Morbidity and mortality of coronary heart disease: a study of spatial epidemiology

U. PORTO
FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

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Ao abrigo do Art.º 8º do Decreto-Lei nº 388/70 fazem parte desta dissertação os seguintes artigos:

I. Ribeiro A, Pina MF. Incidence of coronary heart disease: a matter of geographic coordinates? A systematic review of studies on the international and intra-national spatial variation in coronary heart disease incidence. *(submetido)*

II. Ribeiro A, Pina MF, Lopes C, Barros H. Time trends in Coronary Heart Disease Mortality in Portugal: After a quarter of century overall better but accentuated regional inequalities. *(submetido)*

III. Ribeiro A, Pina MF. The geographic distribution of coronary heart disease hospitalizations in Portugal between 1997 and 2008. *(em preparação)*

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CONTENTS

1. Introduction

INTRODUCTION

Coronary heart disease (CHD) is the first cause of death worldwide, causing millions of deaths and hospitalizations, disability and reducing quality of life. It costs not only lives but also huge economic resources (direct and indirect costs) [1].

The high-fat and energy-rich diet, smoking and a sedentary lifestyle are associated with the emergence of CHD. With urbanization in the developing world, people became more prone to adopt the unhealthy habits of the high-income countries and suffer from CHD. Consequently, most of the global burden of CHD is now occurring in low and middle-income countries [2-4].

Portugal belongs to the set of nations where the mortality from CHD is below the world average. In 2008, 7,784 died from CHD, corresponding to 7.4% of all deaths and 23.0% of the deaths from CVD [5]. The highest mortality and incidence rates from CHD are found in Finland, England and, more recently, in the Eastern Europe; on the contrary, Mediterranean countries (like Spain and France), as well as Japan, have the lowest incidence and mortality from CHD [6]. The existence of geographical differences in the occurrence of CHD within and between counties is often noticed and investigations are cyclically carried out to quantify these variations and interpret them [7-11].

However, the interpretation of geographic patterns has been revealed a herculean task, since CHD, as the majority of the chronic diseases, have a complex multi-factorial etiology. Ischemia is caused by the unbalance between oxygen/blood supply and the heart demand. The most common cause of myocardial ischemia is atherosclerotic disease, sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the affected coronary artery [12-13]. So there is a long list of risk factors that play a part in this process, which are frequently divided into modifiable and non-modifiable ones, as follows [1, 14]:

Table 1 – Modifiable and non-modifiable coronary heart disease risk factors

Modifiable		Non-modifiable
High blood pressure	Alcohol intake	Age
Abnormal blood lipids	Use of certain medication	Hereditary or family history
Cigarette smoking	Lipoprotein (a)	Gender
Sedentary lifestyle	Left ventricular hypertrophy (LVH)	Ethnicity or race
Obesity	Excess homocystein in blood	
Unhealthy diets	Inflammation	
Diabetes mellitus	Infection	
Low socioeconomic status	Abnormal blood coagulation	
Psychological illness and stress	Metabolic syndrome	

To justify the spatial differences in CHD incidence, authors have been making use of several individual risk factors related to lifestyle and to biological markers, but also of some environmental variables – such as temperature, altitude, rainfall, water hardness, socioeconomic context, and so on [15-17].

The main objective of this dissertation was to analyze the burden of coronary heart disease (CHD) in Portugal.

Attempting to compile and synthesize the scientific literature about the geographic disparities in CHD incidence, a **systematic review** about what have been documented until nowadays on such variations was conducted and was the first aim of the present dissertation resulting in a scientific article already submitted to an international journal with referee.

Additionally, it was investigated if there were spatial differences in CHD mortality (one of the outcomes that measure the burden of the disease) in Portugal and if the spatial and temporal pattern persists over decades. This corresponds to the second objective of the present work, **CHD mortality rates were analyzed from 1981 to 2005** to understand how they behaved nationwide and through Portuguese districts and to compare the geographic pattern at the beginning and at the end of the study period.

Established the geographical pattern of CHD mortality in Portugal, it became important to check if such geographic variations were reflecting differences in incidence. To perform the analysis, secondary data from the National Hospital Discharge Register (NHDR) were prepared and used[1]. In a first step, exploiting the NHDR database, the burden of CHD hospitalization was estimated in terms of expenditure and demographic impact and to see the evolution of major healthcare indicators, such as lethality or length of stay. To the major objective of the thesis, the **geographic distribution of CHD hospitalization was examined** by municipality. A Bayesian approach was used to obtain in order to smooth this hospitalization rates and deal with the random fluctuations associated small areas. Additionally, spatial clusters were detected and mapped.

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2. Aims

AIMS

The main purpose of the present study is to understand the epidemiology of the CHD hospital admissions and mortality in Portugal since 1997 until 2008 (from 1981 to 2005 for mortality) paying special attention to its geographic distribution.

Beyond this major aim, some specific objectives emerge:

1. To review the scientific literature about the geographic patterns of CHD incidence and discuss the referred explanations.

2. To examine the time-trends and the geographic distribution of CHD mortality.

3. To characterize hospital admissions for CHD in terms of sex and gender distribution, length of stay, final outcome (death and destiny after discharge) and costs.

4. To examine the time-trends and the geographic distribution of CHD hospital admissions.

3. Papers

3.1. Incidence of coronary heart disease: a matter of geographic coordinates? A systematic review of studies on the international and intra-national spatial variation in coronary heart disease incidence

Incidence of coronary heart disease: a matter of geographic coordinates? A systematic review of studies on the international and intra-national spatial variation in coronary heart disease incidence

Ana Ribeiro, BS[1,2,3], Maria de Fátima de Pina, PhD[1,2,3]

[1]INEB – Instituto de Engenharia Biomédica; [2]Faculdade de Medicina, Serviço de Higiene e Epidemiologia, Universidade do Porto; [3]ISPUP – Instituto de Saúde Pública da Universidade do Porto

Abstract

Introduction: Coronary Heart Disease (CHD) is the main cause of death worldwide. However, many aspects of its geographical distribution remain unknown. The aim of this review is to compile the published findings on geographic patterns of CHD incidence and to discuss the suggested explanations.

Methods: A systematic review was conducted on three bibliographic and citation databases, *Pubmed*, *ISI-Web Of Knowledge* and *LILACS*. 33 studies were included.

