrell 1995) and even though these points may have attributes associated that distinguish them, the important issue are the geographical coordinates that represent the exact location of the events and the configuration and arrangement of them (Assunção 2001). The randomness of this process is in the location of the event and therefore the typical problems raised by this spatial data are if there is a random pattern or some form of regularity? This data set is useful for the study, for example, of the occurrence of various diseases or types of crimes (Bailey and Gatrell 1995).

In spatially continuous data there is also a set of point locations in the region of study, however this data distinguishes itself from the point process data because here the focus is not on the exact location but on the values of the attributes on the whole region of study, given the values at a fixed number of points (Bailey and Gatrell 1995). Usually, through this data, one wishes to estimate the values of the attributes on points that where not sampled. The randomness, of this data set, is in the surface of the phenomenon under study rather than in the location (Assunção 2001). The methods used in this data set can be useful, for example, in climate studies, hydrology or geology studies (Bailey and Gatrell 1995).

Area data is the data that have been aggregated to a set of aerial units, that can be regular like remotely sensed images, or irregular such as municipalities, districts, census zones, etc. (Bailey and Gatrell 1995; Assunção 2001). Mathematically this data can be represented as a vector, where each value y_i is associated to one of the areas Ai. With area data the objectives usually are trying to find spatial trend in the attributes and try to "explain" spatial variation in the attributes of the variable of interest in terms of covariates measured (Bailey and Gatrell 1995), as well as trying to detect sub areas where the values are more high than the expected under some statistical method. This objectives are particularly important in the studies concerning demography, health, political or economical activities (Bailey and Gatrell 1995). The randomness of this process is in the spatial distribution of the attributes through the areas.

Spatial interaction data is the data related to a pair of points or areas, one of which is considered the destinations other the origins. The randomness of this process is the flux of the number of people, goods or services between the origins and the destinations (Assunção 2001). Mathematically, this set of data can be define as one of the series of observations y_{ij} $(i=1,\ldots, m; j=1,\ldots,n)$ of a random variable Y_{ij} each corresponding to a movement between the spatial locations i and j (Bailey and Gatrell 1995). Some objectives, when studying this kind of data, are: understand the arrangement of flows and ultimately to build models in order to make predictions. Examples of studies using are, for example, the flux of patients between health centres in order to plan or allocate resources.

These four categories of spatial data allows us to resolve most of spatial problem and these divisions may be intentional or occasional, for example, suppose that the data is only available at the area level, then the results are undoubtedly related to the area level, in oppose if the data is available at the point level the analysis and results can be done at the point level but also at the area level, by simply aggregating the data according to some criteria. Although the y_i is associated to the area i as an all, and it is impossible to allocate each case to its exact location, some techniques require some point within the polygon (area), the point used can be the geometric centre of the area, the centroid, or for example, if the area is a municipality, the point can be defined by the coordinates of the capital of the municipality (Assunção 2001; Pina 2003).

The geographically indexed health data because of the importance that human attributes to the resolution of health issues has been the object of thoroughly investigations using spatial statistics and every type of data.

Having exposed the categories of the spatial data, and having defined spatial statistics as a set of methods, it is easily understandable that for each category there are more suitable methods.

Any statistical analysis should start with the application of exploratory techniques to seek a good description of the data, and thus help the definition of hypothesis as well as the choice of the appropriated models (Bailey and Gatrell 1995), spatial statistics is no exception. Exploratory tools are the ones that can be used with little or no *priori* information (Bailey and Gatrell 1995; Lawson 2001b) and usually are design to be as resistant as possible to the effects of outliers, i.e., extreme values present in the data (Bailey and Gatrell 1995). The techniques used usually are an adaptation of the techniques used in common data.

Geography plays an important role in our understanding of reality, when dealing with spatial data it is essential, if not crucial, to plot the data in a map to help the visualization, a task that as been extremely facilitated through the use of GIS (Bailey and Gatrell 1995; Bithell 2000). The visualization of the disease map is considered an exploratory technique and used in the visual exploration ever since the first map of disease location was built (Lawson 2001b). As advantages of the visualization of the data in a map, one can mention the facilitation of the description, the suggestion of hypothesis for further investigation, the help in assessing of the fitness of a model or the validity of prediction derived by them (Bailey and Gatrell 1995; Bithell 2000; Bailey 2001).

The construction of expressive maps must have in consideration the nature of the spatial data in question: a bad choice of a map type or a wrong choice of the scale used may be misleading and suggest inappropriate models (Bailey and Gatrell 1995). Therefore, for each category of spatial data a different approach to the visualization may have to be considered.

The point process data is usually represented through a *dot map*, this map is obtained by simply placing the points, and an example is the famous map of John Snow (Bithell 2000) (figure 2.18). During an outbreak of cholera in 1854, in London, during a ten-day period 500 people died, John Snow a physician, used a dot map showing the location of deaths to identify the source of the outbreak as the Broad Street Pump (McLeod 2000).

However, if the data contains any other attributes rather than the simple location, then it as to be used other resources such as labels or the use of different colours or symbols, to distinguish the values of such attributes (Pina 2003).

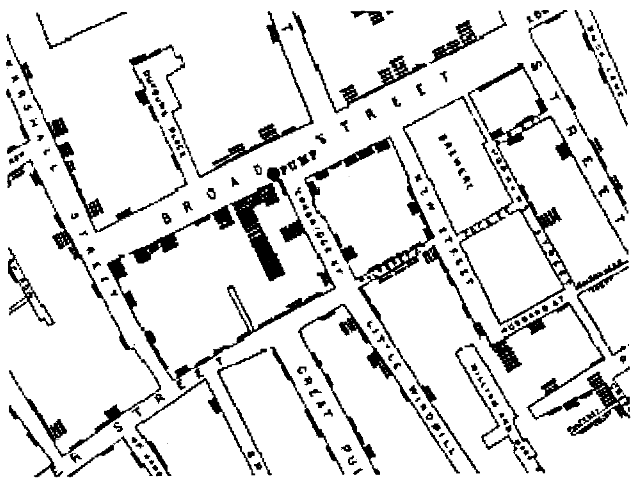

Figure 2.18 - Classical picture of cholera case distribution in London, first constructed by John Sow.

When using this kind of spatial data as well as these kinds of maps, the information of the population at risk that most likely varies through the region of interest, is not present. Therefore one is likely to have more cases of a disease where the population at risk is higher. The use of symbols with different sizes inversely proportional to the size of the population can be used, in order to involve the information about the population at risk, for example, events in areas of low population could show larger symbols then events in areas of high population. However, and because information of population would, most likely, be available only in the form of counts in some administrative areas, usually with the use of some methods it is possible to transform an initial set of point data in an area data (Bailey and Gatrell 1995).

The simplest map containing the visualization of spatially continuous data may be done with the use of a symbol at each site, the nature of this symbol may carry important information of the variable value. This sort of visualization of spatially continuous data is useful for the preliminary analysis, however the objective is to produce maps that show continuity, this is obtained by an interpolation of the several sample points (Bailey and Gatrell 1995), producing a surface.

In the maps that make use of symbols, the circles and rectangles with sizes proportional to the values that they represent are widely used. The overlap of symbols, when using proportional symbols, is a problem difficult to eliminate (Bailey and Gatrell 1995). In order to overcome this problem when the data presents many values, the use of small symbols of fixed size that can be shaded or coloured according to a classification of the data (Tyner 1992). This classification should be done in a careful way, because different number of classes as well as different limits of intervals may lead to different conclusions.

The number of classes used is sometimes determined by the following formula $(1+3.3\log n)$, where n is the number of observations. However this is not a standard procedure and the number of classes is sometimes determined using "common" sense, usually the ideal number of classes must be between four and six (Pina 2003).

The choice of the more appropriated limits to the classes can be achieved by several different methods.

The method of the equal intervals, is based on the fact that every class must have the same range intervals. The equal intervals are especially useful when the data is reasonably uniformly distributed over their range, because if the distribution is skewed a large number of values will fall in just a few classes (Tyner 1992). The range of each class can be determined by the quotient of the difference between the highest and the lowest value by the number of classes, the limits are then obtained through the addition of the range of the classes to the inferior limit, and so on, being the inferior limit of one class, the superior limit of following (Pina 2003). The range of each class can be also obtained through the use of standard deviations, a statistical measure that gives the dispersion of the observations to the mean; each class would have a range of a fixed number of standard deviations. The limits are obtained in a similar way as the previous (Pina 2003).

The use of quantile method assure that an equal number of observations fall into each class.

The method of natural breaks makes use of the histogram of the variable, and uses the break or changes on the frequency to obtain the limits of the classes (Pina 2003).

In practice, is important to test different cut point in order to obtain a good exploratory analysis.

The visualization of area data can be achieved through the use, as the spatially continuous data, of maps using proportional symbols, however the problems encounter there are the ones that will be encountered here. Therefore the most commonly use maps to visualize area data are the choropleth maps, in this map each area Ai is coloured or shaded according to the values of the variable under study. Like in spatially continuous data, the data may be classified, and the same cautions should be taken, because different choice of class intervals, will lead to different visual impressions, that may lead to different and misleading conclusions.

However these kinds of maps present other kind of problems, like: physical large areas tend to dominate the display and the problem of *modifiable area unit problem*. One solution to the problem of the dominance of physical large areas is to geometrically transform each of the areas Ai, in a way to make its area proportional to the corresponding attribute and maintaining the spatial contiguity of the areas producing a cartogram. The *modifiable area unit problem* can be described as following: if the value of the variable is the result of the aggregation of individual data in these areas, that can be designed arbitrarily on basis of administrative convenience or ease of enumeration (Openshaw 1984), then the patterns are dependent of the boundaries chosen, and therefore, different definition of areas will necessary lead to different patterns (Pina 2001). A solution for this problem is difficult to obtain, the only way is avoiding using area aggregated data altogether. Another component of such problem is that: when the average size of aerial units increases, the variation in data values between areas is smoothed out. Is recommend that area data should always be analysed on the basis of the smallest areal units for which is available and the aggregation to arbitrary larger areas should be avoided, and the inferences drawn should be checked using different areal configuration of the areas.

For visualizing spatial interaction data, the same idea of proportional symbols used in point or area data may be used. The symbols used are lines where the width of the lines is proportional to the volume of flow; arrowheads may be added to indicate the direction of the flow (Tyner 1992; Pina 2003). When a sufficient number of pairs are to be displayed, maps using proportional symbols may become difficult to "read".

The majority of maps of disease occurrence are maps of area data, the reason for this may be due to the fact that population data is gather from the censuses or other administrative sources (Bithell 2000; Lawson 2001a) or may be due to confidentiality constrains relating to the identification of the exact address location of health events (Lawson 2001a), that could lead to a point map.

Even though, the usual way to show the spatial distribution of a disease is through the use of maps, maps do not do the work by themselves, one has to describe, compare and interpret them; the descriptive or inferential statistics is useful to explicit what is implicit in the maps. The statistics adds precision to a qualitative description, facilitates the comparisons between the different populations in time or space, and may draw attention to details that escape a more qualitative analyse. These three characteristics are present in the three usual application of statistics: systematize the way of collecting the data, explore and visualize this data in maps or summary measures, and extract conclusions about the generator processor of the data based in probabilistic models (Assunção 2001).

From what was said in the previous paragraph the mapping of diseases can not be defined only as the plot of incidence of a determined disease, but as it was defined by Bailey (2001), and Lawson (2001b), as an area of spatial epidemiology that is concerned in producing a map of the real distribution of a disease though the use of the observed rates data. From a statistical point of view, the first author considers that the objective of disease mapping is obtaining a good estimate of the geographic heterogeneity of the disease rate over the study area.

The widespread of disease mapping began around the 19th century, with the availability of the health data and the desire of evaluating the geographical patterns in disease as well as the desire to identify the risk factors that might affect such patterns (Walter 2000). This maps started by represent only infectious diseases and used by a limited number of countries such as yellow fever in the United States and cholera in Europe have now broaden their limits to almost every disease as well as every country, facilitating the international comparisons (Walter 2000).

The simplest way to plot a disease in a map is to plot the location of case-events or represent the count of a track (area) through the use of a symbol in suitable locations such as centroids. However such map can lead to wrong interpretation, because it does not give information of the background population that might be at risk (Lawson 2001a), and areas with a great number of cases could only be the result of a great number of population at risk. Therefore, in order to achieve an efficient disease mapping, there has been development of exploratory and modelling methods.

One way to overcome problems involving information of population at risk is to plot the standardized mortality/morbidity ratios and other results from standardizations, that estimates the expected incidence/mortality and then compares it to the observed incidence; this expected incidence is assessed using other kind of aggregation or using the map of another disease (Lawson 2001a). The plot of results of standardization methods, which usually are applied to map counts within areas can also be used in case-events maps, however in order to estimate the differences in local disease risk the point locations are converted into a continuous surface describing the spatial variations in the intensity of the cases, like Lawson (2001b) proposed.

A method used very often to assess the intensity of the all area of study is the Kernel estimation. Let:

- s represent a general location in the region $\Re$, under study;
- $s_1,\ldots, s_n$ represent the locations of the n observed events;
- $\tau > 0$ represent the bandwidth;
- $\frac{1}{\delta_\tau(s)}$ represent an edge correction;
- $k(\ )$ represent a kernel function;

then

$$\hat{\lambda}_\tau(s) = \frac{1}{\delta_\tau(s)} \sum_{i=1}^{n} \frac{1}{\tau^2} k\left(\frac{(s - s_i)}{\tau}\right)$$

is an estimate of the intensity at s, $\lambda(s)$, events per unit area (Bailey and Gatrell 1995).

The parameter τ that is denoted as bandwidth is the radius of the disc centred on s within which points s_i will contribute to the estimative of the intensity, this parameter determines the amount of smoothing because it defines the region of influence. A very large τ, will produce a flat surface and local features may be obscured, in opposite, a very small τ, will produce a very spiky surface, "with peaks" in every s_i. The literature suggests (Cressie 1993; Bailey and Gatrell 1995) $\tau = 0.68n^{-0.2}$,considering n the number of observed events, as a "rough" choice for the bandwidth when $\Re$ is the unit square. However, in practice, one should experiment different values for the bandwidth. It is also possible to adjust the value of τ at different points in the region, such methods are designated adaptive kernel estimation (Gatrell, Bailey et al. 1996). As for the edge correction, is a function of the bandwidth, and can be defined as the volume under the scaled kernel centred on s that lies "inside" the region of study. At last, the kernel function $k(\ )$ is a suitable bivariate probability function that is symmetric about the origin (Bailey and Gatrell 1995). When one is concerned in getting a good estimative for the intensity, then the concern must be on the choice of the bandwidth and not so much on the function (Cressie 1993). A representation of such parameters is given in the figure 2.19.

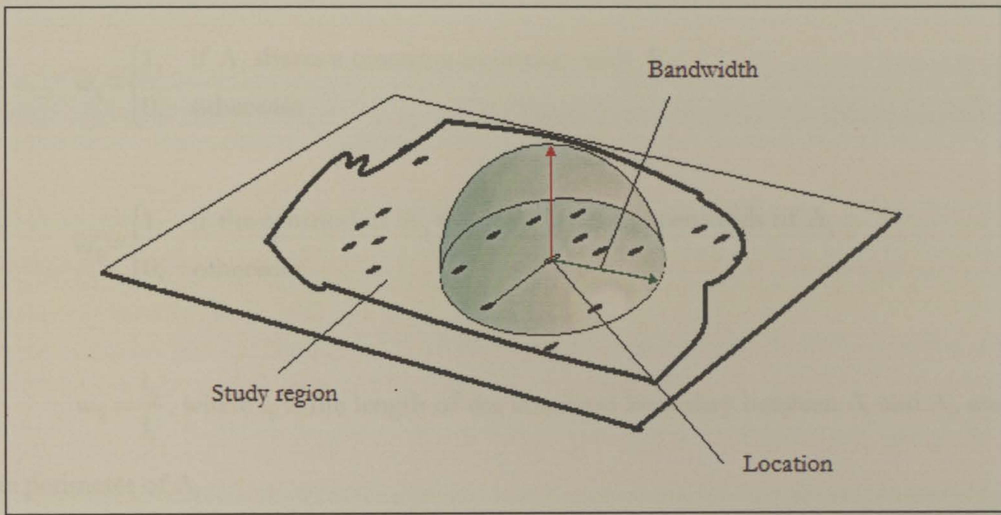

Figure 2.19 - Diagram representing a kernel estimation of a point pattern.

The definition of measure between observations is of crucial importance to some statistical methods. The measure of the distance between observations in point data does not present a problem, because each observation is linked to a point in the region under study and one can obtain the distance, for example using the Euclidean measure. In area data, one can also use the Euclidean measure between the centroids, however by doing so it would be disregarding the spatial nature of the areas (Bailey and Gatrell 1995). However if regarding the spatial nature, and because the most frequent situation is one where areas are irregular shaped this brings an additional problem in assessing the distance or the "proximity". Since this issue is present in most methods concerning area data, it is useful to start with the definition of how to assess such a proximity measure between each Ai.

It is usual for each region $\Re$ under study with *n* areas, to construct $(n \times n)$ matrixes $W^{(k)}$, where *k* is the order of the neighbors, therefore these matrixes are called neighborhood or proximity matrix of order k (Bailey and Gatrell 1995; Câmara, Carvalho et al. in press). Each element $w_{ij} \geq 0$ of the matrixes represent the neighborhood *k* measure between the areas A_i and A_j. This measure can be defined through different criteria, next will be presented a list of a few of such possibilities for measures of the $W^{(1)}$:

$$w_{ij} = \begin{cases} 1, & \text{if the centriod of } A_i \text{ is within a certain distance of } A_j \\ 0, & \text{otherwise} \end{cases}$$

$$w_{ij} = \begin{cases} 1, & \text{if } A_i \text{ shares a common boundary with } A_j \\ 0, & \text{otherwise} \end{cases}$$

$$w_{ij} = \begin{cases} 1, & \text{if the centriod of } A_i \text{ is one of k nearest centroids of } A_j \\ 0, & \text{otherwise} \end{cases}$$

$w_{ij} = \frac{l_{ij}}{l_i}$, where l_{ij} is the length of the common boundary between A_i and A_j, and l_i, the perimeter of A_i

Obviously that these measures may have to suffer some adaptation when working with matrixes of order k>1, for example a measure for a matrix of second order could be defined as following:

$$w_{ij} = \begin{cases} 1, & \text{if } A_i \text{ shares a common boundary with the neighbors of } A_j \\ 0, & \text{otherwise} \end{cases}$$

In some cases it is usual to standardize the lines of the matrix, making the sum of the weights of the area *i* equal to one, $w_i = \sum_j w_{ij} = 1$ (Assunção 2001).