Results: In Europe, a North-South gradient was predominant, with incidence rates of CHD increasing with latitude. However, other patterns seem to exist in some European countries and in North America, where an East-West decreasing trend was found. The geographic gradients were mainly attributed to blood lipids and fat intake, other classic risk-factor distribution and water hardness.

Conclusion: Strong geographic patterns in CHD incidence were reported, but no unambiguous explanation for international and intra-national inequalities had yet been found. Although a North-South gradient was often observed, other spatial patterns also exist in Europe and North America. For a better understanding, studies should extend to other continents.

Key-words: epidemiology, coronary disease, morbidity, geographic inequalities, risk factors.

Introduction

Coronary heart disease (CHD) is the main cause of mortality worldwide and this scenario is foreseen to continue in the near future [1-2]. In 2008, 7.2 million people died worldwide, from CHD, even more were hospitalized and a great proportion suffered disabilities. Nevertheless, mortality rates have been decreasing in more developed countries, since 1970, when they peaked in Europe and North America [3-5]. According to the results from the World Health Organization (WHO) Multinational MONItoring of trends and determinants of CArdiovascular disease (MONICA) Project, two thirds of the reduction in CHD mortality can be explained by the decline in incidence rates, while the remaining one third can be attributable to the decline in case-fatality rates [6].

However, the decline in CHD mortality is not true worldwide, and newly industrialized countries, such as China, India, Mexico, Singapore, some former Eastern Bloc nations, and also some countries in Africa [3, 6-8] are presenting, nowadays, the highest CHD mortality rates ever registered, significantly higher than the USA or Northern Europe precedent peaks [9]. Consequently, CHD still maintains its position as main cause of death, disability and hospitalization in the World.

Despite the magnitude of the problem, the multifactorial etiology of CHD remains to be discovered. Classic cardiovascular risk factors such as smoking, elevated blood lipids, obesity, diabetes, sedentary lifestyle), mostly identified in the 50´s by the Framingham Study, do not fully explain the development of the disease and new risk factors such as C-reactive protein, lipoprotein(a), homocysteine, calcium, fibrinogen or even infectious agents) have often been suggested, identified and tested as hypotheses for the development of CHD [10].

One key question for the understanding of the occurrence of CHD is the geographical distribution of the incidence and mortality rates related to such disease. Besides the well-known temporal variation, several studies have reported spatial clustering and geographical patterns of CHD, with East-West or North-South gradients [11-13]. Some researchers hypothesized that spatial patterns emerged from an unequal distribution of the classic risk factors [14]. However, attempts to associate those risk factors with spatial distribution of CHD were not totally successful and, to a certain degree, geographical patterns remained unexplained [15-17].

The frequently cited 'Mediterranean/French Paradox' expresses the scenario well: a lower than predicted incidence of CHD is observed in some Southern European countries, suggesting that additional factors play a part in the development of CHD. Some studies of migrant populations enforced this view: the individual risk alters when individuals move to new places of residence[18]. Researchers have pointed to several aspects, either environmental (water quality, climate, air pollution, topography), cultural, genetic and/or/ socioeconomic as a possible explanation for the difference in risk associated with the changes in place of residence [13, 19-20].

Interest in understanding the geographical variation of diseases, and in particular of CHD, led to the publication of several studies on the matter of CHD geographical variation. Also, systematic reviews have been published focusing on the differences in the mortality or incidence of CHD at neighborhood level, in which the socioeconomic context can play an important role [21-23].

The aim of this article is to compile and discuss the published findings and explanations for the geographic patterns of CHD incidence, both at regional and/or international levels. The decision to focus this work on the incidence of CHD rather than mortality caused by CHD is related to the fact that incidence can better reflect the association with risk factors (environmental, genetic, cultural or others) whereas mortality is strongly linked to the access and quality of health care systems in the process of management of CHD, once installed.

Methods

Between October and December 2009, a systematic review was conducted on three bibliographic and citation databases, Pubmed, ISI-Web Of Knowledge and LILACS, using the following expression: (coronary heart disease OR ischemic heart disease OR ischaemic heart disease OR angina or myocardial infarction) AND (incidence OR admission* OR discharge* OR hospitalization* OR hospitalisation) AND (geography OR geographical OR geographic OR spatial). These keywords were searched through titles and abstract fields. The search was restricted to studies performed in humans and to articles written in English, French, German, Italian, Portuguese and Spanish. No temporal limits were established.

Four hundred and twenty-three articles conformed to the above limits. After all duplicate references had been eliminated, two reviewers selected the potentially relevant articles by screening all the titles and abstracts. The exclusion criteria used were:

i. Drug, treatment or intervention effectiveness studies.

ii. Experimental studies.

iii. Methodological studies.

iv. Studies that focus on Cardiovascular Diseases without separating CHD from other diagnosis or did not clearly state which is the outcome variable.

v. Studies that focus mainly on the temporal variation of CHD incidence.

vi. Studies that focus on the association between place of residence and CHD.

vii. Studies that do not explicitly present the results of the spatial distribution found.

Therefore, studies were selected when the following inclusion criteria were met:

i. Studies on the geographic differences/variations of CHD incidence between countries and/or regions (counties, provinces, states, towns).

ii. Observational studies (ecological, case-control, prospective or retrospective cohort and cross-sectional studies).

iii. Studies measuring CHD through incidence, hospitalization or event rates (sometimes referred as attack rates).

Following the above criteria, from the initial list of 423, 51 articles were selected as potentially relevant. To verify whether they were actually appropriate, complete texts were carefully examined and a total of 25 articles were excluded, namely:

Three review articles on the epidemiology of cardiovascular diseases [24-26]. One analysing the geographical pattern of the seasonality of Acute Myocardial Infarction (AMI) admissions [27]. Two articles focusing on the geographic distribution of cardiovascular risk, but not on CHD events [28-29]. Two other articles using exclusively mortality rates and one using only prevalence of CHD [30-32]. One methodological study examining the effect of the definitions of coronary events on trends and geographical disparities [33]. Two studies whose main objective was to test statistical models rather than geographical patterns [34-35]. One study on the spatial correlation between medical procedures, but not incidence rates of CHD [36]. Two studies analysing the association between water hardness and Myocardial Infarction (MI), without results about the geographic distribution [37-38]. One article on the incidence of CHD in immigrants which accounted for country of origin of the individuals, but not country of residence [39]. One article examining the association between socioeconomic conditions, at municipality level, and MI hospitalizations but without information on the geographical pattern of the results [40]. Three articles focusing on the prevalence of cardiovascular risk factors [41-43]. One article analysing aggregated data for several diseases (including CHD) [44]. Three others presenting the incidence rates of MI for defined areas but in which the data were not analysed by region [45-47]. Finally, one reference corresponding to a conference abstract was excluded [48].

From the 26 remaining selected articles, the reference lists were checked and seven additional publications were included, totalling 33 articles included in the study. Figure 1 shows the selection process using PubMed, IsiWebOfKnowledge and LILACS.

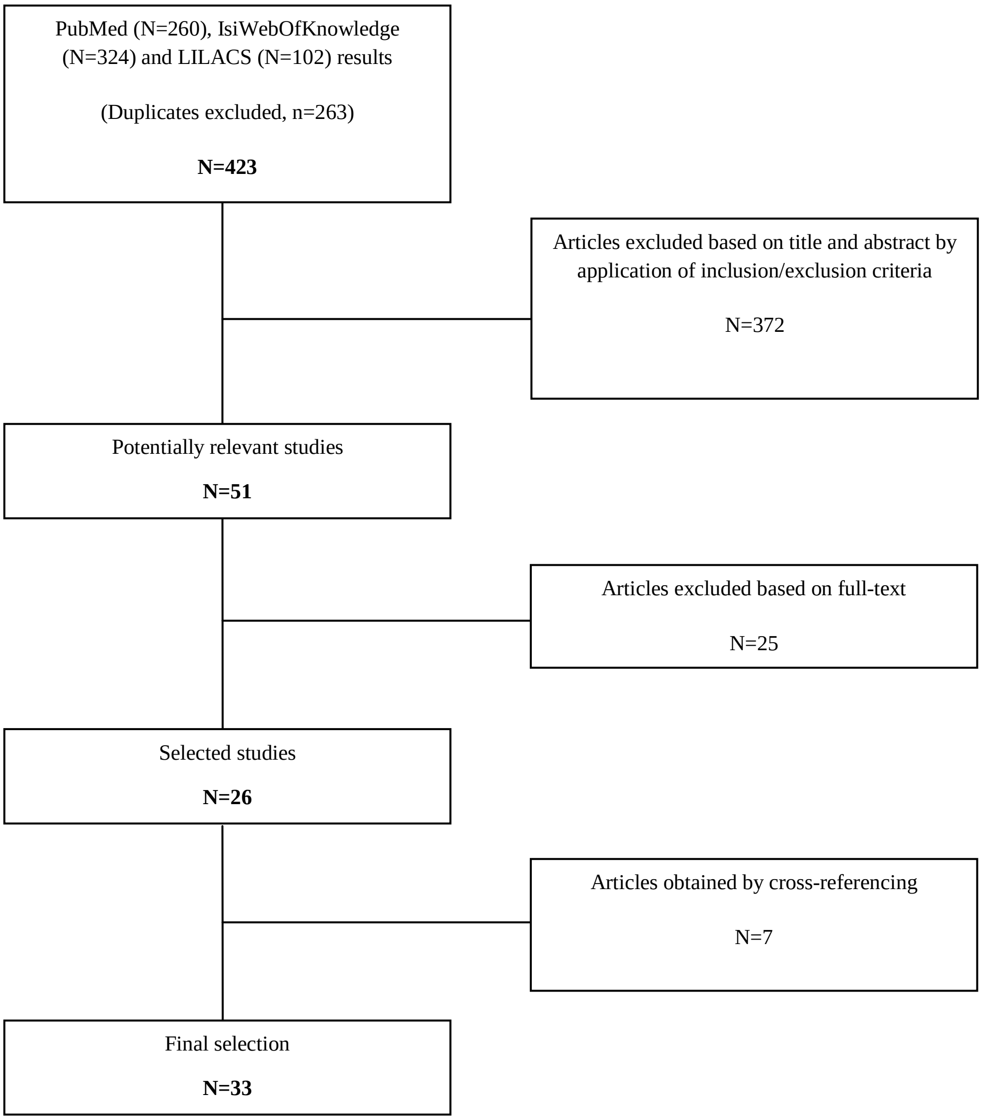

Figure 1. Flow diagram of selection process

Table 1 shows the main characteristics of the selected studies, with information on the geographic variation of CHD incidence. Other diseases or indicators, if described in the articles, were not included in the table.

Results

Among the 33 studies, 26 were performed in Europe, 5 in North America, one in Asia and another worldwide.

The majority of the studies were population-based registers (n=18), followed by prospective cohorts (n=8), ecological studies (n=5), one retrospective cohort and one population-based case control study. The studies of population-based registers tend to be more descriptive, whereas cohorts and ecological design enable the interpretation of geographic patterning. The majority of the studies are recent – from the 1990s and the 21st century. About 6% were published before this period.

67% of the studies focused on subjects belonging to age groups between 25 and 74. Some studies investigated specific population segments: men/women, rural/urban, physicians and diabetics. Worthy of notice is the fact that 27% of studies were exclusively carried out among male populations.

Regional variations

a) General patterns

In general, incidence of CHD varied widely across the world: the highest event rates (/100,000 inhabitants) were found in Finland (915 - men) and United Kingdom (256 – women) whereas the lowest were in China (76 – men) and Spain (30 – women) [49]. In Europe, there is a broad North-South gradient in CHD rates: northern European countries showing consistently higher incidence rates than southern [50-51].

Finland is among the countries with the highest incidence of CHD, and the studies reported incidence rates of MI increasing from southwestern to northeastern regions of the country [52-53]. Within Finland, significant differences were found at provincial levels: North Karelia, the more eastern province had a constantly higher MI incidence than the more western Kuopio; in addition, the border between them had even higher risk; the same was true for rural areas, when compared to urban areas [54]. In the 1970s, higher incidence was also found in Northeast and lower in Southwest, varying by multiples of 1.9 to 3.5 difference, but, in contrast, rural areas presented the lowest incidence rates [55].