Another alternative way to map the data, as well as an alternative exploratory method for area data is mapping for each area, the mean of the neighbors. This method tends to reduce the spatial variability, because it produces a surface with less fluctuation than the original data and therefore gives a more precise idea of the phenomenon (Câmara, Carvalho et al. in press). This mean can be estimated through the average (usually weighted) calculated through the use of the neighborhood matrix as showed next (Bailey and Gatrell 1995):

$$\hat{\mu} = \frac{\sum_{j=1}^{n} w_{ij} y_j}{\sum_{j=1}^{n} w_{ij}}$$

where:

- w_{ij}, represents the measure between the areas A_i and A_j;
- y_j, represents the value of the attribute in area i;

Obviously the "results" of this method are dependent upon the choice of the measures (Bailey and Gatrell 1995).

Kernel estimations can also be used for the area data, for estimate the mean value, of an attribute. For computational reasons, because multiple integration of the kernel function would be required, kernel estimation for area data does not make use of the information of the geometry of the boundary of the areas, but it links each observation y_i to a point location s_i within the area i, usually the centroid (Bailey and Gatrell 1995). Therefore an estimative of the mean value $\hat{\mu}(s)$ of an attribute y_i sampled at the location s_i can be given by:

$$\hat{\mu}(s) = \frac{\sum_{i=1}^{n} k\left(\frac{(s-s_i)}{\tau}\right) y_i}{\sum_{i=1}^{n} k\left(\frac{(s-s_i)}{\tau}\right)}$$

where

- s, represents a general location in the region $\Re$, under study;
- s_i, represents a locations within the area I;
- $\tau > 0$, represents the bandwidth;
- $k(\ )$, represents a kernel function;
- y_i represents the value of the attribute in area i;

Bailey and Gatrell, 1995, acknowledge that a sensible interpretation of such value may often be possible only when s is considered a small area around the point and not only a point.

The concept of spatial dependency is designated spatial autocorrelation, because it measures the correlation between observations of the same variable in different positions in space (Bailey and Gatrell 1995). This concept can be measure by global and local indicators, that are a good tool in exploratory methods. The global indicators of spatial autocorrelation translate how the values of the variable of the all set of areas are correlated in space and are useful to characterize the region as an all; they provide a single value to all areas (Câmara, Carvalho et al. in press). The local indicators translate how the value of the variable of one area is correlated to the values of the same variable in the neighborhood areas; they provide a value for each area and allow the identification of groups. The local indicators are more sensible to variations of the values of the variable especially when the range of values is wide (Câmara, Carvalho et al. in press).

One way to measure the global spatial autocorrelation is through the use of Moran index (I). The Moran's I is calculated using the formula (Anselin 2002b):

$$I = \frac{n\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}(y_i - \bar{y})(y_j - \bar{y})}{\left(\sum_{i=1}^{n}(y_i - \bar{y})^2\right)\left(\sum\sum_{i \neq j} w_{ij}\right)}$$

where:

- *n*, is the number of areas;

- *W* is the neighborhood matrix $(n \times n)$, in which the elements w_{ij} represent the relation of neighborhood of the areas A_i e A_j;

- y_i, value of the variable measured in the A_i area;

- y_j, value of the variable measured in the A_j area;

- $\bar{y}$, average value of the variable in the region of interest.

The choice of the neighborhood relation depends on the type of data that is being used and of the mechanisms through which one wish the spatial dependence to "appear". The most common situation is one in which the neighborhood relation is defined by the sharing of common boundaries, where:

$$\begin{cases} 1, & \text{if } A_j \text{ has a common boundary with } A_i \\ 0, & \text{else} \end{cases}$$

Another global indicator used is the Geary's C, that differs from the Moran's I because it uses the difference between values whereas the Moran's I uses the difference between each value and the global mean (Câmara, Carvalho et al. in press). The Geary's C can be calculated through the expression (Anselin 2002b):

$$C = \frac{(n-1)\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}\left(y_i - y_j\right)^2}{2\left(\sum_{i=1}^{n}(y_i - \bar{y})^2\right)\left(\sum\sum_{i \neq j} w_{ij}\right)}$$

where:

- *n* is the number of areas;

- *W* is the neighborhood matrix $(n \times n)$, in which the elements w_{ij} represent the relation of neighborhood of the areas A_i e A_j;

- y_i, value of the variable measured in the A_i area;

- y_j, value of the variable measured in the A_j area;

- $\bar{y}$, average value of the variable in the region of interest.

Neither of these indexes are constrained to lie between -1 to 1, however they can be modify in order to restrict the values to such interval, like any other non-spatial correlation coefficient (Bailey and Gatrell 1995). However, the following interpretation can be done:

- Positive values indicate a positive autocorrelation, in this case the areas tend to have similar values, showing a direct spatial dependency;
- Values close to 0 indicate the inexistence of spatial autocorrelation, i.e., spatial independency;
- Negative values indicate a negative autocorrelation, in this case the areas tend to have dissimilar values, showing a indirect spatial dependency (Wakefield, Kelsall et al. 2000; Assunção 2001; Câmara, Carvalho et al. in press).

Both indicators can be used to assess the spatial autocorrelation in different lags, by simply using the correspondent proximity matrix, for example the Moran's I for a lag *k* would be given by:

$$I^{(k)} = \frac{n\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}^{(k)}(y_i - \bar{y})(y_j - \bar{y})}{\left(\sum_{i=1}^{n}(y_i - \bar{y})^2\right)\left(\sum\sum_{i \neq j} w_{ij}^{(k)}\right)}$$

where:

- n is the number of areas;
- $W^{(k)}$ is the neighborhood matrix of order k;
- y_i, value of the variable measured in the A_i area;
- y_j, value of the variable measured in the A_j area;
- $\bar{y}$, average value of the variable in the region of interest.

The relationship between the value of an area and the values of its neighbors can be more easily visualize by the Moran's Scatter Plot. This object can be looked upon as a bi-dimensional graphic, divided in four quadrants, which represent the relationships between y_i (value of the variable measured in the A_i area) and w_y (average value of the variable measured in the neighbors of y_i). The four quadrants in the graph provide a classification of the four types of spatial autocorrelation: high-high (upper right), low-low (lower left) for positive autocorrelation, and high-low (lower right), low-high (upper left) for negative autocorrelation (Anselin 2002b).

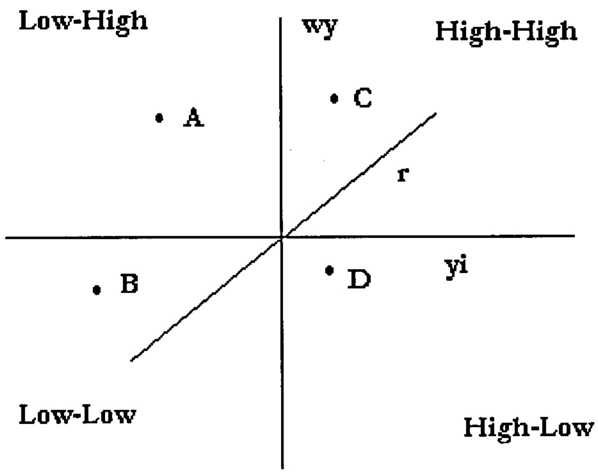

Figure 2.20 - Diagram representing a Moran's Scatter Plot.

In figure 2.20, is represented how a Moran's scatter plot is builted. The point A represents an area where the value of the attribute is low and the mean values of the neighbors is high, indicating a negative spatial auto correlation; point B represents an area where the value of the attribute is low as well as the mean values of the neighbors, indicating a positive spatial auto correlation; point C represents an area where both the values of the attribute and the mean values of the neighbors are high, indicating also a positive spatial auto correlation; finally, point D represents an area where the value of the attribute is high and the mean values of the neighbors is low, indicating a negative spatial auto correlation. The slope of the regression line, r, is the Moran's I index (Anselin 2002a). Usually this diagram is built with standardized values, so that units in the graph correspond to standard deviations (Anselin 2002a). The "result" of such plot can be visualized through a thematic map, designated Box Map, in which each polygon is classified by their quadrant Q1, Q2, Q3 and Q4 (Anselin 2002b).

When dealing with a great number of areas is possible that different spatial associations occur; therefore there are also local indicators of spatial autocorrelation, like said before, that provide a specific value for each area. One of such indicator is the local Moran index, known as LISA (Local Index of Spatial Autocorrelation). The index is calculated through the formula:

$$I_i = \frac{y_i \sum_{j=1}^{n} w_{ij} y_j}{\sum_{j=1}^{n} y_j^2}$$

where:

- n is the number of areas;

- w is the neighborhood matrix;

- y_i, value of the variable measured in the A_i area;

- y_j, value of the variable measured in the A_j area.

For each area A_i, I_i is calculated allowing the identification of clusters (group of areas with similar values) and outliers (areas with uncommon values). The interpretation is done in the same way as for global indicators.

The set of methods presented so far can be designated as ESDA (Exploratory Spatial Data Analysis), and are considered a set of tools used to describe and visualize spatial distributions, identify atypical situation, discover spatial association patterns and grouping of similar values (clusters) (Anselin 2002b). The next statistical step is to seek a more formal confirmation of the hypothesis gather by the use of ESDA, or estimate indicators, through the use of statistical models applied to the data.

With the use of ESDA, the spatial autocorrelation indexes can calculated, but one can consider them significant, or just a matter of chance and if other values were observed the type of autocorrelation would be different. Both global and local indicators after calculated can be tested for significance in similar ways (Câmara, Carvalho et al. in press). One way to do so is associating a statistical distribution, usually the normal distribution to the statistics of the test, that has as a null hypothesis the spatial independence (Câmara, Carvalho et al. in press). These kinds of tests make the assumption that the observed values represent a subset of the possible results (Bailey and Gatrell 1995). In opposite, other test described next, consider that no other values can ever been observed (Bailey and Gatrell 1995). The other possibility to test the significance is to create a number of simulations, doing permutations of the values, each permutation produces a new rearrange of the values, and therefore a new I index, if the I value observed corresponds to an extreme value of the values produced by the simulation it is significant (Bailey and Gatrell 1995; Câmara, Carvalho et al. in press), this method is called the pseudo-significance test (Câmara, Carvalho et al. in press).

The "result" of such significance test may be use to form a map, where only the areas with significant autocorrelation are plotted, such maps can be designated by Lisa or Moran map (Anselin 2002b).

The methods described so far, to explore spatial data, assumed that the data or some transformation of it could be approximately considered normally distributed (Bailey and Gatrell 1995), however when dealing with counts and proportions the normal distribution is not used and therefore other methods must be applied.

In every phenomenon there is always some kind of element that cannot be controlled, such elements are also present in health data, in disease mapping context refer to as random effects. The past years the methods related to disease mapping have been developed in order to "create" methods that could model such effects (Lawson 2001b), that if not "controlled" can lead to deviated results.

One problem that can not be ignored is the problem of "small numbers"; when calculating rates in areas, the population may be small, and the rates may not be reliable and just a result of random fluctuation (Wakefield, Best et al. 2000; Câmara, Carvalho et al. in press). Câmara, Carvalho et all, proposed the following exercise in order to exemplify such problem, for example, considering a region where of 15 born children no one dies, apparently we would have an ideally situation, however if only one child dies we would go from a rate of 0 to a rate of 66 per 1000. Such problems are frequent when working with political administrative areas, where the range of population at risk is wide (Câmara, Carvalho et al. in press).

Some of the methods that have been developed to remove the "noise" caused by randomness are the Bayesian methods (Elliot, Wakefield et al. 2000). This methods use the information of other areas to estimate the risk of each area, and by doing so reduce the random fluctuation not due to risk. Taking into account the spatial autocorrelation between nearby areas, the maps became more smooth and informative (Assunção, Barreto et al. 1998).

Bayesian methods as all Bayesian statistics uses prior knowledge or beliefs as well as information from the experience or from the sample to achieve the objectives; Bayesians consider that any information known *a priori* can only bring advantages to the process (Paulino, Turkman et al. 2003). These methods convert the prior probability distribution (derived from the prior knowledge) for the values of the parameters of interest in a posterior distribution using the data that are actually observed and the Bayes Theorem (Bailey and Gatrell 1995; Paulino, Turkman et al. 2003). Obviously, the specification of the prior distribution is not error free, it has uncertainty attached, the quantification of such uncertainty as been the object of many critics to Bayesian statistic in general (Paulino, Turkman et al. 2003). There are several ideological approaches to Bayesian methods, with different levels of "purity", from the empirical bayes (the less pure) to the full bayes (the more pure), passing through others with intermediate levels of purity (Spiegelhalter, Abrams et al. 2004).

Empirical Bayes methods avoid the specification of the prior distribution as they also derive it from the data (Spiegelhalter, Abrams et al. 2004). The Empirical Bayes Estimation can be mathematically formulated as following, let:

- θ_i be the true unknown rate in each area i;

- $r_i = \frac{y_i}{n_i}$ (where y_i is the number of cases in area i and n_i the population at risk in area i) be the observed rate.

- γ_i and ϕ_i be the mean and variance of the prior distribution for each θ_i;

Than the best Bayes estimate of θ_i, based on the prior distribution and the observed rates is given by:

$$\hat{\theta}_i = \omega_i \times r_i + (1-\omega_i)\gamma_i$$

where $$\omega_i = \frac{\phi_i}{\left(\omega_i + \frac{\gamma_i}{n_i}\right)}$$ (Bailey and Gatrell 1995)

The ω_i and $(1-\omega_i)$ are considered the weighting factors and are functions of the population at risk n_i and the variance ϕ_i of the prior distribution. In areas where the population at risk n_i, is relatively large the weight ω_i is bigger than the weight $(1-\omega_i)$ and reflects the confidence on the observed rate r_i, whereas in areas where the population at risk is small, the weight $(1-\omega_i)$ is bigger than the weight ω_i and reflects the confidence of our prior beliefs (Bailey and Gatrell 1995).

In empirical Bayes methods, as mentioned before, the γ_i and ϕ_i are estimated from the data, and there are several ways to do so. One of this ways is to consider γ_i and ϕ_i constant in all areas, and estimates would be given by (Bailey and Gatrell 1995):

$$\hat{\gamma} = \frac{\sum y_i}{\sum n_i}$$

and

$$\hat{\phi} = \frac{\sum n_i (r_i - \hat{\gamma})^2}{\sum n_i} - \frac{\hat{\gamma}}{\bar{n}}$$

where

- $\hat{\gamma}$, estimative of γ;
- y_i, cases of area *i*;
- n_i, population at risk of area *i*;
- $\hat{\phi}$, estimative of ϕ;
- r_i, observed rate at area *i*;
- $\overline{n}$, average population across all areas.

By convention $\phi = 0$ whenever the $\hat{\phi}$ is negative (Bailey and Gatrell 1995).

In order to obtain a more sensible estimative it is possible to use instead of the global data, the neighbourhood data. Therefore to achieve a more sensible estimative, one can allow the mean and variance for the distribution of θ_i to be related to a neighbourhood of *i* rather than being constant for all areas; than the observed rate is recalculated towards a neighbourhood mean rather than a global mean (Bailey and Gatrell 1995).

Full Bayesian methods, in opposite to empirical ones, specify the prior distribution and apply the probability theory to it (Spiegelhalter, Abrams et al. 2004), however when dealing with real data the computation of the posterior distribution may involve difficult computation, including integrations of high difficulty, and therefore for several years this methods were restricted to rather simple examples (Wakefield, Best et al. 2000). However this problem seems to be overcome, with the help of some computational methods such as Markov Chain Monte Carlo (MCMC), which allows the integrals or sums to be calculated through simulation from a Markov Chain, rather than exact or approximate algebraic analysis (Bailey 2001; Spiegelhalter, Abrams et al. 2004) and some computational software like Win Bugs, that allows the implementation of such methods as well as the use through other statistical software (Spiegelhalter, Abrams et al. 2004).

Empirical Bayesian methods and full Bayesian methods often give similar general results (Diggle 2000). Lawson, et al (2000), referred a study that when comparing the two methods found that even though the absolute relative risk estimates varied between methods, the ranking of relative risks across the area remained the same (Lawson, Biggeri et al. 2000).

Disease mapping, as mentioned before, could be considered as having the aims not only of describing the spatial variation of the disease, but also:

- provide a "clean" map of disease risk, in order to assess the spatial variation in risk;
- identify areas of unusually high risk, in order to assess clusters (Lawson, Biggeri et al. 2000).

The distinction between this to aims is sometimes blurred (Diggle 2000). A reason stressed by, Diggle (2000), is related to the definition not always clear of cluster. Several definitions of this concept can be encountered in the literature. Lawson (2001b), presents two kinds of definitions for clusters, a non-parametric and a parametric one. The author citing another font, defines cluster as follows: "a geographically bounded group of occurrences of sufficient size and concentration to be unlikely that have occurred by chance", that can be translated as following: "any area within the study region of significant elevated risk". In this definition also referred as "hot-spot" clustering any area with elevated risk could qualify as a cluster provided that it met some statistical criteria (Lawson 2001b). It can also be found in the literature the term cluster indicating areas with significant lowered risk (Knorr-Held and Raßer 2000). The parametric definition, presented by the same author, goes as follows: "the study region has a prespecified cluster structure". This definition implies a restriction on the cluster form and also some parameters to control it through all the region (Lawson 2001b).