In Scandinavia, Sweden, the incidence rates of CHD also presented a similar geographical pattern. A North-South gradient was reported, although results were not consistent (especially when compared to the unambiguous mortality pattern) since it was detected only for men aged between 50 and 59 [56]. A strong geographical disparity in the incidence rates of CHD in two northern counties was found in another study, although without a clear North-South gradient [57]. In addition, those living in northern rural counties had roughly 30% higher risk of developing MI than those living in the southern urban Stockholm county, suggesting that rural lifestyle is related to increasing incidence [58-59]. Much less conclusive is the longitudinal variation, where a study pointed an East-West increasing gradient [60], but others did not show a spatial pattern [57].

In the United Kingdom, the populations from northern regions had a higher incidence of CHD: particularly Scotland, with incidence rates several times higher than Southern England.

Results from Great Britain indicated a strong North-South gradient in incidence of CHD [61-63].

In France, one of the countries with the lowest CHD incidence rates in the world, there is also a moderate North-South gradient, which could be observed by comparing WHO MONICA centers of Lille and Strasbourg, respectively in the North and Northeast, with Toulouse, in the Southwest, which presented the lowest incidence of MI [64]. MONICA French centers contrasted with the Belfast one, which had a considerably higher risk of all forms of CHD [65-67]. Differences were also found between southern regions of France and Germany, the incidence and event rates being significantly higher in Augsburg, Germany (higher latitude) than in Toulouse, France [68].

Nearby, in Belgium, two neighboring but culturally different MONICA regions, showed contrasting event rates that were higher in Charleroi (South, Wallonia) than in Ghent (North, Flanders), a situation in which the usual European North-South gradient is inverted [69].

In Italy, an underlying North-South gradient also seems to exist. Men living in the South had a 29% lower risk of CHD than those living elsewhere and Brianza and Friuli MONICA regions (North) showed higher event rates than Latina (center) [70-71]. In addition, it was also found that AMI hospitalization rates for populations from Tuscany (North) are more than double the national average [72].

MONICA Spanish regions showed a two-fold variation in MI incidence and, unlike the majority of European countries, an inverted North-South gradient emerges, ie the lowest incidence rates were found in North. For men, Murcia and Valencia (South) have significantly higher incidence rates than Gerona (North), Castilla-la-Mancha (Central) and the Basque Country (North). For women, Murcia (South) had higher incidence rate than the Basque Country and Navarra (North) [73].

Outside Europe, in China, where CHD incidence rates are below the world average, there was also an underlying North-South difference with higher rates in the North [74]. In Canada, MI showed a moderate variability and angina hospitalization rates showed a higher degree of regional variation. Both diseases appeared to be concentrated in the most rural and remote areas, with an increasing trend from West to East. In addition, after mapping the angina hospitalization rates, a cluster in the western provinces emerged [75].

With an intermediate position, the geographical differences of CHD incidence rates in the USA were less consistent than those for strokes, but still MI hospitalization rates varied between states and were clustered in the Appalachian (East) region – matching the so-called Stroke Belt – and broadly the non-west part of the country had higher CHD incidence [76-77]. However, another study (focused on male physicians) did not find any association between regions of residence and MI events [78]. Nevertheless, the incidence rates in the Southeast of the USA were lower than the national average and a study made of the restricted group of white and black diabetics suggested that living in the South protects blacks against CHD and MI, i.e., place of residence interacts with factors such as race [79].

b) Probable explanations

In order to explain the variation in CHD incidence rates across Europe, the prevalence of several genetic susceptible factors was computed in several European WHO MONICA regions, but the results did not show any association that could explain the remarkable North-South gradient [80]. In a study that compared the incidence rates of CHD in Northern Ireland and France [65-66], an increase risk was observed in the former which was mainly explained by fibrinogen and classic risk factors such as age, diabetes, smoking, systolic blood pressure, blood lipids (cholesterol, lipoproteins) and BMI. Genetic differences apparently were not associated with the differences in the incidence rates of CHD in the two countries An ecological study found that the increase of CHD with latitude could result from higher fat consumption and softer drinking water in Northern Europe [50].

In Finland, the differences established between regions partially lie on ground water mineralization: Magnesium is suggested as reducing the risk of MI, as the highest Mg^{2+} concentrations were found in the Southwestern region, where incidence rates were lower [81]. The same explanation was proposed in a study in Italy, where the authors found an association between low water hardness (and subsequent small concentrations of Mg^{2+} and Ca^{2+} ions), and high hospitalization rate for MI [72].

In Sweden, the North-South geographical differences in CHD incidence were related to differences in risk factor prevalence, since Västernorrland had a higher prevalence of obesity, blood lipids levels among men (in women, the pattern is not so evident) [58]. Tobacco consumption was not a determinant of the geographic variation of MI, but mean serum cholesterol, blood pressure and socioeconomic factors explained part of it [57]. Differences in hospitalization diagnosis apparently could not justify the differences between the cities of Gävleborg and Stockholm [59].

Classic risk factors seem to account for much of the variability of CHD incidence in the United Kingdom: more than 75% of the variance was attributable to eight variables (mainly classic risk factors). But, although the differences between regions have been reduced after adjustment for those factors, a fraction remained to be explained [61-62].

In general, studies that used statistical models to explain geographic differences of CHD found a smaller geographical variation after adjustment for confounders, usually classic cardiovascular risk factors [51, 61-63, 78], meaning that a large proportion of the spatial disparities were due to the geographic distribution of these factors.

Rural lifestyle was a determinant in explaining some geographical variations in CHD, although the reasons are unclear. In Finland, Sweden and Canada, remote rural regions were related to a higher CHD incidence and hospitalization rates, but the reasons for such differences are not yet understood [54, 58-59, 75].

Discussion

The present review synthesizes the available epidemiologic studies of spatial distribution of CHD incidence. A North-South gradient emerged in Europe, with the exceptions of Spain and perhaps Belgium, which both showed an inverse pattern. In China, the North-South pattern of CHD was also observed, although in North America (Canada and USA) a West-East gradient was detected. In other words, different patterns of distribution coexist and it became clearer that the North-South gradient is not a universal phenomenon even in the European continent.

However, it should be noted that the above-mentioned Belgian regions were only 0.6 degrees apart (approximately 70 km) in terms of latitude and the Spanish study only involved provinces from the eastern half of the county and consequently the inverse North-South pattern that was found could not be the same for the whole country.

The studies of incidence rates selected for this work have revealed approximately the same patterns shown by several studies on geographic distribution of CHD mortality (not included in this review) which also documented higher rates in northern regions in several European countries, with the exceptions of Spain, Portugal and Belgium which had an opposite pattern: higher mortality rates in the south [82-85].

The greatest enigma is, therefore, not the patterns of CHD incidence itself, for which studies have presented concordant results, but its explanation. Genetic legacy or diagnostic policy did not explain the European North-South pattern, rather blood lipids and fat intake were a better explanation for the differences between and within European countries. However, genetics seems to play a role in the risk of CHD. Even after migration to Sweden, individuals from Southern and Western Europe and from some Baltic countries (Estonia, Lithuania and Latvia) retained their lower risk profile, while those from Central and Eastern Europe retained their higher CHD incidence rates (compared with the Swedish) and surprisingly second generation immigrants ran the same risk as their parents [39]. This is a situation that is not universal, since other studies have concluded an opposite risk pattern in migrants [18].

Although part of the geographic variations remained, adjustment for classic risk factors such as smoking, BMI, cholesterol, hypertension and diabetes reduced (at different levels) the ratios between higher and lower incidence regions. Only one environmental measure – ground water hardness and particularly its Magnesium content – was inversely related with CHD incidence, which explained the differences found between several European countries and within Finland.

Such conclusions as to the role of cardiovascular risk factors on regional inequalities of CHD were also found in studies comparing the prevalence of risk factors in countries with contrasting CHD incidence and mortality rates. Diet was the major factor reported as the cause of regional differences. Countries with lower intake of cholesterol and saturated fat also had lower CHD mortality rates [86]. An inverse and statistically significant association between fish consumption and mortality from CHD was found in 36 countries [87]. There was an elevated daily consumption of products with higher fat content and elevated serum cholesterol levels in Southern Belgium where the highest CHD mortality rates in the country were presented; on opposition, polyunsaturated fats were more frequently used in the northern provinces [85].

Nevertheless, the frequency of risk factors did not differ that much between countries with low incidence and mortality rates, such as France and the rest of Europe [88]. The so-called French paradox remained a mystery for years and comparisons with UK were made to explain why countries so similar in terms of fat intake had several-fold differences in CHD mortality. Initially, epidemiologists pointed to the type of ingested fat: in France, vegetable oils were more used, as opposed to milk and butterfat in Britain, plus the moderate consumption of wine, which is more frequent in France and which had a protective effect [89]. Currently, the difference is being endorsed to a time lag of at least 25 years, between increase in blood cholesterol and the subsequent rise in coronary complications; ie, the French increased their fat intake two decades ago, but its consequences are yet to appear [89].

A similar situation was also seen across Spain, where Mediterranean provinces had higher CHD mortality rates in spite of their lower lipid intake. The suggested explanation was the absence in those provinces of the protective effect of fish and the moderate consumption of wine [90].

It is important to stress that the present review had some limitations. Heterogeneity of the included studies was one of them: along with the more conventional study designs (like cohort and case-control), ecological analysis (with no access to individual characteristics) and population-based registers were included, reason why generalizations must be regarded with caution. In addition, since the majority of the studies depend on secondary data, it is difficult to obtain a true and unequivocal measure of CHD incidence, because no standardized and validated diagnoses were involved: the accuracy and definitions have a high degree of variability throughout time, hospitals and geographical areas [91]. Finally, there is an appreciable risk of publication bias and so the potential absence of geographic patterning in some countries or continents could not be assessed in the present review.

Several studies were made in order to describe and explain the spatial patterns of CHD incidence, but no unambiguous explanation for international and intra-national differences was yet found. Nevertheless, the knowledge that its spatial distribution is not random is an important result which can help to elaborate and coordinate effective preventive measures, since more attention is given to certain areas; it facilitates the management and allocation of health resources and can also give clues for further study of risk factors.

For a better understanding of the spatial distribution of CHD, studies should extent to other regions such as Asia, South America, Australia and Eastern Europe in order to allow one to establish whether spatial patterning of CHD is a universal phenomenon and to find out common conditions between regions with similar CHD incidence rates. On the other hand, it will be important to investigate to what extent the international discrepancies in incidence rates could be due to differences in diagnostic patterns or death certification.