Note that through the non-parametric definition, Diggle (2000), propose that any method use to detect cluster, such implicit or explicit make use of the hypothesis of complete spatial randomness, where this term means:

1. cases occur independently of each other;
2. all members of the population at equal risk.

The second reason for the definition of cluster and spatial variation of risk present some intersection is that both can be detected through tests with the same null hypothesis presented previously, however they differ in the alternative hypothesis. The spatial variation of risk tests, assume that the alternative hypothesis is a departure from the assumption 2 (all members of the population at equal risk) of the null hypothesis (Diggle 2000), i.e., members of the population differ in terms of risk. As for test to detect clusters, they make use of an alternative hypothesis that is a departure from the assumption 1 (cases occur independently of each other) of the null hypothesis in the direction of positive dependence, i.e., the conditional probability of the existence of a case in a location, A, close enough of location, B, where a case exists, is higher than the unconditional probability of having a case in the location A (Diggle 2000).

In addition, if one takes into account that cluster may be due to, as Wakefield et al (2000), proposed an infectious agent or a genetic susceptibility and/or risk factors, measured and unmeasured, one can conclude that the spatial variation of the risk may be involved in the cause of the cluster itself, and therefore completely distinction between both terminologies is difficult.

Note that clusters of areas as well as clusters of points can be defined; to assess the identification of clusters of points, the methods can be classified into two main categories: the fist category test the hypothesis described previously but they identify the probable font of risk, they try to answer the question: is there evidence to state that there is a significant increase of risk near a suspicious font? The second category test the same hypothesis but without previous specification of which and how many suspicious fonts, they try to answer the question: is there evidences to state that there is one or more regions with significant higher risk than the mean value observed in the map as an all (Assunção 2001). To assess the clusters of areas, usually the tests used are the ones that try to assess the spatial autocorrelation and its significance.

Bibliography

Anselin, L (2002a). Exploring Spatial Data with DynESDL, Center of Spatially Integrated Social Sciences.

Anselin, L. (2002b) URL: http://geog55.geog.uiuc.edu/sa

Assunção, R (2001). Estatística Espacial com Aplicações em Epidemiologia, Economia e Sociologia. SP, UFSCar.

Assunção, R A, S M Barreto, et al. (1998). "Mapas de taxas epidemiológicas: uma abordagem Bayesiana." Cadernos de Saúde Pública **14**(4): 713-723.

Bailey, T C (2001). "Spatial statistical methods in health." Cadernos de Saúde Pública **17**: 1083-1098.

Bailey, T C and A C Gatrell (1995). Interactive Spatial Data Analysis, Longman.

Bithell, J F (2000). "A classification of disease mapping methods." Statistics in Medicine **19**: 2203-2215.

Câmara, G, M S Carvalho, et al. (in press). Análise espacial de áreas. Análise Espacial de Dados Geográficos. S. D. Fucks, G. Câmara, M. S. Carvalho and A. M. Monteiro, Editora Embrapa.

Cressie, N A C (1993). Statistics for Spatial Data, John Wiley & Sons.

Diggle, P J (2000). Overview of statistical methods for disease mapping and its relantionship to cluster detection. Spatial Epidemiology: Methods and Applications. P. Elliot, J. C. Wakefield, N. G. Best and D. J. Briggs, Oxford University Press.

Elliot, P, J C Wakefield, et al. (2000). Spatial epidemiology: methods and applications. Spatial epidemiology Methods and Applications. P. Elliot, J. C. Wakefield, N. G. Best and D. J. Briggs: 3-14.

Gatrell, A C, T C Bailey, et al. (1996). "Spatial point pattern analysis and tis application in geographical epidemiology." (21): 256-274.

Knorr-Held, L and G Raßer (2000). "Bayesian detection of Clusters and Discontinuities in Disease Maps." Biometrics(56): 13-21.

Lawson, A B (2001a). "Tutorial in Biostatistics - Disease map reconstruction." Statistics in Medicine **20**: 2183-2204.

Lawson, A B (2001b). Satistical methods in spatial epidemiology, John Wiley & Sons, Ltd.

Lawson, A B, A B Biggeri, et al. (2000). "Disease mapping models: an empirical evaluation." Statistics in Medicine **19**: 2217-2241.

McLeod, K S (2000). "Our sense of Snow: the myth of Jonh Snow in medical geography." Social Science & Medicine **50**: 923-935.

Openshaw, S (1984). "The Modifiable Areal Unit Problem." Concepts and Thecniques in Modern Geography **38**.

Paulino, C D, M A A Turkman, et al. (2003). Estatística Bayesiana, Fundação Calouste Gulbenkian.

Pina, M F (2001). Aplicação e Avaliação de Técnica de Interpolação Espacial para geração de superfícies de densidade a partir de dados populacionais em uma região do município do Rio de Janeiro. COPPE. Rio de Janeiro, Universidade Federal do Rio de Janeiro.

Pina, M F (2003). "Representação Cartográfica de Dados Espaciais." Arquivos de Medicina **17**(5): 233-240.

Spiegelhalter, D J, K R Abrams, et al. (2004). Bayesian Approaches to Clinical Trials and Health-Care Evaluation, John Wiley & Sons.

Tyner, J (1992). Introduction to Thematic Cartography. New York, Prentice Hall.

Wakefield, J C, N G Best, et al. (2000). Bayesian approaches to disease mapping. Spatial Epidemiology: Methods and Applications. D. J. Briggs, Oxford University Press.

Wakefield, J C, J E Kelsall, et al. (2000). Clustering, cluster detection, and spatial variation in risk. Spatial epidemiology Methods and Applications. D. J. Briggs: 129-152.

Walter, S D (2000). Disease mapping: a historical perspective. Spatial epidemiology Methods and Applications. D. J. Briggs: 223-239.

3. Materials and Methods

3.1. Materials

The materials used in the execution of this project can be divided into three groups: the databases, the maps and the software. The databases themselves can be divided into two subgroups: the health data and the census data.

3.1.1. Databases

The health data was provided from the Health Informatics and Financial Management Institute (Instituto de Gestão Informática e Financeira da Saúde – IGIF), of the Portuguese Health Ministry, which is responsible for the management of the National Hospital Inpatients Data Register; this national database was created as a result of the use of the classification of patients according to their clinic characteristics into Diagnosis Related Group (DRG), nationwide (Queirós 2000).

It was solicited the data related to cases of femur fracture that occurred in the period of 1996 to 2002, although the IGIF provided only the data related to the years 2000 to 2002. The database contains information relative to every institution of the National Health Service (Serviço Nacional de Saúde - SNS), and since the majority of such fractures require hospitalisation for chirurgical intervention, that are costly procedures, the overwhelming majority of the individuals go to hospitals of SNS.

The Diagnosis Related Groups is a method of classification of patients submitted to internment, in which the objective is the allocation of each internment episode to a unique group according to clinic characteristic, inspite of the number of services in which the patient was treated from the admission to the discharge. This system of classification was first developed in the USA, in the late 1960's, and as been in constant evolution (Assessment 1983). Its design considered the following objectives: make use of the data that is commonly available, identify the patients with similar expected resources used, and construct a meaningful classification to physicians (Assessment 1983).

The process of allocating an internment episode to a DRG is done considering five independent variables, such as: age, principal and secondary diagnosis, chirurgical procedures and destination after discharge, the dependent variable: time of internment that is used as a measure of the resources consumed, (it is possible, through a mathematical algorithm, to determine the influence of the independent variables in the dependent one) (Queirós 2000). The first variable to be taken in account is the principal diagnosis, that can be defined as the reason, after study, that the patient is admitted (Queirós 2000). This diagnosis is allocated to meaningful but broad categories called Major Diagnostic Categories (MDCs) (Assessment 1983). There were created 23 MDCs, most of which concerning only a single organ system (Assessment 1983; Queirós 2000), but soon it was realised that there were diseases that did not fit these categories, therefore there were created other categories such as MDC 22 – Burns (Queirós 2000). In one of these groups can be allocated every possible principle diagnosis, and excluding the exception of the MDC 12 - Disorder and Disease of Male Reproductive System and MDC 13 - Disorder and Disease of Female Reproductive System, they are mutually exclusive (Queirós 2000). These groups are subdivided into subgroups considering the other variables, when possible the first subdivision is based upon the presence or absence of chirurgical intervention in an operating room, but others are used, such as comorbidity/complications or age (Assessment 1983). The DRGs are therefore the groups resulting of such subdivisions.

The diagnosis and procedures are codified, using the International Classification of Diseases, 9 th Revision Clinical Modification, ICD-9-CM proposed by the WHO. This operation allows the increase of precision in the data and consequently the decrease of the number of mistakes in the attribution of a DRGs.

Note that this systemic process of classification meets the objectives that were defined to its design: uses the data available, it is natural for physicians to interpret each group, and it is expected that patients with similar clinical conditions make use of similar resources.

The use of the DRG classification has some useful advantages: the possibility of each hospital to design the profile of their patients, the DRG may also play an important role to assure the quality of treatment, because it allows the comparison of treatments performed in individuals under the same clinical situation, cit. by Queirós, 2000. The use of DRG may also be useful in a construction of a more equity form of distribute the finance between hospitals, as well as in the distribution of finance between services within hospitals.

The implementation of the DRG system in the Portugal, in 1984, had as objective the creation of an information system that would be helpful in the elaboration of budgets and in the flowing of standardize data between hospitals and between hospitals and central administration, cit. by Queirós 2000.

Periodically the Health Ministry defines the prices that the institutions of the SNS can charge for medical care supplied, considering the DGR. During the period under study this prices were reviewed. In the beginning of the period the prices were the defined by the Portaria n° 384-B/1998"D. R. I Série B, in the year 2001, the prices were reviewed again and defined in the Portaria n° 189/2001"D. R. I Série B. In order to eliminate doubts and diminish the discrepancies between similar cases, the same document also defines several terms, such as: the term patient submitted to internment and time of internment. Are to be considered patients submitted to internment all individuals that occupy a bed, in an health institution, in order to obtain diagnosis or treatment for at least a night. Whereas the time of internment, is to be calculated as the number of days consumed by each patient submitted to an internment, considering the days of admission and ignoring the day of discharge.

The National Hospital Inpatients Data Register database provided by IGIF contained the following variables:

- Sex;
- Age;
- Provenience (for example, emergency room, other hospital);
- First cause of admission (and 19 secondaries), coded by the ICD-9-CM;
- Admission Diagnosis e 19 other secondary diagnosis, also coded by the ICD-9-CM (each variable "diagnosis" has a related variable "cause");
- Clinical Procedures (up to 20);
- Destination after discharge (for example, home, another Hospital from the SNS, decease);
- Days of hospitalisation;
- Costs of internment;
- DGR;
- MDC;
- Place of the residence in three geographical units (Freguesia, Concelho and Distrito).

The responsible entity of the health database, however, did not gave the information about the patient code, therefore it was impossible to assess the re- incidents, each register was then handled as a new case.

The demographic data used was the result of the 2001 National Census, and was provided by the INE. A Census is an inquiry, theoretically performed to the universe of individuals living in a certain country, that provides demographic and socioeconomic information about the conditions of life of the habitants. In Portugal, these Censuses are of the responsibility of the INE and are made with ten years intervals, and the 2001 data is the more recent data available for the country. The demographic database contained the number of people living in each Concelho, grouped by gender and by 5 years age groups.

3.1.2. Maps

The digital maps of administrative limits were produced by the INE.

3.1.3. Softwares

The GIS software used was the ArcView ™ 8.3 and the statistical package S-Plus™ and SPSS™ as well as the free packages Crimestat and GeoDa to perform the spatial statistics.

In the handling of the databases, as well as a supporting tool it were also used the ACCESS™ database and EXCEL™.

3.2. Methods

3.2.1. Data Manipulation

The first step of data manipulation was the classification of each case to the following age groups: 0 to 14 years old, 15 to 24 years old, 25 to 39 years old, and form the age of 40 onward groups of five years old. The age groups were constructed considering the fact that the osteoporotic incidence rate increases with age (Dennison and Cooper 2000), starting with low rates in children and young adults and suffering an exponential increase after the age of fifty (O'Neill and Roy 2003). Therefore the age groups were constructed in order to capture the children and young adults in only three groups were the rates do not differ, and from the age of fifty on more were created in order to assess the possible differences between age groups.

The data manipulation consisted also in the process of georeferencing, selection and analysis of the data.

3.2.1.1. Georeferencing

The registers of the National Hospital Inpatients Data Register were georeferenced introducing new fields in the data registers containing the code of *freguesias*, *concelhos* and *distritos*, that are the administrative hierarchical units used in Portugal. The small unit used in the georeferencing was the *freguesia* and the largest the districts, however not all the internment episodes, i.e., not all the registers presented the field of *freguesia* filled on, and there are also cases in which this field was not correctly filled (e.g. names of non existent *freguesias*).

The "product" of the georeferencing were classified in three groups: the exact, the approximated and the non-georeferenced.

The cases in which the georeference was exact, were the ones were the fields of territorial units were filled on correctly, i.e., the name of the freguesia was a valid one in the concelho and distrito referred. In these cases the correspondent code was introduced.

There were two situations where the georeferencing was considered approximate because the field of territorial unit was not correctly filled; the methodology used is described in the following paragraphs.

The cases in which the field of *freguesia* was not correctly filled on (the name of the *freguesia* was the same as the name of *concelho* and it didn't correspond to a valid name for *freguesias*); in these cases the methodology used was:

If in the corresponding *concelho* existed *freguesias*, whose names contained the name of the *concelho* (e.g., the *concelho* Setúbal contains *freguesias* with names such as Setúbal (Santa Maria da Graça) and Setúbal (N. Sra da Anunciada)), then the cases were divided by the *freguesias* in this condition;

If not, then the cases were distributed by the central *freguesias* with more resident population.

And the cases where the field of freguesia was not filled, only the field of *concelho*; in these cases the methodology used was:

The cases were distributed by the central *freguesias* with more resident population.

Finally, the cases that were considered non georeferenced were the ones that none of the fields *freguesias*, *concelhos* and *distritos* were filled and the ones were only the field *distrito* was filled, no *freguesia* was allocated, in these cases the georeference was not possible and the cases were discarded.

3.2.1.2. Selection of the different Femur Fractures

In the this section it will be exposed the methodology used in the selection of the different type of femur fractures, types based on different causes or based on different sites where the fracture occurred within the femur.

- Selection of the fractures by cause

It was done a selection considering different causes; it were selected the fractures caused by traffic accidents and the fractures caused by falls, as represented in the figure 3.1.

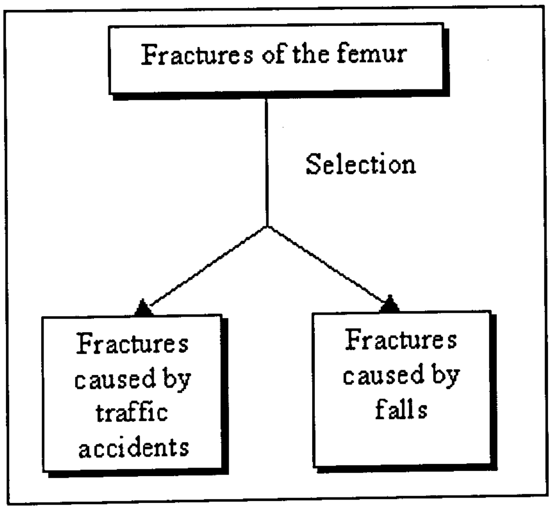

Figure 3.1 - Schematic view of the process of selecting the fractures according to the cause.

The selection of the cases where the femur fracture was caused by traffic accidents was done using the variables Cause of Admission. It were considered all the cases with codes E 810-E 819 (Motor Vehicle Traffic Accidents) and derivates, in the first three causes of admission.

The selection of the cases where the femur fracture was caused by falls was preformed in a way similar to the previously one, also using the variables Cause of Admission. It were considered all the cases with codes E 880-E 888 (Accidental Falls) and derivates in the first three causes of admission.

The objective of this selection was comparing the patients profile in both causes, in order to assess differences if such differences existed.

- Selection of the fractures by places where the fracture occurred within the femur

It was done a selection of the cases considering the place where the fracture occurred within the femur, it was divided in two parts: the neck (proximal femur) and other parts rather than the neck. Previous to this selection were done other two selections. It were selected the cases were the cause was low trauma and the patients over fifty years of age or more. A scheme of such selections is presented in figure 3.2.