Table 1. Characteristics of the studies included in the review

Reference	Country/Region Period Study design*	Subjects	Geographic Units	Variables			Results†	
				Outcome (ICD9)	Area level	Individual level	Rates (/100,000 unless stated otherwise) and/or ratios	Geographical pattern
Tunstall-Pedoe, 1994[49]	21 countries from 4 continents 1983-1985 (10 yrs follow up) PBR	Subjects aged 35-64	38 WHO MONICA centers	CHD fatal events and MI non-fatal events			Age-standardized event rates: Men - from 915 in North Karelia (Finland) to 76 in Beijing (China). Women - from 256 in Glasgow (UK) to 30 in Catalonia (Spain).	Europe: North-South decreasing gradient.
Masironi, 1979 [50]	Europe E	Residents aged 45-64	17 towns (Northern, Central and Western Europe)	CHD (410x) fatal and non-fatal events	Water hardness, latitude, lowest yearly temperature, animal fat consumption		Age-standardized event and incidence rates associated with water hardness (negatively) and latitude. Fat consumption associated in men aged 50-54.	Event and incidence rates decreasing form North to South.
Menotti, 2000[51]	Europe 1958-1964 (10 yrs follow-up) PC	13 Cohorts of men aged 40-59 (n=8,210)	Northern Europe (Finland, Netherlands) Southern (Italy, Croatia, Greece)	CHD hard events and CHD any events		Age, smoking habits	Age-standardized incidence rates ratios (North vs South Europe): CHD hard events: 1.43 – 1.96 CHD any events: 1.68 – 1.95	Incidence rates higher in North than in South Europe.
Havulinna, 2008[52]	Finland 1991-2003 E	Residents aged 35-84	10x10 km grid cells	MI first fatal (410-414x) and non fatal (410x) events			Age-standardized incidence rates: Men – Northeast 855.6; Southwest 707.3 (RR = 1.21) Women – Northeast 351.4; Southwest 278.3 (RR = 1.26)	Higher incidence rates in Northeast than in Southwest, for both men and women.
Mähönen, 2000[53]	Finland 1991-1995 PBR	Residents aged 25-74	Hospital district	CHD (410-414, 798x) hospitalizations and deaths			Age-standardized incidence rates: Men - between 588 (Kainuu) and 361 (Vaasa) Women - between 195 (Kainuu) and 82 (Aland) Age-standardized event rates: Men - between 865 (Kainuu) and 488 (Vaasa) Women - between 288 (North Karelia) and 104 (Aland)	Higher incidence rates in Northeast than in Southwest. Differences wider in women and in event rates.
Viik-Kajander, 2003[54]	Finland, North Karelia and Kuopio 1983-1992 PBR	Men aged 25-64	10x10 km grid cells	MI (410x) first fatal and non-fatal events			Age-standardized incidence rates: North Karelia (East) – 403 Kuopio (West) – 377. Incidence rates in rural areas 15% higher than in urban areas.	Higher incidence rates in East than in West.
Romo, 1982 [55]	Finland 1972 PBR	Residents aged 40-64	12 provinces grouped in 5 regions	CHD (410-414x) fatal and non-fatal events			Age-standardized incidence rates: Men – from 2198 (North Karelia) to 760 (Aland) Women – from 736 (Oulu) to 0 (Aland). Urban areas had 1.3 (men) and 1.1-fold (women) higher incidence.	Higher incidence rates in Northeast than in Southwest, for both men and women.
Johansson, 1992[56]	Sweden 1975-1982 PBR	Residents aged 20-64	Towns: Boden (North), Falun and Gävle (Center), Göteborg and Malmö (South)	MI (410x) non-fatal events			Event rates: Men (50-59) – from Boden (546) to Göteborg (447)	North-South gradient of attack rate in men aged 50-59. No significant regional variation found in other ages and women.
Hammar, 1992[57]	Sweden 1976-1981 PBR	Residents aged 30-64	Gävleborg, Kopparberg, Uppsala, Stockholm, Södermanland, Kalmar, Skaraborg and Malmöhus counties and Mälmo	MI (410x) first non-fatal and fatal events	Smoking prevalence, mean serum cholesterol and mean BP		Age-standardized incidence rates: Men – from 502.3 (Gävleborg) to 363.9 (Uppsala) Women – from 114.5 (Kopparberg) to 75.1 (Uppsala) Smoking did not explain differences; cholesterol and BP and socioeconomic factors, yes.	Strong geographical disparities.

*E – Ecological, PBCC –Population based case-control, PBR – Population based registry PC – Prospective cohort, RC – Retrospective cohort, † Adjusted for individual level variables

Reference	Country/Region Period Study design*	Subjects	Geographic Units	Variables			Results†	
				Outcome (ICD9)	Area level	Individual level	Rates (/100,000 unless stated otherwise) and/or ratios	Geographical pattern
Hammar, 2001[58]	Sweden 1993-1994 E	Persons aged 45-64 yrs	Stockolm (Southern urban county), Västernorrland (Northern rural county)	MI (410x) first fatal and non-fatal events	Education, job strain, shift work, smoking, low physical activity, coffee intake, obesity, diabetes, family history of CHD, elevated BP, high cholesterol and triglycerides		Events per 100,000 person-years Stockholm – men (326.6), women (86.2) Västernorrland – men (433.2), women (133.2) Higher prevalence of risk factors (obesity and elevated blood serum lipids) seems to explain higher incidence in Västernorrland for men.	Higher incidence in Västernorrland comparedwith Stockholm.
Hammar, 1994[59]	Sweden 1981 PBR	Patients aged 30-94	Stockholm (urban, center), Gävleborg (rural, north)	MI (410x) first fatal and non-fatal events			Age-standardized events RR (Gävleborg /Stockholm): Males (1.34) and females (1.21). Differences in diagnoses cannot explain this	Event rates systematically higher in Gävleborg than in Stockholm.
Nerbrand, 1991[60]	Mid-Sweden 1972-1981 PBR	Patients aged 45-74	Värmland (West) and Uppsala (East) counties	CHD (410-414x) hospitalizations			Age-standardized discharge rates: Värmland – 3498 (men) and 1415 (women) Uppsala – 1819 (men) and 719 (women)	Värmland always had higher rates than Uppsala, fitting mortality distribution.
Morris, 2003[61]	Great Britain 1978-1980 (20 yrs follow-up) PC	7,735 men aged 40-59	24 towns between 50,000 and 100,000 inhabitants	Major CHD (410-414x) first fatal and non-fatal events	Southern England/rest of Britain	Smoking, systolic BP, physical activity, social class, height	Hazard ratios (rest of Britain vs. South): 1.17	Significantly increased hazard in North than in South.
Morris, 2001[62]	Great Britain 1978-1980 (15 yrs follow-up) PC	7,735 men aged 40-59	24 towns between 50,000 and 100,000 inhabitants	Major CHD (410-414x) first fatal and non-fatal events	Water hardness, maximum and minimum temperature, daily rainfall, sunshine hours	Age, smoking, alcohol intake, serum total cholesterol, systolic BP, physical activity, social class, BMI, height.	Age-standardized incidence (/100 person-years) varied from 0.52 in Maidstone to 1.07 in Dewsbury. OR between opposite ends was 1.59.	Higher rates in Scottish and northern English towns than in southern English towns. The eight individual risk factors explained the majority of the North-South gradient.
Dunn, 2000[63]	Great Britain 1993-1995 PBR	Women aged 16-44	Regions: Scotland, North England, Midlands and Wales, South England	MI (410x) first fatal and non-fatal events		Age, smoking	Age and smoking standardized incidence rates (/100.000 person-years) South England – 1.32 (RR – 1) Midlands and Wales – 2.37 (1.8) North England – 2.33 (1.8) Scotland – 4.83 (3.7)	Incidence rates increase from South to North.
Arveiler, 2005[64]	France 1997-2000 PBR	Persons aged 35-74	Lille (North), Strasbourg (NE), Toulouse (SW) MONICA centers	MI (410x) fatal and non-fatal events			Age-standardized event rates (1997,1998,1999,2000): Strasbourg: Men (177,197,177,189); Women (38,37,42,39) Lille - Men (176,208,194,185); Women (26,28,32,37) Toulouse - Men (157,151,154,161); Women (17,20,16,18)	Higher event rates in North than in South, for both men and women.
Parra, 1992[65]	France, Northern Ireland 10 yr register PBCC	1,140 male cases and controls aged 25-64	Belfast, Strasbourg, Toulouse and Lille MONICA centers	MI (410x) non-fatal events		Age, BMI, smoking, alcohol intake, cholesterol (HDL, VLDL, LDL) triglycerides, Apo A-I-II, Apo B, Lp A-I, Lp A-II:A-I, Lp C-III:B, Lp E:B, Lp(a):B	Lp A-I level and high levels of Lp E:B and Lp(a):B could explain part of excess risk in Northern Ireland.	

Reference	Country/Region Period Study design*	Subjects	Geographic Units	Variables			Results†	
				Outcome (ICD9)	Area level	Individual level	Rates (/100,000 unless stated otherwise) and/or ratios	Geographical pattern
Scarabin, 2003[66]	Northern Ireland, France 1991-1993 (5 yrs follow-up) PC	10,600 men aged 50-59	MONICA centers: Lille, Strasbourg, Toulouse, Belfast	MI (410x) events, definite coronary death (410-414x), angina pectoris (413x) events		Age, BMI, systolic BP, total cholesterol, HDL cholesterol, diabetes, smoking status, fibrinogen, factor VII activity	Age- adjusted relative risk for CHD for Northern Ireland vs. France is 1.51. Classic risk factors explained 25% of excess risk and fibrinogen 30%.	Significantly increased risk in North than in South.
Ducimetière, 2001[67]	Northern Ireland, France 1991-1994 (5 yrs follow-up) PC	10,600 men aged 50-59	MONICA centers: Lille, Strasbourg, Toulouse, Belfast	MI (410x) fatal and non-fatal events Hard coronary cases (fatal and non-fatal) Angina pectoris cases			Incidence rate of all coronary events (per 1000 person-years): Belfast – 10.51 France – 5.48 (Lille – 4.78; Strasbourg – 5,.56; Toulouse – 6.08) Belfast/France ratio – 1.92	Higher incidence rates in Northern Ireland than in France
Marques-Vidal, 1997[68]	Germany and France 1985-1989 PBR	Aged 35-64	Augsburg (Germany) Toulouse (France) MONICA centers	CHD fatal events and MI non-fatal events			Age-standardized incidence and event rates significantly higher (p<0.001) in Augsburg than in Toulouse	Incidence and event rates higher in Augsburg than in Toulouse.
De Henauw, 1999[69]	Belgium 1983-1992 PBR	Residents aged 25-69	Ghent (North), Charleroi (South) MONICA centers	Acute coronary fatal and non-fatal events			Age-standardized event rates (ratio Charleroi/Ghent): 1.5 both for men and women	Event rates systematically higher in Charleroi than in Ghent.
Avogaro, 2007[70]	Italy 1998-1999 (4 yrs follow-up) PC	11,644 type 2 diabetics	North, Center, South and Islands	CHD first fatal and non-fatal events		Anthropometric measures, lifestyle data, clinical history and data relevant to microvascular and macrovascular complications, laboratory data; pharmacological treatment	Hazard ratios: South vs. North: Men 0.71; Women 0.97.	Significantly increased hazard for men in North than in South.
Ferrario, 2001[71]	Italy 1983-1985 (10 yr follow-up, except Latina) PBR	Persons aged 35-64	Brianza (NW)and Friuli (NE) Latina (Central) MONICA centers	Coronary and MI (410-414x) fatal and non-fatal events			Age-standardized mean event rates of MI: Latina – men (267.9), women (48.3) Friuli – men (267.9), women (49.4) Brianza – men (306.1), women (48.1) Age-standardized mean event rates of CHD: Latina – men (339.4), women (75.2) Friuli – men (373.8), women (89.8) Brianza – men (422.4), women (77.5)	CHD event rates increase from North to South, for both men and women. MI has a less geographical variability.
Bernardi, 1995 [72]	Italy 1992 PBR		Tuscany	MI (410x) hospitalizations			Hospitalizations (% of population) Tuscany – 0.21%; Italy – 0,09%	Hospitalizations higher in Tuscany (with soft water springs) than national average.
Marrugat, 2004[73]	Spain 1997-1998 PBR	Patients aged 25-74	Regions: Basque Country, Castilla-la-Mancha, Gerona, Majorca, Murcia, Navarra, Valencia	MI (410-414x) non-fatal events			Age-standardized cumulative incidence rates: Girona: Men (175), Women (42) Castilla-la-Mancha: Men (188), Women (39) Basque Country: Men (193), Women (36) Navarra: Men (203), Women (42) Majorca: Men (209), Women (47) Valencia (217), Women (48) Murcia: Men (252), Women (65)	Higher incidence rates in South than in North, for both men and women.
Wu, 2001[74]	China 1987-1993 PBR	Persons aged 35-64	17 Sino-MONICA centers	Non-fatal coronary events			Age-standardized incidence rates: Highest: Shangdong – men (108.7), women (34.0) Lowest: Anhui – men (3.9), women (0.7)	Among both men and women age-standardized incidence low by international standards. Rates tend to be higher in North.