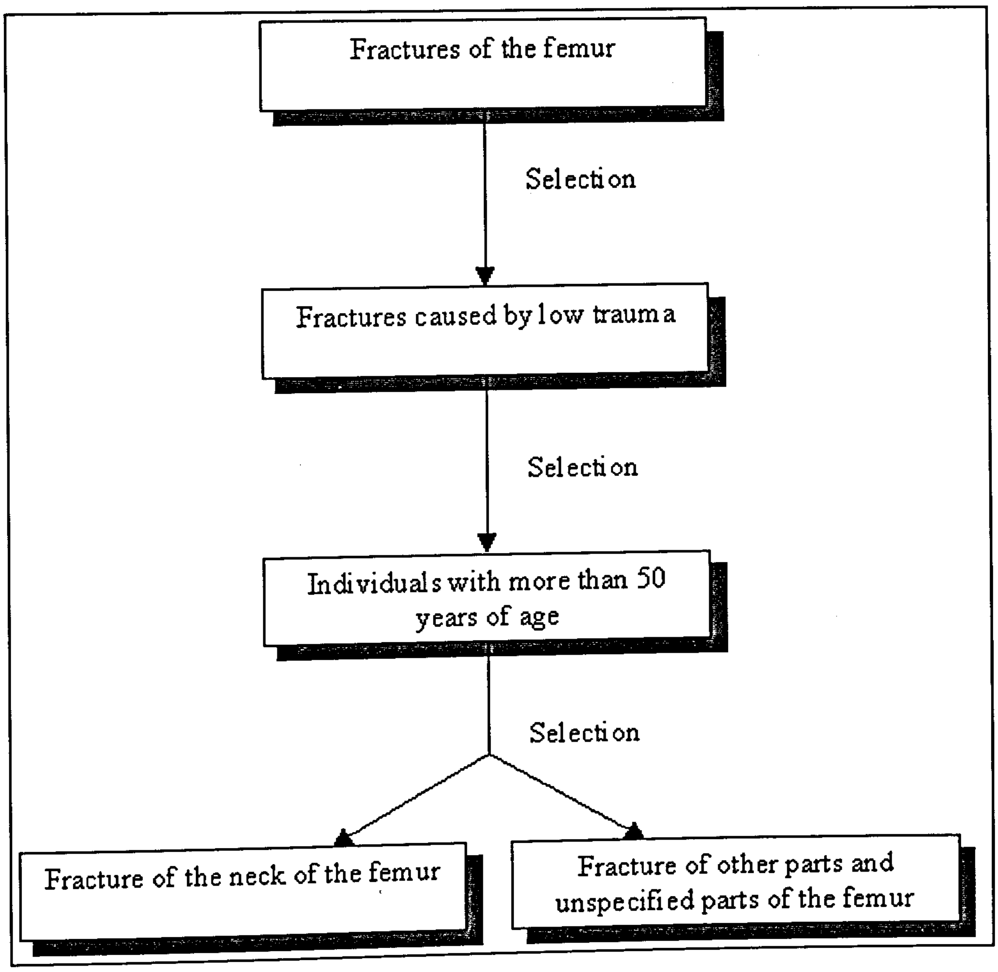

Figure 3.2 - Schematic view of the process of selecting the fractures according to the place in the femur.

In the cases were the fracture was caused by low trauma were included the ones which presented codes relative to causes by low impact (table 3.1) in the fist cause of admission. Note that all except two are relative to accidental falls. The ones that are not codes that refer to the place of occurrence; such codes were included because a previous analysis showed cases of hospital that had an unusual short number of cases leading to the possibility of incorrect filling of the field cause of admission.

Table 3.1 – ICD-9-CM codes of low impact

ICD-9-CM CODE	DESIGNATION
E 849.0	Place of occurrence – Home
E 849.7	Place of occurrence –Residential Institution
E 880	Accidental Falls – Fall on or from stairs or steps
E 880.0	Accidental Falls – Fall on or from stairs or steps – escalator
E 880.9	Accidental Falls – Fall on or from stairs or steps – Other stairs or steps
E 881	Accidental Falls – Fall on or from ladders or scaffolding
E 881.0	Accidental Falls – Fall on or from ladders or scaffolding – Fall from ladder
E 884	Accidental Falls – Other fall from one level to another
E 884.2	Accidental Falls – Other fall from one level to another – Fall from chair
E 884.3	Accidental Falls – Other fall from one level to another – Fall from wheelchair
E 884.4	Accidental Falls – Other fall from one level to another – Fall from bed
E 884.5	Accidental Falls – Other fall from one level to another – Fall from other furniture
E 884.6	Accidental Falls – Other fall from one level to another – Fall from commode
E 884.9	Accidental Falls – Other fall from one level to another – Other fall from one level to another
E 885	Accidental Falls – Fall on same level from slipping, tripping, or stumbling
E 885.9	Accidental Falls – Fall on same level from slipping, tripping, or

	stumbling - Fall from other slipping, tripping, or stumbling
E 886	Accidental Falls – Fall on same level from collision, pushing, or shoving, by or with other person
E 886.9	Accidental Falls – Fall on same level from collision, pushing, or shoving, by or with other person – Other and unspecified
E 887	Accidental Falls – Fracture, cause unspecified
E 888	Accidental Falls – Other and specified fall
E 888.0	Accidental Falls – Other and specified fall – Fall resulting in striking against sharp object
E 888.1	Accidental Falls – Other and specified fall – Fall resulting in striking against other object
E 888.8	Accidental Falls – Other and specified fall – Other fall
E888.9	Accidental Falls – Other and specified fall – Unspecified fall

The selection of the cases with fractures in the neck of the femur was performed using the variables Admission Diagnostic. It were considered all cases with codes 820 (Fracture of neck of femur) and derivates in all the 20 fields relative to admission diagnostic.

The selection of the cases with fractures in other parts or unspecified parts of the femur was performed, similarly with the previously one, using the variables Admission Diagnostic. It were considered all cases with codes 821 (Fracture of other and unspecified parts of femur) and derivates in all the 20 fields relative to admission diagnostic.

From these cases were also removed the individuals with bone cancer, codes: 170 (Malignant neoplasm of bone and articular cartilage) and derivates, and 171 (Malignant neoplasm of connective and other soft tissue) and derivates. Because the database did not contemplated a code for each patient it was impossible to remove all the re incidents, however it was possible to identify and remove the ones that were coded by 996.4 (Complications peculiar to certain specified procedures – Mechanical complication of internal orthopaedic device, implant, and graft) and V54 (Other orthopaedic aftercare) and derivates. It were also removed the cases of Madeira and Azores Archipelagos because at the time of receiving the data the information about all insular cases was not complete, therefore it was decided that the few cases present in the database concerning the Portuguese islands was not to be object of the study.

After these filters of the database, it were obtain the cases that can be considered indicators of osteoporosis: the ones with fracture of the neck of the femur caused by low impact and occurring in individuals with more than 50 years old (Center and Eisman 1997; Dennison and Cooper 2000; Walker-Bone, Dennison et al. 2001). As well as cases with fractures in other but unspecified parts of the femur caused by low impact trauma and occurring in individuals with more than 50 years of age. The objective of obtaining such cases was comparing the patients profile in both groups, in order to assess differences if such differences existed.

3.2.2. Analysis

The analysis started by exploring the data of all the cases of femur fractures and in the several groups created by the selections exposed in the previous section.

It were calculated the statistical measures of several variables presented in the database, and exploring the differences between groups created by some variables (e.g. the differences between the number of cases in each year or the differences of the number of femur fractures between both sexes, these differences were assessed by the Chi-Square to test the proportions in three groups, Binomial to test the proportions in two groups and Independent Sample T-Test to test the means in two groups). It was also calculated the Spearman coefficient, in order to access the correlation between the total days of internment and the total cost, this coefficient was used because the variables were not normal distributed (accessed by the Kolmogorov – Smirnov).

The data were also submitted to the calculation of epidemiological indicators such as the correspondent direct age standardized incidence rates for the country or NUT II (NUTS – Nomenclature of Territorial Units for Statistics), used in Countries Members of European Union, these regions present three levels, in Portugal the NUT II, "divides" the country in five regions: Norte, Centro, Lisboa and Tejo Valley, Alentejo and Algarve). And the cases fatality rates for both sexes. In this task the GIS were used as a simple visualizing tool to explore the data.

The only analysis that evolved into a more complex one was just that performed in the fractures which can be attributed to osteoporosis, enclosing not only the usual exploratory analysis used before, but also the spatial methods. The reason for this was that the objective was centred in this kind of fractures, therefore a more "deep" analysis in the other groups was out of the scope of this work.

The exploratory analysis consisted in the calculation of some statistical measures of a few variables presented in the IGIF database.

Some epidemiological indicators were calculated, manly the direct age and sex standardized rates, for each Concelho, using the age groups created previously. The direct method was preferred to the indirect one in order to obtain a more reliable comparison between different geographical areas as exposed in chapter 2, section 2.1 (Epidemiology). To diminish the problem of the small numbers, described in chapter 2, section 2.4 (Spatial Statistics) it was used the Bayesian approach, described in the same section and the local empirical bayesian rates (EB) to each Concelho were calculated.

It was developed an ESDA, to identify if there were some spatial clusters of areas (*concelhos*) with similar incidence rates, that is, if there is some spatial dependency between the geographical areas. To achieve the objective it were used spatial statistical methods as well as GIS. The indicator used to measure the spatial dependency was Moran's I (described in chapter 2, section 2.4 (Spatial Statistics)), the Moran's scatter plot was used to visualize the relation between the rates of each Concelho and the rates of its correspondent neighbors. It was builted a Moran map with the significance values (also described in chapter 2, section 2.4 (Spatial Statistics)).

Bibliography

Assessment, O T (1983). Diagnosis Related Groups (DRG's) and the Medicare Program: Implications for Medical Technology - A Technical Memorandum. Washington, DC, U S Congress.

Center, J and J Eisman (1997). "The epidemiology and pathogenesis of osteoporosis." Bailliéres Clinical Endocrinology and metabolism **11**(1): 23-62.

Dennison, E and C Cooper (2000). "Epidemiology of Osteoporotic Fractures." Hormone Research **54**: 58-63.

O'Neill, T W and D K Roy (2003). "The epidemiology and scale of the problem." Hospital Medicine **64**(9): 517-520.

Queirós, A J A V (2000). Sub-Notificação dos Acidentes de Trabalho. Faculdade de Medicina. Coimbra, Universidade de Coimbra: 103.

Walker-Bone, K, E Dennison, et al. (2001). "Epidemiology of Osteoporosis." Rheumatic Disease Clinics of North American **27**: 1-18.

4. Results

4.1. Exploratory Data Analysis Results

4.1.1. Femur Fractures

The initial IGIF database had a total of 36 846 cases, that were distributed through the period of three years (2000-2002) in the following way: the cases in the year 2000 represented a total of 33%, the cases in the year 2001 a total of 34,1%, whereas the cases in the year 2002 represented a total of 32,9% of all the cases in the database. It was assessed if the proportions in the years could be considered different by the Chi-Square test, these differences proved to be statistically significant at 0,01 level. The cases of femur fractures were distributed by gender in the way presented in table 4.1, where it is also presented such distribution considering the different years.

Table 4.1 - Distribution of the femur fracture cases by gender, considering the different years.

Year	Sex	Number of cases (%)	Crude rate (per 100 000)
2000-2002	**Male**	12 892 (35%)	257
	Female	23 954 (65%)	447
2000	**Male**	4320 (35,6%)	86
	Female	7822 (64,4%)	146
2001	**Male**	4433 (35,2%)	88
	Female	8144 (64,8%)	152
2002	**Male**	4139 (34,1%)	82
	Female	7988 (65,9%)	149

It was also assessed the differences between the proportion of male and female cases considering the entire period. This difference was assessed by the Binomial Test that showed to exist statistical differences at 0,01 level.

During the process of georeferencing, it were created three categories of georeferencing: the exact, the approximate and the non-georeferenced. The percentage of cases in each category is displayed in the following table (table 4.2).

Table 4.2 - Distribution of the femur fracture cases by the three categories of georeference.

	Percentage
Exact	97,2
Approximated	2,1
Non-georeferenced	0,7

Some statistical indicators concerning the age, are presented in table 4.3, whereas in figure 4.1 are displayed the box-plots.

Table 4.3 - Some statistical measures of the distribution of the variable age (femur fractures).

	Mean Age (Years)	Standard Deviation (Years)
All Cases	69,1	23,3
Male	54,9	27,4
Female	76,7	16,2

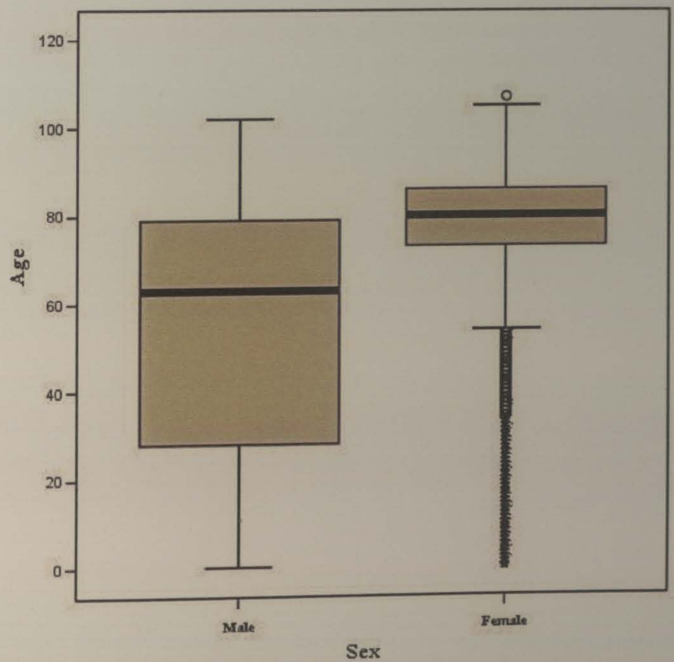

Figure 4.1 - Box-plots of age for both sexes (femur fractures).

The differences in the variable age in both sexes were assessed by the Independent Sample t-Test, that proved to have statistical significant differences at 0,01 level.

The following figure (figure 4.2) presents three graphs of distribution of the femur fractures by age, showing accentuated differences by sex.

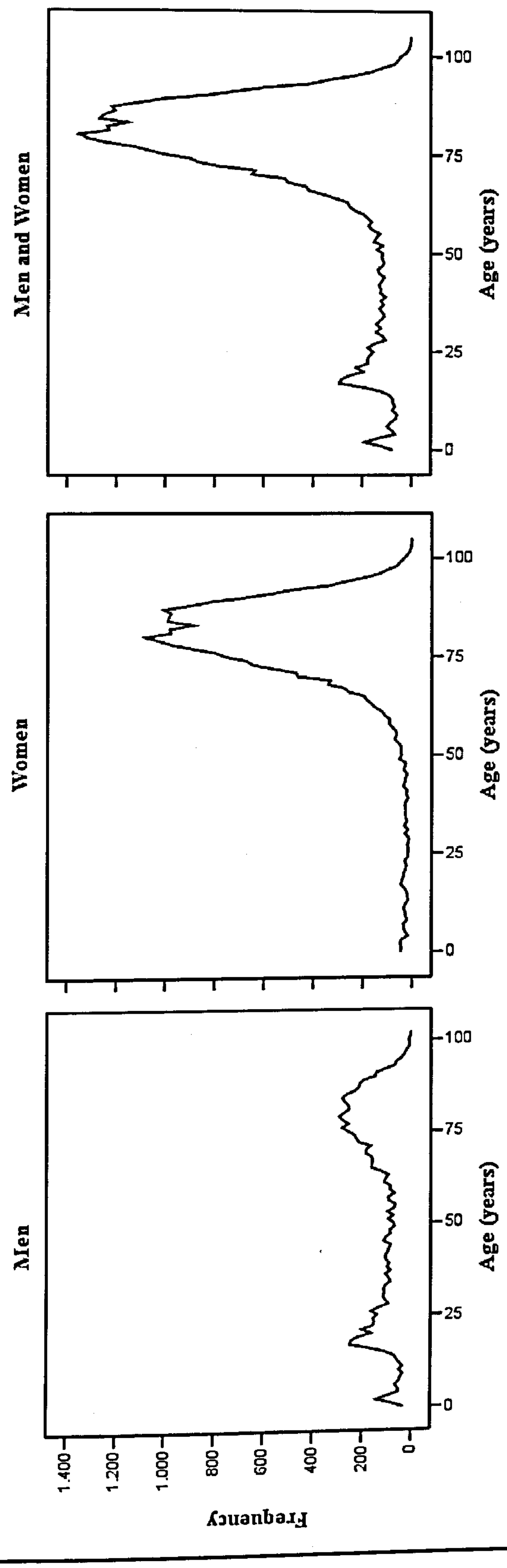

Figure 4.2 - Distribution of the femur fractures by age (femur fractures)

The results of the analysis performed in the variables: number of days of remaining in the hospital and the cost of the internment episode are summarized in the next tables, which present the mean, standard deviations and medians (as well as sum for the variable cost) (tables 4.4 and 4.5).

Table 4.4 - Some statistical measures of the distribution of the total of days of internment (femur fractures).

	Mean (Days)	Standard Deviation (Days)
All Cases	16,7	17,0
Male	17,3	19,5
Female	16,3	15,5

Table 4.5 - Some statistical measures of the distribution of the costs per internment (femur fractures).

	Sum (Euros)	Mean per year (Euros)	Mean per patient (Euros)	Standard Deviation per patient (Euros)
All Cases	185 284 412,6	61 761 470,9	5028,6	2901,8
Male	62 211 302,3	20 737 100,8	4825,6	3316,9
Female	123 073 110,3	41 024 370,1	5137,9	2645,2

It were assessed the differences in the variables total days and costs of internment in both genders, through the Independent Sample t-Test. This test proved that the differences are statistically significant at 0,01 level.

The correlation coefficient Spearman's rho correspondent to the variables total of days of internment and cost, using both sexes was 0,429, significant at the significance level of 0,01.

When calculating the Spearman's rho coefficient of the same variables by gender the values were for male and female sex, respectively 0,536 and 0,362, both significant at the significance level of 0,01.

In the next figure (figure 4.3) are displayed the average days and costs of internment by municipality.

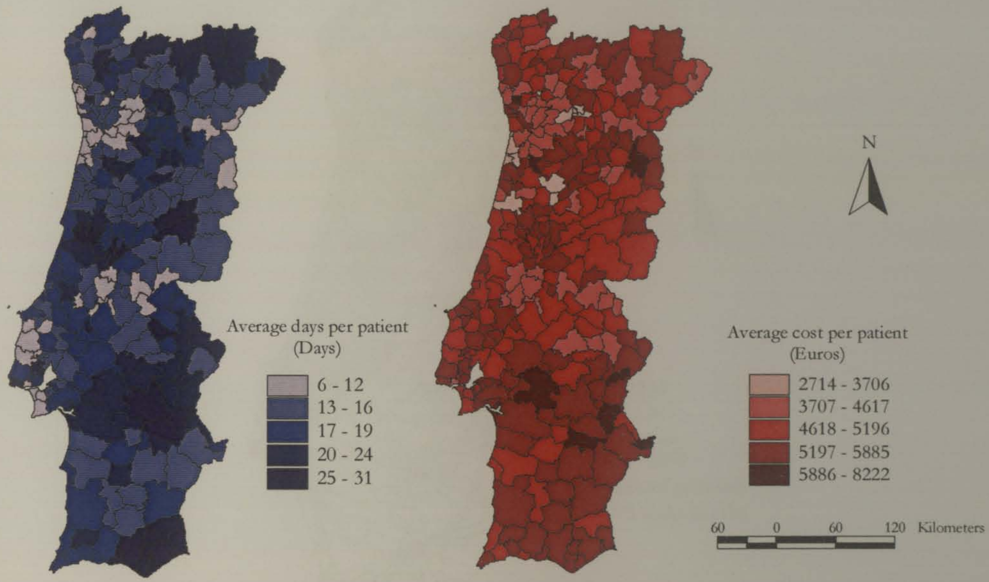

Figure 4.3 – Map of the municipality average days and costs of femur fracture by patient, 2000-2002.

In the database were present 92 different hospitals and figure 4.4 displays their location with a circle proportional to the number of cases attributed to each one (it were not mapped the hospitals with less than 5 cases). In this figure is also displayed the flux of patients from place of residence to the hospitals, it were only mapped the hospitals that received more than five cases.

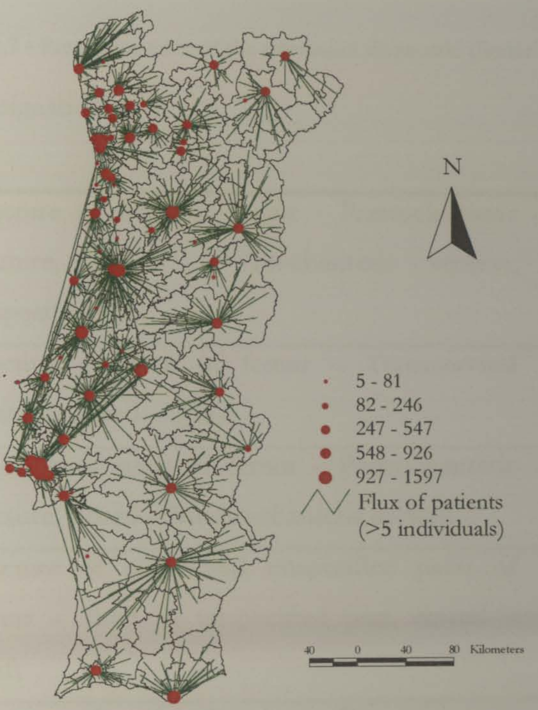

Figure 4.4 – Map of flux of patients with femur fracture: place of residence to hospital of admission, period 2000-2002

The five more frequent causes of admission are displayed in table 4.6.

Table 4.6 - Frequency table of the first cause of admission (femur fractures).

ICD-9-CM	Designation	Relative frequency (%)
E 888	Accidental Falls – Other and unspecified fall	64,2
E 819.9	Motor vehicle traffic accident – Unspecified person	7,2
E 885	Accidental Falls – Fall on same level from slipping, tripping, or stumbling	6,7
E 887	Accidental Falls – Fracture, cause unspecified	3,3
E 849.0	Place of occurrence -Home	2,8

The five more frequent admission diagnostics are displayed in table 4.7.

Table 4.7 - Frequency table of the admission diagnostic (femur fractures).

ICD-9-CM	Designation	Relative frequency (%)
820.20	Fracture of neck of femur - Pertrochanteric fracture, closed – Trochanteric section, unspecified	19,8
820.09	Fracture of neck of femur – Transcervical fracture, closed – other	18,2
820.21	Fracture of neck of femur - Pertrochanteric fracture, closed – Intertrochanteric section	17,1
821.01	Fracture of other and unspecified parts of femur – Shaft or unspecified part, closed – Shaft	9,2
820.22	Fracture of neck of femur - Pertrochanteric fracture, closed – Subtrochanteric section, unspecified	4,7

In table 4.8 are displayed the different destinations of patients after living the hospital, and the respectively percentages of cases.

Table 4.8 - Distribution of the femur fracture cases by the destination after release.

	Percentage
Home	84
Other institution with internment service	9,3
Decease	5,6
Without doctor approval	0,9
Nursing home care	0,3

4.1.2. Femur Fractures caused by Traffic Accidents and by Falls

The number of cases of femur fractures caused by traffic accidents was 5285 that correspond to about 14 percent of all the fractures, whereas the number of femur fractures caused by fall was 28 923, that correspond to about 78,5 % of the total of fractures. It was performed a Chi Square Test in order to assessed the differences of the proportion in the three years of study, for both causes, both tests showed existence of statistically significant differences at the 0,01 level.

In the following table (table 4.9) is displayed the distribution of the cases considering both causes of admission and both genders by year.

Table 4.9 - Distribution of the femur fracture cases, by gender and cause of admission, considering the different years (traffic accidents and falls).

Year		Sex	Number of cases (%)
2000-2002	**Traffic Accidents**	**Male**	4037 (76,4%)
		Female	1248 (23,6%)
	Falls	**Male**	7709 (26,7%)
		Female	21 214 (73,3%)
2000	**Traffic Accidents**	**Male**	1431 (75,3%)
		Female	470 (24,7%)
	Falls	**Male**	2451 (26,9%)
		Female	6675 (73,1%)
2001	**Traffic Accidents**	**Male**	1357 (76,8%)
		Female	409 (23,2%)
	Falls	**Male**	2697 (26,9%)
		Female	7318 (73,1%)
2002	**Traffic Accidents**	**Male**	1249 (77,2%)
		Female	369 (22,8%)
	Falls	**Male**	2561 (26,2%)
		Female	7221 (73,8%)

Through the Binomial Test it was assessed the difference in the proportion of cases in both sexes. This test was performed in both causes and showed statistical significant differences at 0,01 level.

The summary of some statistical indicators concerning the age, are presented in table 4.10. Whereas in figures 4.5 and 4.6 are displayed the box-plots for both genders.

Table 4.10 - Some statistical measures of the distribution of the variable age (traffic accidents and falls).

		Mean Age (Years)	Standard Deviation (Years)
All Cases	**Traffic Accidents**	34,4	21,2
	Falls	75,8	16,8
Male	**Traffic Accidents**	32,1	18,8
	Falls	67,4	23,1
Female	**Traffic Accidents**	41,9	26,4
	Falls	78,9	12,4

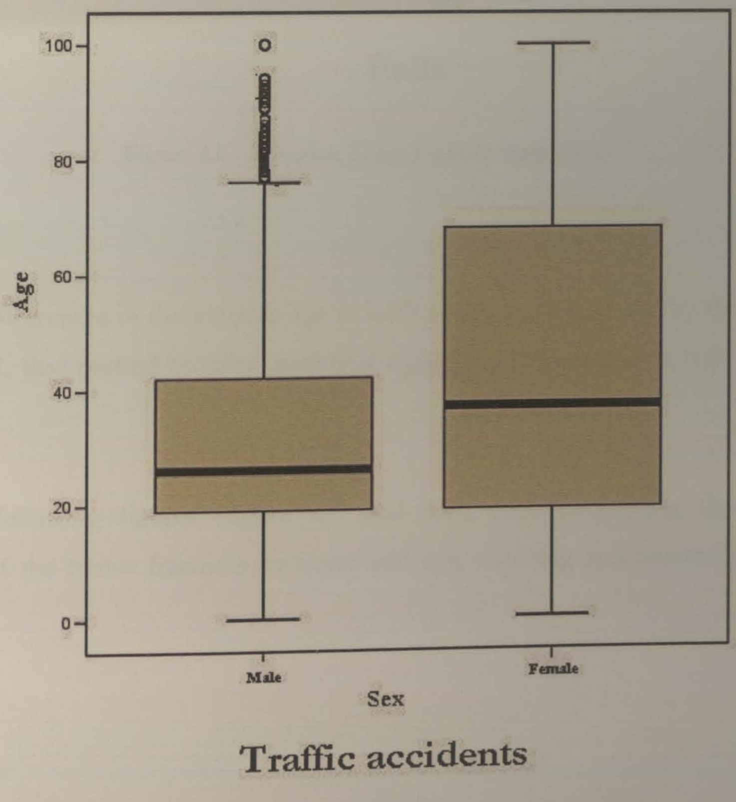

Figure 4.5 – Box-plots of age for both sexes (traffic accidents).

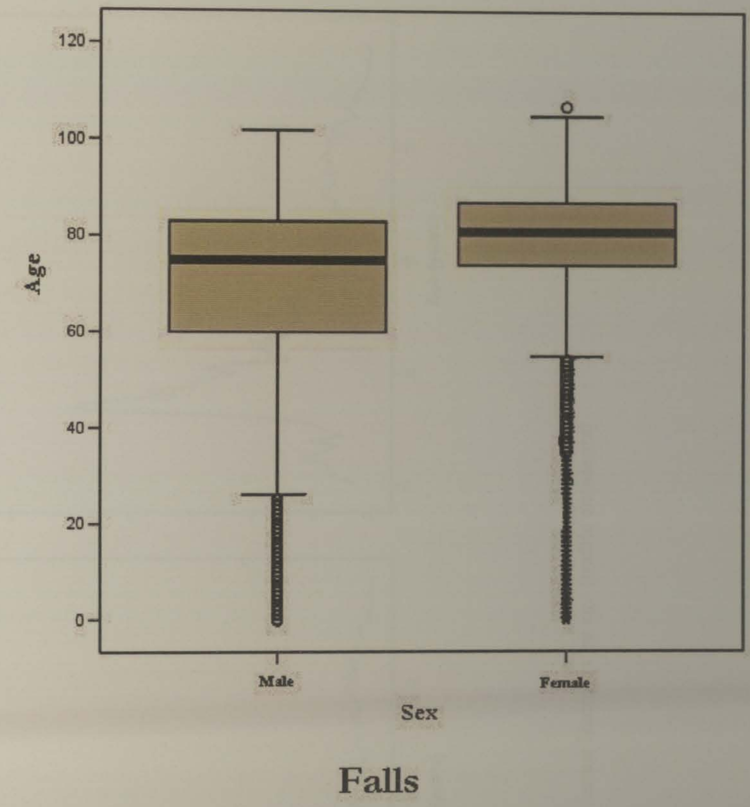

Figure 4.6 - Box-plots of age for both sexes (falls).

The differences in the variable age in both sexes, were assessed by the Independent Sample t-Test, that proved to have statistical significant differences at 0,01 level in both causes.

The following figures (figure 4.7 and 4.8), each presenting three graphs of distribution of the femur fractures by cause and age, showing accentuated differences by sex.

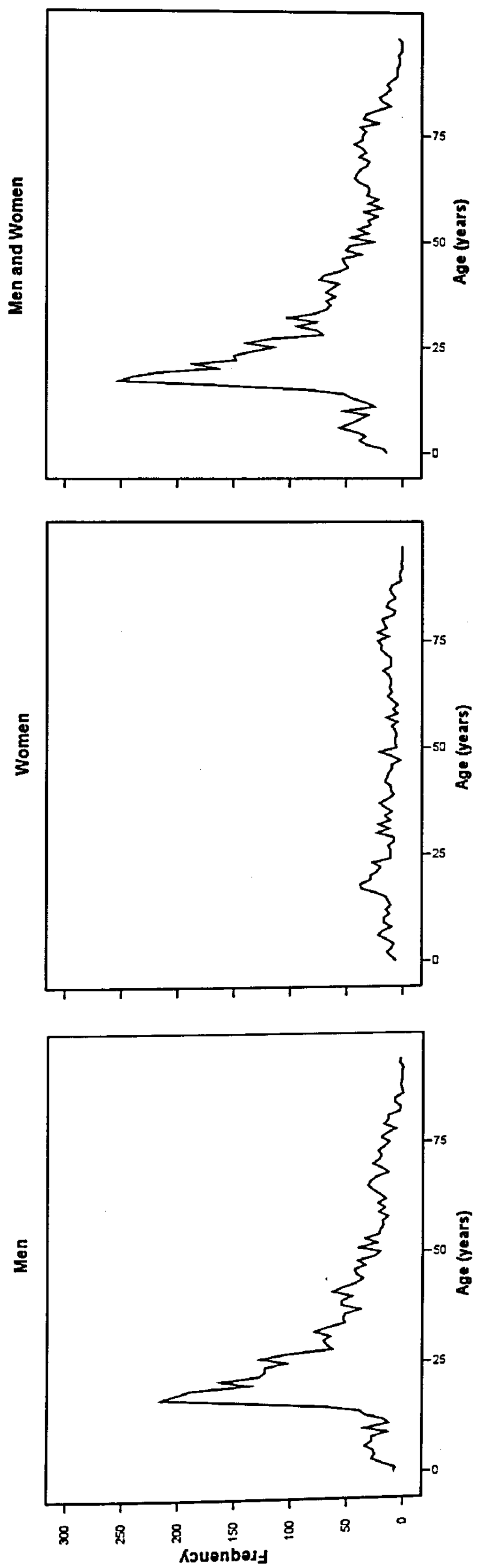

Figure 4.7 - Distribution of the femur fractures by age (traffic accidents)

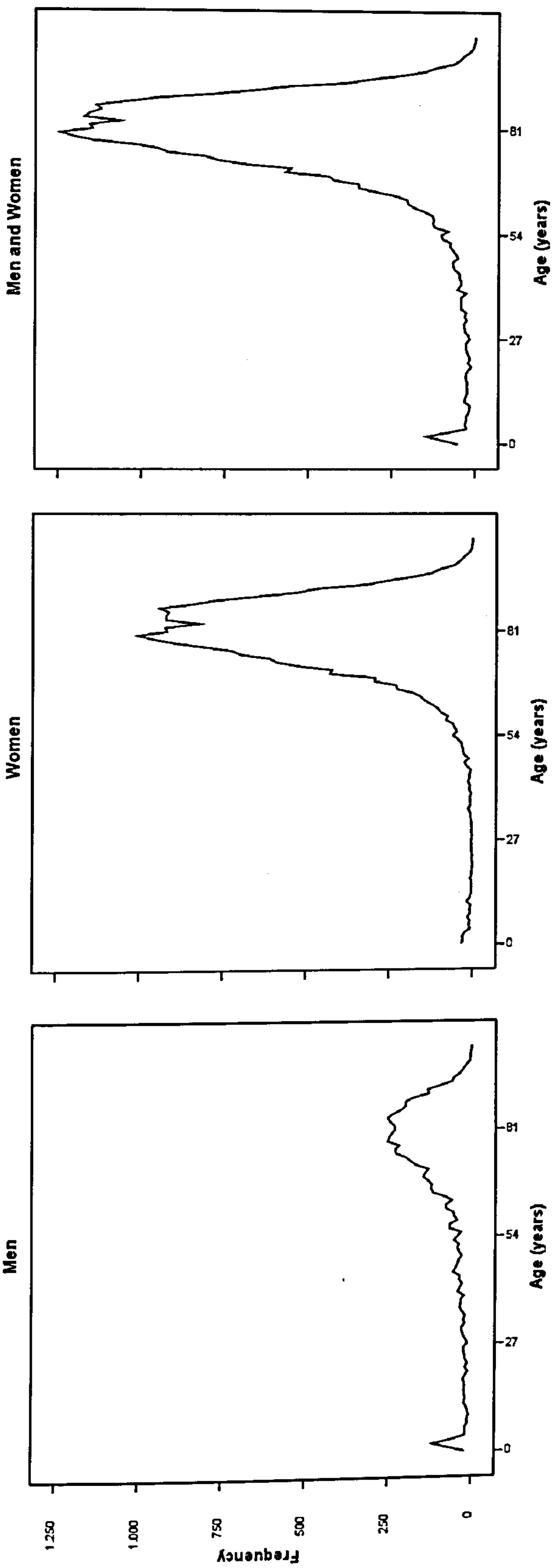

Figure 4.8 - Distribution of the femur fractures by age (falls)

In the following figure (figure 4.9) are displayed the direct age standardized average annual rates for the two causes of admission by NUT (II). Each NUT is colored according to its rate considering both sexes, and presents a graph that shows the rates for male and female patients.

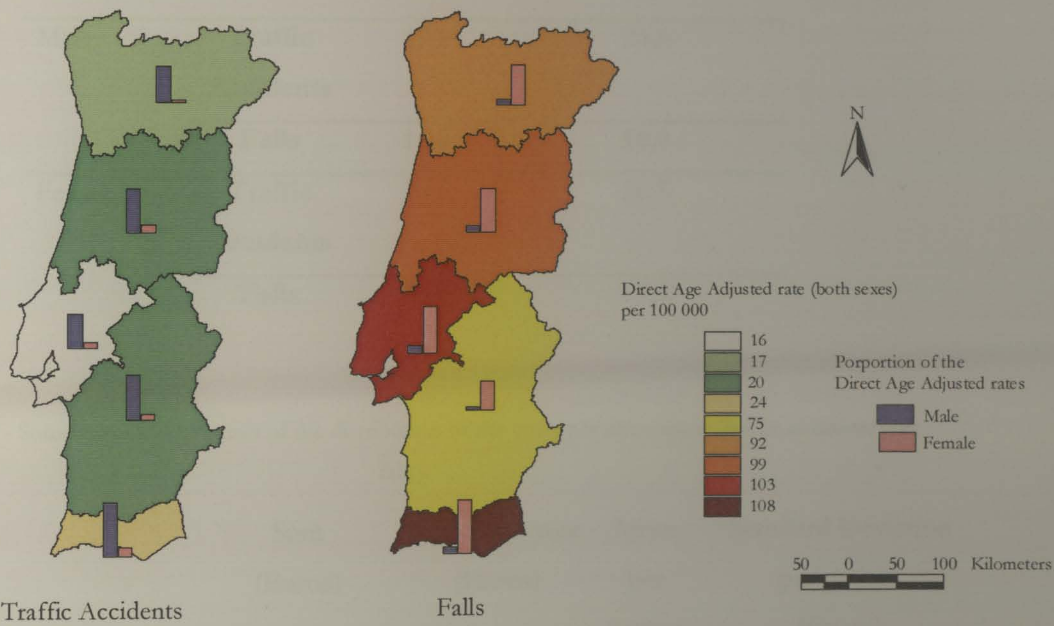

Figure 4.9 – Map of direct age standardized mean annual rates for traffic accidents and falls

In the next two tables are presented the results of the analysis performed on the variables number of days of remaining in the hospital and the cost of the internment episode (tables 4.11 and 4.12, respectively) for both causes.

Table 4.11 - Some statistical measures of the distribution of the total of days of internment (traffic accidents and falls).

		Mean (Days)	Standard Deviation (Days)
All Cases	**Traffic Accidents**	19,5	25,0
	Falls	16,0	14,0
Male	**Traffic Accidents**	19,1	24,6
	Falls	16,4	16,0
Female	**Traffic Accidents**	20,6	26,5
	Falls	15,9	13,1

Table 4.12 - Some statistical measures of the distribution of the costs per internment (traffic accidents and falls).

		Sum (Euros)	Mean per year (Euros)	Mean per patient (Euros)	Standard Deviation per patient (Euros)
All Cases	**Traffic Accidents**	26 801 238	8 933 746	5071,2	4126,1
	Falls	145 982 267	48 66 755,7	5047,3	2592,1
Male	**Traffic Accidents**	20 434 697	6 811 565,7	5061,9	4140,2
	Falls	36 812 398	12 270 799,3	4775,3	2816,2
Female	**Traffic Accidents**	6 366 541	2 122 180,3	5101,4	4081,7
	Falls	109 169 869	36389956,3	5146,1	2498,5

Through the Independent Sample T - Test were assessed the differences of the distributions of the variables total days and costs of internment in both genders. The test showed that there are statistical evidence to state that a difference exist at 0,1 level in the total days of internment of both causes. In the variable cost, in the cases of accidents, no difference can be state at 0,1 level, whereas in the cases of falls there exist statistical evidence to state that a such difference exist at 0,01 level.

The correlation coefficient Spearman's rho correspondent to the variables total of days of internment and cost, using both sexes was 0,66 for the fractures caused by traffic accidents and 0,363 for the fractures caused by falls, significant at the 0,01 level.

When calculating the Spearman's rho coefficient of the same variables but considering the sexes separately, the values are, for male and female sex, respectively 0,664 and 0,646, both significant at 0,01 level, for the fractures caused by traffic accidents. Whereas, the coefficients for both genders (male and female) in fractures caused by falls are, respectively, 0,438 and 0,334, both significant at 0,01 level.

In table 4.13 are displayed the different destinations of patients after living the hospital, and the respectively percentages of cases, for both causes.

Table 4.13 - Distribution of the femur fracture cases by the destination after release (traffic accidents and falls).

		Percentage
Home	**Traffic Accidents**	73,9
	Falls	86,1
Other institution with internment service	**Traffic Accidents**	21,2
	Falls	6,8
Decease	**Traffic Accidents**	3,7
	Falls	5,9
Without doctor approval	**Traffic Accidents**	1,1
	Falls	0,8
Nursing home care	**Traffic Accidents**	0,1
	Falls	0,8

The case fatality rate found for traffic accidents was for male sex 34,7 per 1000, whereas the same rate for falls was 77,7 per 1000. These rates for female sex were, 44,1 per 1000 for the traffic accidents and 52,6 per 1000 for falls.

4.1.3. Femur Fractures in other places of the Femur, rather than the Neck, caused by low trauma and occurring in individuals over 50 years old

After the selection of the cases that present the fracture in other places rather than the neck of the femur, caused by low trauma and with more than 50 years old, the number of cases encounter was 2114, that correspond to about 6% of all femur fractures. From these cases 75,2% were female patients, whereas the remain 24,8% were male patients. In order to assess the differences of proportion in male and female sex, it was performed a Binomial Test, that showed statistically significant differences at the 0,1 level.

The distribution of the cases by years were more or less constant, with the year 2000 representing 32,5% of the cases, the year 2001 32,7%, and finally the year 2002 34,8%. It was performed a Chi Square Test in order to assessed the differences of the proportion in the three years of study. The test showed that it cannot be state the existence of statistically significant differences at the 0,1 level.

Some statistics for the variable age, considering the gender, are displayed in the following table (table 4.14). In figure 4.10 are displayed the box-plots for both sexes.

Table 4.14 – Some statistical measures of the variable age concerning genders (Femur Fractures in Other Places of the Femur, rather than the Neck, Caused by Low Trauma and occurring in Individuals over 50 years old).

	Mean Age (Years)	Standard Deviation (Years)
All Cases	74,5	10,9
Male	69,5	11,0
Female	76,2	10,3

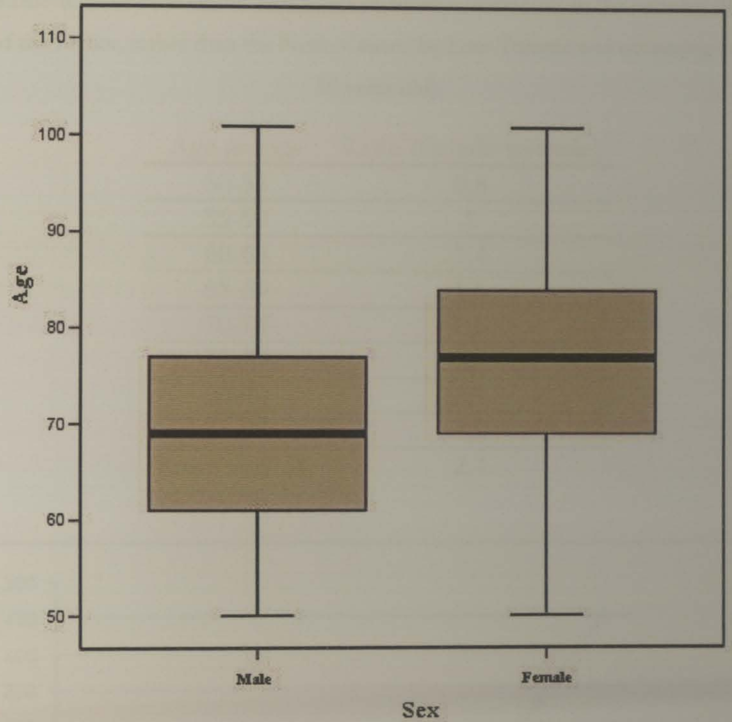

Figure 4.10 – Box-plots of age for both sexes (Femur Fractures in Other Places of the Femur, rather than the Neck, Caused by Low Trauma and occurring in Individuals over 50 years old)

In order to assessed the differences of the variable age in both sexes it was performed an Independent Sample T – Test that showed the existent of such differences at a level of 0,01.

In the following table (table 4.15) are displayed the ratios (Female-to-Male) of the crude cumulative incidence rates of this kind of fractures nationwide, for each age group and in figure 4.11 is represented the evolution of these rates separately for both men and women, considering the age.

Table 4.15 - Female-to-Male ratio of the cumulative incidence crude rates in the country (Femur Fractures in Other Places of the Femur, rather than the Neck, Caused by Low Trauma and occurring in Individuals over 50 years old).

Age groups	Ratio (female-to-male)
50-54	0,8
55-59	1
60-64	1,4
65-69	1,6
70-74	2,6
75-79	2,7
80-84	3,1
85-90	4,2
More than 90	2,4

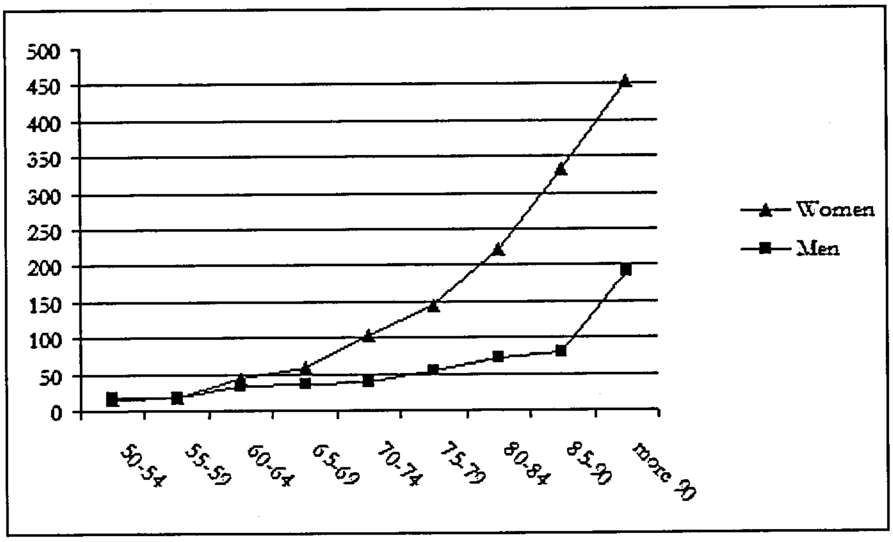

Figure 4.11 - Cumulative incidence rate for both sexes (Femur Fractures in Other Places of the Femur, rather than the Neck, Caused by Low Trauma and occurring in Individuals over 50 years old).

The results of the analysis performed in the variables: number of days of remaining in the hospital and the cost of the internment episode are summarized in the next tables, for these kinds of fractures (table 4.16 and 4.17).

Table 4.16 - Some statistical measures of the distribution of the total of days of internment (Femur Fractures in Other Places of the Femur, rather than the Neck, Caused by Low Trauma and occurring in Individuals over 50 years old).

	Mean (Days)	Standard Deviation (Days)
All Cases	20,0	19,2
Male	21,5	23,3
Female	19,5	17,7

Table 4.17 - Some statistical measures of the distribution of the costs per internment (Femur Fractures in Other Places of the Femur, rather than the Neck, Caused by Low Trauma and occurring in Individuals over 50 years old).

	Sum (Euros)	Mean per year (Euros)	Mean per patient (Euros)	Standard Deviation per patient (Euros)
All Cases	8 858 707,0	2 952 902,3	4190,5	2285,6
Male	2 320 202,7	773 400,9	4419,4	2867,7
Female	6 538 504,3	2 179501,4	4114,9	2053,6

The differences between both sexes in the distributions of the variables total days and costs were assessed by the Independent Sample T- Test, in both causes it can be state evidences of statistical significant differences at 0,1 level.

The correlation coefficient Spearman's rho correspondent to the variables total days of internment and cost, using both sexes was 0,516, significant at the significance level of 0,01.

When calculating the Spearman's rho coefficient of the same variables by gender, the values are for male and female sex, respectively, 0,534 and 0,508, both significant at the significance level of 0,01.

In table 4.18 are displayed the different destinations of patients after living the hospital, and the respectively percentages of cases.

Table 4.18 - Distribution of the femur fracture cases by the destination after release (Femur Fractures in Other Places of the Femur, rather than the Neck, Caused by Low Trauma and occurring in Individuals over 50 years old).

	Percentage
Home	86,6
Other institution with internment service	7,2
Decease	4,9
Without doctor approval	0,9
Nursing home care	0,4

The case fatality rates encountered for these fractures were respectively for male and female sex, 57,1 and 46,6 per 1000.

4.1.4. Fractures in Proximal Femur caused by low trauma and occurring in individuals over 50 years old

After the selection of the proximal femur fractures that can be attributed to osteoporosis in Continental Portugal and after removing the patients with cancer and the re-incidents, the number of cases was 25 604, that represent about 70% of all femur fractures. From these cases 77,1% were female patients, whereas the remain 22,9% were male patients. In order to assess the statistical significance of such proportion it was performed a Binomial Test that showed differences at the 0,01 level.

The percentage of cases were distributed by the years of period in the following way: 31,9% happened in the year 2000, 34,5% in the year 2001 and the remain 33,6% in the year 2002. In order to assess the statistical significance of such proportions it was performed a Chi-Square test that showed differences at the 0,01 level.

Some statistics for the variable age, considering the gender, are displayed in the following table (table 4.19). In figure 4.12 are displayed the box-plots for both genders.

Table 4.19 - Some statistical measures of the variable age concerning the gender (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old)

	Mean Age (Years)	Standard Deviation (Years)
All Cases	79,9	9,0
Male	77,7	10,0
Female	80,6	8,6

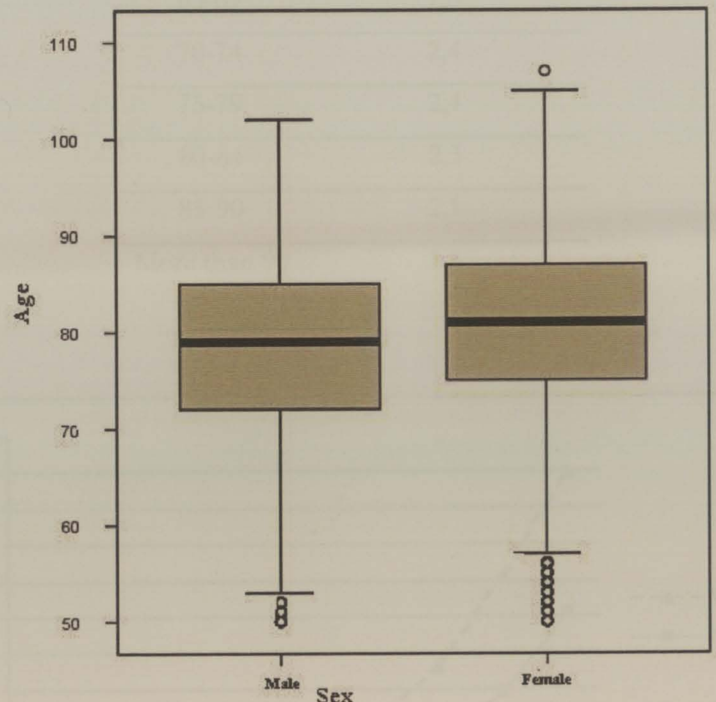

Figure 4.12 – Box-plots of age for both sexes (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

The differences of the variable age in both genders was assessed by the Independent Sample T – Test, that showed the existence of statistical significant differences at 0,01 level.

In the following table (table 4.20) are displayed the ratios (Female-to-Male) of the crude cumulative incidence rates of the osteoporotic femur fractures nationwide, for each age group and in figure 4.13 is represented the evolution of these rates separately for both men and women, considering the age.

Table 4.20 - Female-to-Male ratio of the cumulative incidence crude rates in the country (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

Age groups	Ratio (female-to-male)
50-54	0,9
55-59	1,2
60-64	1,6
65-69	1,6
70-74	2,4
75-79	2,4
80-84	2,3
85-90	2,1
More than 90	1,8

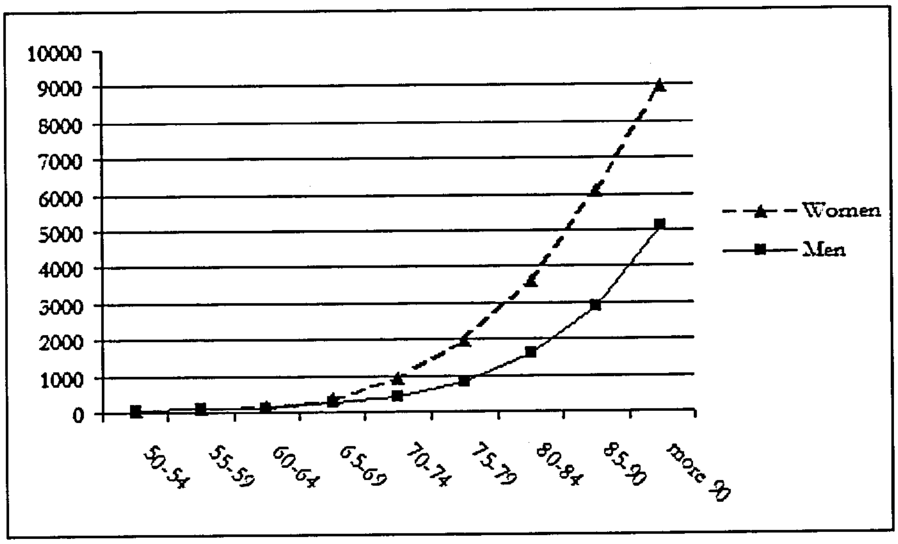

Figure 4.13 - Cumulative incidence rate for both sexes (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

In the following figure (figure 4.14), are displayed the Female-to-Male ratios by NUT (II) of the direct age standardized cumulative rates.

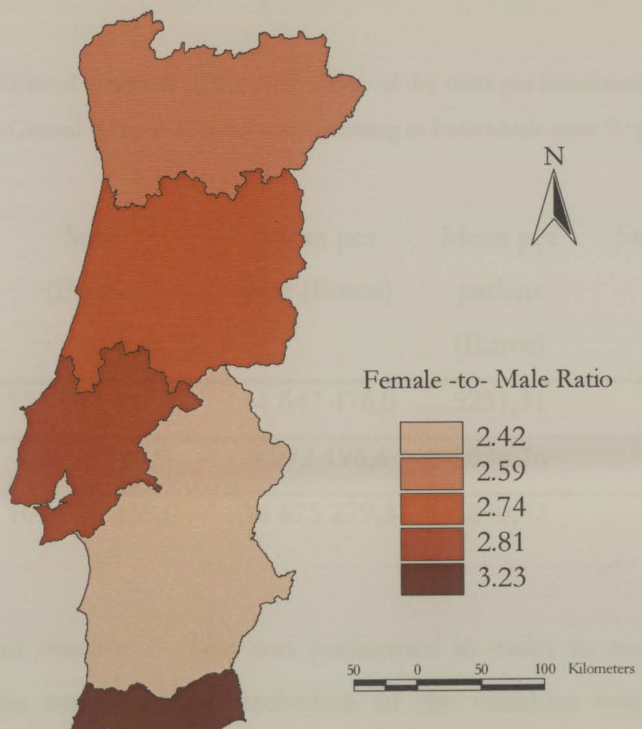

Figure 4.14 – Map presenting the female-to-male ratio of the direct age standardized cumulative rates by NUT's II (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

The results of the analysis performed in the variables: number of days of remaining in the hospital and the cost of the internment episode are summarized in the next tables (tables 4.21 and 4.22, respectively).

Table 4.21 - Some statistical measures of the distribution of the total of days of internment (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

	Mean (Days)	Standard Deviation (Days)
All Cases	15,90	12,87
Male	16,61	14,27
Female	15,68	12,42

Table 4.22 - Some statistical measures of the distribution of the costs per internment (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

	Sum (Euros)	Mean per year (Euros)	Mean per patient (Euros)	Standard Deviation per patient (Euros)
All Cases	133 942 427,9	44 647 476,0	5231,31	2540,41
Male	29 916 589,9	9 972 196,6	5098,26	2709,27
Female	104 025 838,0	34 675 279,3	5270,87	2486,70

Independent Sample T- Test was performed in order to assess the existence of differences between sexes in the distribution of the variables total days and costs of internment. The tests showed statistical significant differences in both variables at 0,01 level.

The correlation coefficient Spearman's rho correspondent to the variables total of days of internment and cost, using both sexes was 0,328, significant at the significance level of 0,01.

When calculating the Spearman's rho coefficient of the same variables for both genders separately, the values were for male and female sex, respectively, 0,364 and 0,318, both significant at the significance level of 0,01.

The five more frequent causes of admission are displayed in table 4.23.

Table 4.23 - Frequency table of the first cause of admission (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

ICD-9-CM	Designation	Relative frequency (%)
E 888	Accidental Falls – Other and unspecified fall	80,7
E 885	Accidental Falls – Fall on same level from slipping, tripping, or stumbling	8,4
E 887	Accidental Falls – Fracture, cause unspecified	3,7
E 849.0	Place of occurrence - Home	3,5
E 884.9	Accidental Falls - Other fall from one level to another	1,1

In table 4.24 are displayed the different destinations of patients after living the hospital, and the respectively percentages of cases.

Table 4.24 - Distribution of the femur fracture cases by the destination after release (Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old).

	Percentage
Home	86,1
Other institution with internment service	6,6
Decease	6,3
Without doctor approval	0,7
Nursing home care	0,4

The case fatality rates encountered for these fractures were respectively for male and female sex, 97,6 and 53,9 per 1000.

The result of the mapping of the Empirical Bayesian (EB) rates is displayed in figure 4.15.

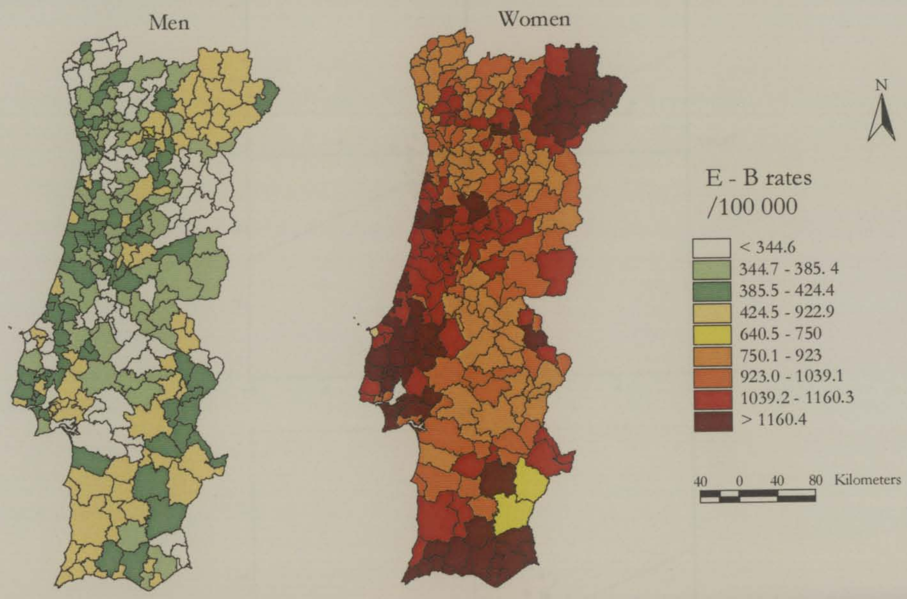

Figure 4.15 – Map of the Empirical Bayesian rates of the Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old, by municipality.

4.2. Exploratory Spatial Data Analysis Results

4.2.1. Fractures in Proximal Femur Caused by Low Trauma and occurring in Individuals over 50 years old

Figure 4.16 displays the Moran's scatter plot of Bayesian rates both sexes as well as all cases independently of the gender, it also displays the Moran's I index of spatial autocorrelation. Whereas figure 4.17 displays the spatial clusters of the cumulative age standardized incidence rates by municipality.

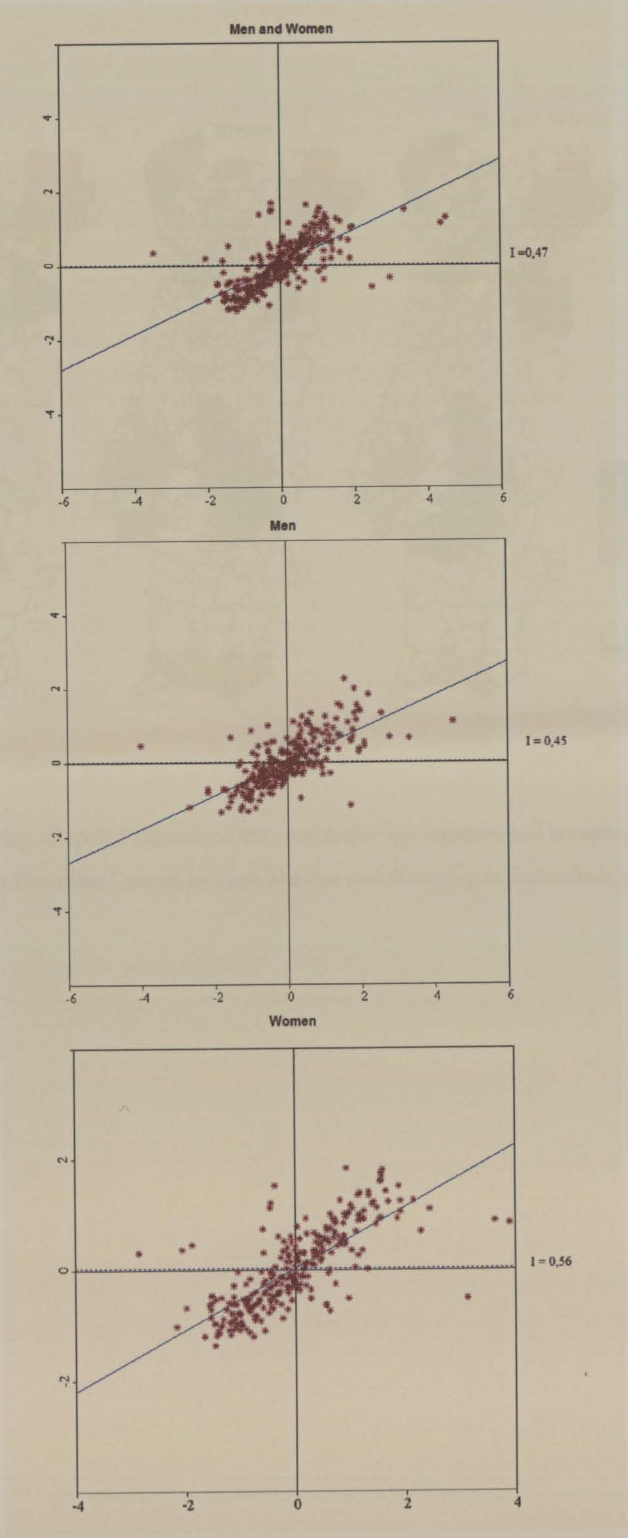

Figure 4.16 – Moran's scatter plot of Bayesian rates (Proximal Femur Fractures Caused by Low Trauma and occurring in Individuals over 50 years old, by municipality).

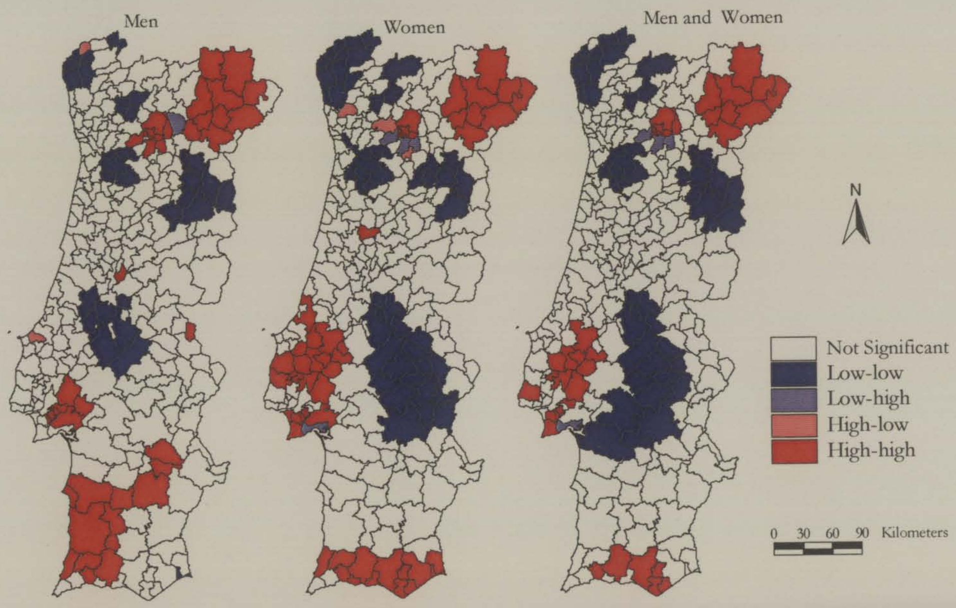

Figure 4.17 – LISA Map of spatial clusters of the cumulative age standardized incidence rates by municipality (Proximal Femur Fractures Caused by Low Trauma and occurring in Individuals over 50 years old)

5. Discussion and Conclusions

5.1. Discussion

According to INE data projection of the population resident in Portugal, the number of people with more than fifty years in the year 2020 will be of 4 329 624 persons, with 1 986 672 men and 2 360 952 women, whereas in the year 2050, the numbers will be 4 669 189 individuals, 2 166 575 being men and 2 502 614 women. Note that according to the population data used in this study (population data of the Census 2000), the Portuguese population with fifty years or more will suffer an increase of about 871 000 individuals in the year 2020, and 1 210 000 of individuals in the years 2050.

Considering the results of this study and making a proportional estimation, if the patterns observed remain, then Portugal will experience 10 684 of individuals with osteoporotic femur fractures in the year 2020 and 11 522 in the year 2050. That will represent a cost to the country of about 55 891 316 Euros in the year 2020 and 60 275 153 Euros in the year 2050 (if the costs with this kind of pathology do not suffer an increase). About 673 will pass away in the year 2020 and 725 in the year 2050 from this pathology.

This study did not assess the percentage of individuals that do or not recover, because it was not possible to obtain information about the patients after their discharge due to the impossibility of tracing them back. However, if applying the results described in some studies cited in the literature (Cooper and Melton III 1996) in Portugal about 3561 people in the year 2020 and 3840 in the year 2050 will become totally dependent in consequence of the fracture.

Note that from the expose the osteoporotic femur fractures will present an even more serious problem of public health in Portugal, not only in terms of financial costs but also in terms of social costs.

5.1.1. Femur Fractures and Proximal Femur Fractures caused by low trauma and occurring in individuals over 50 years old

The great majority of the cases were successfully georeferenced, note that less than one percent of the cases were unable to be georeferenced. However, this does not express a direct association between the quality of the health database, by the contrary the quality of the health databases must be improved. Some problems identified, and that have made the process of georeference more difficult or in same cases even impossible, were for example, the absence of filing the fields of Freguesia, Concelho or Distrito, the incorrect filling with names of non existent Freguesias, the non-use of a unique code for each geographical area, and which would prevent situations of one area being addressed by more than one designation.

The number of cases that can be considered indicator of osteoporosis (proximal femur fractures caused by low trauma in individuals with more than 50 years of age) represented the great majority of the femur fractures, with a percentage of about 70%. This result is in agreement with the facts stated in the literature and that report that the majority of hip fractures result from a fall from standing height or less (Cummings and Melton III 2002), that can be classified as low impact, and that the incidence of Osteoporotic fractures increases sharply after the age of 50 (Lips 1997).

The number of cases of femur fractures suffered a small increase from the year 2000 to the year 2001, however this increase did not hold from the year 2001 to 2002, where the number of cases suffered a small decrease. The fluctuation observed in the number of cases was very small (the differences did not range one and an half percent point), however these differences were considered statistically different. A wider period of time would be needed in order to evaluate the existence of some tendency in the occurrence of femur fractures over the years. The pattern observed suffered an increase from the first year to the second, and a decrease from the second to the third year of study. The same pattern was also present in the proximal femur fractures occurring by low impact and in individuals with more than 50 years.

The distribution of cases of femur fractures, considering the period of time under study (2000/2002), by gender showed a greater number of cases in women, almost the double, than the cases of femur fractures in men (view table 4.1, chapter 4), similar results have been described (Melton III 1999; Walker-Bone, Dennison et al. 2001; Jordan and Cooper 2002). When considering the years separately this pattern still holds, however, if in the men the number of cases consecutively decreases slowly, ranging an overall decrease of little less than one and an half percent point, the cases in women consecutively increases raging an increase of little more than one and an half percent point. In spite, the tendency in both sexes hold through the period of time under study as it was mentioned previously, is not sufficient to evaluate the existence of a tendency.

The differences between the number of patients of both genders, in the proximal femur fractures caused by low trauma and occurring in individuals with more than 50 years of age, is more accentuated than considering all femur fractures, with female patients representing again the great majority of cases, almost 80%. Once again this result is in agreement to the literature, when it states that the occurrence of osteoporotic attributable fractures is more frequent in female than male (Walker-Bone, Dennison et al. 2001). The cause pointed out for this difference is, amongst others, the fact that there are more elderly women than men (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001). In Portugal, the percentage of the female population, with more than 50 years, is about 11 percent higher than male population in the same age group.

The mean age of the patients present in the database was of 69,1 years old, with a standard deviation (SD) of 23,3. When considering the sexes separately, the male patients presented a mean age smaller than the mean present in the female patients (view table 4.3, chapter 4), this difference was confirmed by a statistic test; in addition the male patients present a higher standard deviation than the female sex, which translate a wider dispersion, in average, of the age in male patients than in female patients around their respectively means. Note that the amplitude of the difference between quartile three and one, where 50% of the cases lie, is considerably smaller in female patients than in male ones (figure 4.1, chapter 4).

The patients with proximal femur fractures caused by low trauma and over 50 years old, present a mean age of 79,9 years (SD 9) (table 4.19, chapter 4). The fact that both sexes present different means in age was confirmed through a statistical test that showed the existence of a statistical significant difference. The female patients present a higher mean, in fact all the distribution is higher in female patients (figure 4.12, chapter 4), is perhaps the result of the higher life expectancy of women that result in a higher frequency of women of higher age than men.

In figure 4.2, chapter 4, it is represented the frequency of the femur fractures by the variable age, and it is visible that in female sex the frequency is much bigger around the mean age, presenting a "residual" frequency (in comparison with the frequency present in the mode age, that is around 1000) until the age of 50. In male sex the frequency does not reaches such values, the frequency is more or less constant presenting fluctuations of around 200 and several modes, distributed by the age interval. In the same figure observing the graph of the total patients, it can be identified three modes: one around the age zero, another around the age of 25 years and finally, another around the age of 75. Note also, that this late peak is mostly composed by female patients, whereas the peak in youth is mostly composed by male patients. These results are in agreement with the literature when it states that the distribution of fractures in human is bimodal, with a peak in youth and a peak in the elderly (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001; Jordan and Cooper 2002), and that hip (femur) fractures are one of the main contributors to the peak in the elderly (Walker-Bone, Dennison et al. 2001). No reference to the peak in age zero was founded in the literature, but in these study it was assesses the causes of admission and it was found some cases of violence and some of accidents.

Analysing the variables total days and cost of internment, in the proximal femur fractures occurring in individuals with more than 50 years and caused by low trauma, the mean found in the total days of internment was about 16 days, the results in the literature (Cooper and Melton III 1996) show that this mean is less than that reported in England and Wales (30 days). The cost of internment could not be compared to other costs in the literature because the studies founded present the costs in terms of other variables, such as physical therapy sessions, home health care visits, after the discharge that could not be assessed from the data available for this study.

Considering all femur fractures, and both sexes, the Spearman's rho correlation coefficient of the total days and the costs of internment is considered moderated (Essex-Sorlie 1995) and significant. Analysing the costs and total days separately for each sex, tables 4.4 and 4.5, chapter 4, the means are similar to the mean considering all the individuals. However the differences in these variables between both genders were proved statistically different. With the mean of stay being less in female sex than in male sex and the mean of cost is exactly the opposite, the mean in male sex is smaller than the mean in female sex. The correlations between the two variables in the sexes, however, were both significant, with the correlation in male sex being moderate and the correlation in female sex being weak (Essex-Sorlie 1995).

The same analysis in the proximal femur fractures caused by low trauma and occurring in individuals over 50 years, showed that the correlation, considering the two sexes separately as well as together are weak, and the means are smaller than the means present in all femur fractures. However, the differences between sexes are similar to the ones observed considering all kind of femur fractures; the mean of the total days of internment is higher in male than in female patients, and the mean of cost of internment is higher in female than the means in male patients.

Figure 4.3, chapter 4, displays the mean days and costs of interment per municipality in all femur fractures. The higher averages of days of internment (between 25 to 31 days) were found in some central municipalities such as Covilhã, Fundão, Pedrógão Grande, Figueiró dos Vinhos, higher averages (between 20 and 24 days) were also found some south municipalities Alcoutim and Olhão, and some municipalities of the northern border , Coimbra, Évora and Faro districts. The lower averages were found in some municipalities of Aveiro, Porto, Viseu, Braga, Santarém, Lisboa and Setúbal districts (6 to 12 days). In the case of the mean costs of internment, the highest averages are more disperse towards the entire country, with the south regions presenting higher rates then the north.

In figure 4.4, chapter 4, are displayed the location of the hospitals that received more than 5 cases as well as the fluxes between the place of residence and hospital of admission, in all femur fractures. The hospitals that present greater numbers of admissions are manly Central and General District Hospitals located in the major cities such as for example Lisboa, Porto, Coimbra, Viseu, Aveiro, Faro, Beja.

Analysing table 4.6, chapter 4, for all femur fractures, in the five most frequent causes are included three admissions for accidental falls (code E 888, code E 885 and code E 887). The second most frequent cause is coded as Traffic accident (code E 819.9), and finally the fifth more frequent cause is coded as Place of occurrence - Home (code E 849.0). However, the difference in the frequency of the first and second most frequent cause is almost 60 percent points. This last code is a code that is to be used in order to denote the place where the injury occur and therefore should not be used in the first cause of admission, where it should be state the main cause of the injury. The percentage of cases coded as E 888 (when the code possesses such wide variety of options) and the number of cases coded for place of occurrence of cause rather than the cause itself, should be the object of a reflection by the personnel responsible by the coding, because this operation is of great importance when the data is analyzed for epidemiological proposes.

In table 4.23, chapter 4, is displayed the five more frequent causes of admission of cases with proximal femur fractures caused by low impact and occurring in individuals, and four out of that five causes are coded as Accidental Falls, the only one that is not coded as such cause is the fourth most frequent one and is coded as Home.

In the admission diagnostic, table 4.7 chapter 4, shows that the distribution of the cases of all femur fractures is less disperse, the cases are distributed relatively uniformly by the first three (more frequent) diagnostics that concern fractures of the neck of the femur (coded as 820.20, 820.09 and 820. 21). The fourth most frequent diagnostic is also relative to femur fracture, but concerning other parts of the femur rather than the neck. The fifth most frequent is again related to fracture of the femur neck.

In table 4.8, chapter 4, are displayed the destination after the discharge and correspondent percentages of all femur fractures. It is visible that the great majority of the patients go home after living the hospital, the second most frequent destination after discharge is other institution with internment service; however the difference in the frequency of the first and second most common destinations is more than 75%. With a percentage of around five, and the third most frequent, comes the patients that never leave the hospital, dying while hospitalised. Finally, with residuals percentages, of less than one percent point cames the patients that left without doctoral approval and the ones that received Nursing Home Care. The same distribution is seen in the proximal femur fractures caused by low trauma and in individuals with more than 50 years.

5.1.2. Fractures in Proximal Femur caused by low trauma and occurring in individuals over 50 years old

Table 4.20, chapter 4, displays the female-to-male ratio of the cumulative incidence crude rates for the entire country, and it is observable that the ratios are (in all groups except in the age of 50 to 54) higher than one, meaning that the incidence rates in women were higher that the ones in men. The ratios present an increase between age groups starting from a ratio of 0,91, in the age group of 50 to 54, to a maximum of 2,41 in the age group of 75 to 79. From this age group on, the ratios start to decrease raging the value of 1,76 in the age group of more than 90. This progress is a consequence of the fact that in young population the incidence of femur fractures is higher in men, mostly because of high trauma, then at the time of the menopause the women suffer a rapidly decrease in the bone mineral density (BMD), and the incidence in women overcomes the incidence in men. The decrease of the ratio in more advance age is a consequence of a period in which the loss of BMD in women slows down together with a continuously decrease and consequently an increase in the incidence of proximal femur fractures in men. In figure 4.13, chapter 4, are displayed the progression of the cumulative incidence for both sexes, once again it is visible the higher rates in women than in men in the majority of the age groups and it is also visible the exponential increase of this kind of fracture in both sexes, more accentuated in female sex. These results were expected and are in agreement with the knowledge of the osteoporotic fractures (Cummings and Melton III 2002; Jordan and Cooper 2002; O'Neill and Roy 2003). The female to male ratio higher than one may also be the consequence of a higher tendency to fall in women than in men of the same age (Center and Eisman 1997).

Analysing the direct standardized female-to-male ratios (view figure 4.14, chapter 4) of proximal femur fractures, occurring by low trauma and in individuals over 50 years, for each NUT (II), it is visible that Algarve displays the higher ratio (more than 3 women for each men), then the higher ratios are displayed in Lisboa and Tejo Valley and Centro with ratios higher than 2.7, finally the North and Alentejo, with this later region presenting the only ratio smaller than 2.5.

Considering the case fatality rates of both sexes, in these kind of fractures, the male sex presents a rate almost the double of the rate in female sex, these results were expected because similar results are related in the literature (Cooper and Melton III 1996; Amin and Felson 2001; Walker-Bone, Dennison et al. 2001).

In figure 4.15, chapter 4, are displayed the Proximal femur fractures Empirical Bayesian Rates for Men and Women by municipality. These are the rates after the adjust in function of neighbourhood average rates and size of population of the municipality. The rates in the municipalities vary from 317 per 100 000 to about 1 300 per 100 000, more than four times. Analysing the differences between the sexes, it can be noted that the women rates are higher than the men rates (the men rates vary from 120 to about 700 per 100 000, about six times, whereas women rates vary from about 560 to 1 700 per 100 000, more than three times). In addition, the geographical patterns are slightly different. In male patients, higher rates were found in the northeast around Bragança and Vila Real districts, in some central municipalities and in the south; lower rates were found in northwest around Viana do Castelo, Braga and Aveiro districts, northeast around Guarda and in some south inland municipalities in Alentejo. In female patients, higher rates were found in the northeast around Bragança and Vila Real districts; across all littoral except northwest and a part of Alentejo. Lower rates were found in northwest around Viana do Castelo, Porto and Aveiro districts, around Guarda district and central inland.

The rates were then assessed for spatial autocorrelation, and as presented in figure 4.16, chapter 4, all Moran's I coefficients present positive values, showing that in all groups the spatial dependency is positive, that is in nearby areas the rates tend to have similar values (Wakefield, Kelsall et al. 2000). However, the female rates present a higher coefficient than the others, showing a higher spatial dependency.

In figure 4.17, chapter 4, are displayed the statistically significant spatial associations present in each group of patients. In all three groups, Men, Women and total, clusters of higher rates were found in northeast around Bragança and Vila Real districts, as well as some municipalities around Setúbal, however in Women, a higher number of municipalities present significant higher spatial correlation coefficients in this area. In Men, clusters of high rates were also found in central and littoral Alentejo going all the way, in littoral, to Algarve. In Women, clusters of high rates were found in manly all Algarve.

Clusters of lower rates for both sexes were found in northwest around Viana do Castelo, however in Women the spot is wider. Clusters of lower rates are also found in some northern municipalities of Porto, Aveiro and Guarda, as well in some central municipalities around Santarém, however the spots in Women are wider than the spot in Men.

The pattern seen considering both sexes is similar to the one in Women as expected (the majority of the cases are women).

5.1.3. Comparison between Femur Fractures caused by Traffic Accidents and caused by Accidental Falls

Analysing the two causes considered in this study the results differ. The differences are seen immediately when observing the percentage of cases caused by each one; The causes analysed accounted differently in the femur fractures, traffic accidents accounted for about 14% of all cases, however accidental falls accounted about 78% of the cases, these results are in agreement with the fact that the majority of the hip fractures result of fall (Walker-Bone, Dennison et al. 2001; Marks, Allegrante et al. 2003). The distribution of these groups of cases by the three-year period, was also different in both causes, in the traffic accidents the number of cases suffer a decrease during the entire period, whereas in falls the number of cases suffered an increase from the year 2000 to 2001 and then decreased again from the year 2001 to 2002, in both causes however the proportion was found to be statistically different.

The differences are also observable when analysing, the percentage of cases by sex. In femur fractures caused by traffic accidents the difference between the percentage of male patients is about fifty points higher than the percentage of female patients, in opposite in femur fractures caused by falls this difference is the other way around, with female patients representing a higher percentage, however the difference is again about fifty percent points (table 4.9, chapter 4). These differences in sexes are also present when analysing the direct age adjusted mean annual rates by NUT (II) (figure 4.9, chapter 4). Note that the traffic accidents rates vary from 16 to 24 per 100 000, whereas the falls rates vary from 75 to 108 per 100 000. Note also that in the cause of traffic accidents the male rate is high in all the regions, in opposite in the cause of fall the female rate is higher in all the regions.

The lowest rate for traffic accident was found in Lisboa and Tejo Valley, whereas the lowest rate for falls was found in Alentejo. The higher rates in both causes were found in Algarve.

The mean age of the patients is again different in both causes; the mean age of the patients with femur fractures caused by traffic accidents is about 34 years whereas the mean age in falls is about 76 years (table 4.10, chapter 4), note that the distributions of the cases by age are different (view figures 4.4, 4.5, 4.6 and 4.7, both sexes, chapter 4). In traffic accidents the distribution presents a peak around the age of 25 years, manly due to the number of male patients with age around this number. In falls the distribution, in opposite, presents a peak around the age of 80, due manly to the number of female patients with age close to this. Note that the distribution of cases by age in women in traffic accidents as similar behaviour to that in men in falls, with slightly or none variations with age. These results are in agreement with the literature, when it states that in young people the fractures are more frequent in male, whereas in older people the fractures are more frequent in female (Cooper and Melton III 1996; Walker-Bone, Dennison et al. 2001). In addition, the results are also in agreement with the knowledge that the tendency to fall increases with age and is greater in elderly women than in elderly men (Cooper and Melton III 1996).

When analysing the differences in the total days of internment in both causes the means differ only in about four days (with traffic accidents caused fractures presenting the higher values), however the standard deviation differ in about ten days, with accidents having a higher standard deviation leading to a more disperse distribution (table 4.11, chapter 4). Considering the variable sex, the differences are again visible, with female having the higher means of total days of internment in accident caused fractures and male having the higher mean in fall caused fractures, these differences were found to be statistically different. However, in terms of costs the female patients present the higher means in both causes, and considering both genders together, the means differ in only about 15 euros by cause (with traffic accidents presenting the higher means), and again traffic accidents caused fractures presenting a more disperse distribution (higher standard deviation) (table 4.12, chapter 4). Considering the variable gender, the costs differ slightly, and in the cases of accidents this difference was proven statistically different, however in the cases of falls nothing could be proven about the existence of such difference. In spite of these differences, the correlation coefficients between these two variables, are all positive, representing a direct relationship, that is, when one variable increases, the other also increases (Essex-Sorlie 1995).

The destination after discharge also presents differences in both causes studied; about 74% of the cases in which the facture was caused by traffic accidents went home, whereas about 86% (a percentage more than 10 per cent higher) of the cases caused by falls also went home. The difference between the percentage of cases that went to other institution with internment is also high: 21% of the traffic accidents caused fracture against about 7% of the falls caused fractures. And note that also in the cases of deaths the differences still existed: about 4% of the cases that presented a femur fracture caused by traffic accidents died, whereas about 6% of the cases with femur fractures caused by falls also died (table 4.13, chapter 4). The case fatality rates present higher values for the female sex in traffic accidents caused fractures, in opposite to traffic accidents caused by accidental falls, where the rates are higher in male sex.

5.1.4. Comparison between Femur Fractures in other places of the Femur, rather than the Neck and Neck (proximal femur), caused by low trauma and occurring in individuals over 50 years old

The first difference in the epidemiology of these two groups of fractures in the femur is seen in the number of cases in each situation, note that the osteoporotic fractures account for about 70 per cent, where the fractures in other places of the femur rather than the neck account for only about six percent. Note also, that in opposite to what happens in the proximal femur, in other places of the femur rather then the neck, the number of cases increases continually towards the period under study, however these proportions were assessed for differences, and it could not be proven any difference in the proportions of the three years.

When considering the "contribution" of sexes for each type of fractures in both groups the percentage of female patients is superior to the percentage of male patients. The percentage of women with proximal femur fractures is two percent superior to the percentage of women with fractures in other parts of the femur.

Comparing the mean age in all patients, in men and in women, the proximal femur fractures presented the higher means in all groups. However, the differences between similar groups do not go over nine years, with men patients presenting the higher difference (tables 4.14 and 4.19, chapter 4). However note that both female and male distributions of age in proximal femur fractures are less disperse, note also that the distribution in proximal femur fractures is more "concentrated" around higher values of age: the first quartiles lye between the 70 and 80 years old and the third quartile between the age of 80 and 90 in proximal femur fractures, whereas in the other fractures the same quartiles lye between the age of 60 and 70 and 70 to 90, respectively.

Analyzing the Female-to-Male ratios in the five years age groups created (tables 4.15 and 4.20, chapter 4), the differences in both type of fractures is first seen, in the fact that in fractures in other places of the femur rather than the neck, there are two groups in which the ratio is equal or less than one, in the age group of 50-54 and 55-59, whereas in proximal femur fractures the only group that presents a ratio less than one is the age group of 50-54. The higher values reached are different in both fractures. In addition the ratios reach their higher values in different age groups; in the proximal femur fractures the ratios reach a maximum value of 2,4, in the age groups of 70-74 and 75-79, however in the fractures in other place of the femur rather than the neck, the maximum value reached is 4,2 in the age group of 85-90 (an older group).

The mean of total days of internment is higher in patients with fractures that occur in other parts of the femur rather than the neck, considering all cases, as well as sexes in separate. In both type of fractures, the male patients present higher means in the total days of internment than the mean of female patients in the same variable. However when considering the variable costs of internment, the means are higher in proximal femur fractures in all groups. Considering the genders, the male patients present higher means of costs in fractures in other places rather than the neck, whereas the female patients present the higher means, in the proximal femur fractures.

In spite of the differences observed in the analysis of the variables (total days and costs) all correlation coefficients are positive, representing a direct relationship, however the coefficients are lower in osteoporotic fractures, where they can be classified as weak, whereas the correlation in the other fractures can be classified as moderate (Essex-Sorlie 1995).

Comparing the destination after discharge (tables 4.18 and 4.24, chapter4), the percentages of cases discharge in both kind of fractures are similar, when considering the destinations: home, without doctoral approval and nursing home care. However, in destinations: other institutions with internment service and decease, the percentages differ. In proximal femur fractures, the percentage of patients that go to other institutions with internment service is lower than the percentage of patients that have the same destination in the other fractures. In opposite, the percentage of patients that passed away is higher in proximal femur fractures (difference of about one and an half percent point).

The case fatality rates are higher in male patients than the female in both fractures, however in proximal femur fractures the difference in the rates between sexes is much higher.

5.2. Conclusions

The use of Geographical Information Systems allowed the description of the femur fracture occurrence in Portugal and the identification of significant geographical clusters, which were found to have different patterns for men and women. Osteoporosis is considered an important disease in public health, however its prevention can only be obtained if its real intensity nationwide is knowned. The fact that the standardized rates have different expression within regions of the country, varying up to 6 times in men and 3 times in women, confirms that the appearance of the disease cannot be only the result of aging, suggesting the influence of external factors (such as environmental, social, economical, behavioral). However, these factors may be influencing the disease in each sex in a different way, since geographical patterns found were different.

The Bayesian method proved itself efficient in the determination of significant clusters because it diminished the randomness of the rates within the municipalities, correcting them according to the neighboring rates.

The success of this study depended upon the quality of the database that showed a few problems. One of such problem was the fact that because it did not contemplate a code for each patient, but instead a code for each episode of admission, it was impossible to assess the totality of the cases that were re-incidents. This problem was diminished through the removing of registers that were coded for treatment and complications after an orthopedic chirurgical intervention. Another problem faced that can influence the quality of the results, was the fact that the registers that were coded as Place of occurrence – Home (about 900), for cause of admission instead of being coded correctly for the main cause, were included as low impact accident, even if a residual amount of these might not be true.

During the process of making this work several questions rose, suggesting future works. Concerning the geographical pattern encountered in the country, it is important to assess what factors are contributing for this pattern, including environmental and social factors. Concerning the different pattern encountered for the distribution of the disease for both sexes, especially in the south and in higher rates, it may be important to assess how the different factors are associated to the occurrence of the disease for each sex.

Bibliography

Amin, S and D T Felson (2001). "Osteoporosis in Men." Rheumatic Disease Clinics of North American **27**(1): 19-47.

Center, J and J Eisman (1997). "The epidemiology and pathogenesis of osteoporosis." Baillières Clinical Endocrinology and metabolism **11**(1): 23-62.

Cooper, C and L J Melton III (1996). Magnitude and Impact of Osteoporosis and Fractures. Osteoporosis. D. F. R Marcus, J Kelsey, Academic Press: 419-434.

Cummings, S R and L J Melton III (2002). "Epidemiology and Outcomes of Osteoporotic Fractures." The Lancet **359**: 1761-67.

Essex-Sorlie, D (1995). Medical Biostatistics & Epidemiology, Prentice-Hall International Inc.

Jordan, K M and C Cooper (2002). "Epidemiology of osteoporosis." Best Practice & Research Clinical Rheumatology **16**: 795-806.

Lips, P (1997). "Epidemiology and Predictors of Fractures Associated with Osteoporosis." The American Journal of Medicine **103**: 3S-8S.

Marks, R, J P Allegrante, et al. (2003). "Hip fractures among the elderly: causes, consequences and control." Ageing Research Reviews **2**: 57-93.

Melton III, L J (1999). Epidemiology of Fractures. Osteoporosis in Men. E. S. Orwoll, Academic Press: 1-13.

O'Neill, T W and D K Roy (2003). "The epidemiology and scale of the problem." Hospital Medicine **64**(9): 517-520.

Wakefield, J C, J E Kelsall, et al. (2000). Clustering, cluster detection, and spatial variation in risk. Spatial epidemiology Methods and Applications. P. Elliot, J. C. Wakefield, N. G. Best and D. J. Briggs: 129-152.

Walker-Bone, K, E Dennison, et al. (2001). "Epidemiology of Osteoporosis." Rheumatic Disease Clinics of North American **27**: 1-18.