Reference	Country/Region Period Study design*	Subjects	Geographic Units	Variables			Results†	
				Outcome (ICD9)	Area level	Individual level	Rates (/100,000 unless stated otherwise) and/or ratios	Geographical pattern
Hall, 2003[75]	Canada 1997-2000 PBR	Residents aged ≥ 20	130 regions	MI (410x) and Angina (411-413x) hospitalizations			Age and sex-standardized hospitalization rates: MI – between 135 (Vancouver) and 405 (Nova Scotia) Angina - between 55 (Calgary) and 405 (Quebec)	Hospitalization rates for angina increase from the West to the East. MI has only a modest geographical variation, although similar.
Garg, 1992[76]	USA 1971-1975 (7 to 16 yrs follow-up) PC	1,838 white males aged 55-74	Northeast, Midwest, South, West	CHD (410-414x) first fatal and non-fatal events		Age, region, height, weight, smoking status, educational level, serum cholesterol, BP, history of hypertension and diabetes	Age-standardized incidence rates (/1000 person-year): Northeast – 41.6; Midwest – 39.6; South – 45.9; West – 31.3. Relative risk (non-West/West):1.38. Variation of risk profiles does not explain the difference, their effects varied by region.	Incidence rates increasing from West to East.
Mensah, 2005[77]	USA 2000 PBR	Medicare enrollees aged ≥ 65	States	MI (410x) hospitalizations			Age-standardized hospitalization rates vary between states from 820 to 2030	Low rates in the West. Some clustering along the Appalachians.
Rich, 2007[78]	USA 1982-2004 PC	17,927 male physicians aged 40-84 in 1982	Southeast, West, Midwest, Northeast	MI (410x) events		Age, region alcohol intake, smoking, exercise, BMI, history of cholesterol, hypertension and diabetes, parental history of MI before 60.	Hazard ratios (Northeast = 1): Southeast – 0.86 Midwest – 0.96 West – 1.05	No significant association between MI and region of residence was found.
Bertoni, 2005[79]	USA 1994-1999 RC	126,153 whites and 17,962 blacks aged ≥65 with diabetes	South, West, Midwest, Northeast	MI and CHD first fatal and non-fatal events		Sex, age, race, region, comorbidities	Hazard ratios (South vs rest of USA): MI: Whites – 0.94; Blacks – 0.77 CHD: Whites – 0.95; Blacks – 0.72	Significant decreasing hazard in South, especially for blacks.
Lao, 2008[80]	Europe 1990s E	European MONICA populations	European MONICA centers	Coronary events	Frequency of genetic susceptible factors and non-genetic factors (smoking, average systolic BP, cholesterol, BMI)		Genetic variants uncorrelated with the disease North-South geographic pattern	
Kousa, 2008[81]	Finland 1991-2003 E	Rural residents aged 35-74	10x10 km grid cells	MI first fatal (410-414, 798x) and non-fatal (410x) events	Ca, Mg, Zn, Al, Cu, F, Fe and NO_2 concentrations in ground water		1 mg/l increment in Mg associated with 2% decline in MI age-standardized incidence rates.	Mg concentrations inversely match incidence Northeast/Southwest pattern.

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Disclosures

None.

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3.2. Time trends in Coronary Heart Disease Mortality in Portugal: After a quarter of century overall better but accentuated regional inequalities.

Time trends in Coronary Heart Disease Mortality in Portugal: After a quarter of century overall better but accentuated regional inequalities

Ana Ribeiro, BS[1,2,3], Maria de Fátima de Pina, PhD[1,2,3], Carla Lopes[2,3], Henrique Barros[2,3]

[1]INEB – Instituto de Engenharia Biomédica; [2]Faculdade de Medicina, Serviço de Higiene e Epidemiologia, Universidade do Porto; [3]ISPUP – Instituto de Saúde Pública da Universidade do Porto

Abstract

Background: Portugal presents one of the lowest mortality rates due to Coronary Heart Disease (CHD) among the European Union countries. However, regional and gender variations in CHD mortality might be anticipated on line with other well known social and health inequalities. Thus we aimed to identify geographic and sex disparities in the time trends of CHD mortality in Portugal, from 1981 to 2005.

Methods: CHD age-standardized mortality rates (ASMR /100,000: 95% CI), were calculated by year, sex and district for age 35 to 74 years. Time variations (%) during the study period were obtained using linear regression.

Results: Nationwide, from 1981 to 2005, there was a 47.4% decline in CHD ASMR (46% in men and 52% in women), although the regional differential increased from four to over fivefold. In 1981, the highest ASMR was observed in the Azores Islands (222.7; 193.9-251.5), about twice the national ASMR (103.0; 100.0-106.0), and the lowest in the district of Vila Real (North) (54.7: 41.5-67.9). In 2005, the country ASMR was 49.8 (47.9-51.6), being the lowest in the central district of Leiria (25.4: 19.4-31.5) and the highest in the Azores (135.8: 113.3-158.3). North and Central coastal districts presented the steepest decline, nearly two thirds for men and above 70% in women. The sex-ratio increased from 2.65 in 1981 to 3.00 in 2005.

Conclusion: A decline in the ASMR from CHD in Portugal was observed between 1981 and 2005. The decline was not widespread: in some districts no significant reduction was registered. However, the regional spatial pattern remained unchanged, and the geographic and sex inequalities increased showing that after 25 years of technical improvements, better health care structures and a higher ratio of health care workers/inhabitants inequalities deepened.

Introduction

Cardiovascular diseases (CVD), particularly coronary heart disease (CHD), are the main cause of mortality and morbidity [1]. In 2004, CHD caused 7.2 million deaths worldwide, 12.2% of the overall mortality. In Portugal, stroke is the leading cause of death, presenting one of the highest mortality rates of the World, CHD being less common than the remaining European countries. In 2005, in Portugal 8,637 deaths of CHD occurred, corresponding to a 8.0% of the global mortality [1-2].

CHD mortality has been declining since the late 1970s in the Western World and, in three decades, mortality rates have halved in several regions [3]. The declining tendency started earlier in countries with higher mortality rates, such as UK, Finland and USA, but progressively was extended to countries with lower risk. This decrease in CDH related mortality was also observed in large observational cohort studies, providing more accurate death certification, approaching a 50% decrease in the USA [4-5].

In contrast, CHD mortality is rising in Eastern Europe, as well as in newly industrialized countries such as China, India and Mexico, and for this reason the burden of CHD will continue to increase in the next decades [3, 6-7]. According to the results of the World Health Organization (WHO) project Multinational MONItoring of trends and determinants of CArdiovascular disease (MONICA), the reduction in CHD mortality has resulted from a simultaneous decline in event rates and in case-fatality rates, respectively by two thirds and one third [8].

Along with time trends in CHD mortality, many studies addressed the sex-ratio issue across countries and regions. The higher frequency of CHD among males is well established, with a sex-ratio ranging from 2.5 to 4.5 as documented in a set of 52 countries, presenting high or low mortality rates [9]. Significant differences in sex-ratio were also found within countries [10].

However, geographical heterogeneity and time-trends of the disease in low-risk countries, such as Portugal, remains poorly documented and it would be useful to monitorize if the preventive measures have been successful across the whole country and, if not, what could have failed. Thus, we aimed to estimate regional and sex trends of CHD mortality, from 1981 to 2005 in Portugal.

Materials and methods

Study area

The geographical area of study was Portugal, including the Continental area and the Atlantic Archipelagos of the Azores and Madeira which are two Autonomous Regions (AR). Continental Portugal is divided into 18 districts being, together with the AR, the geographic units of analysis. In 2005, Portugal had a population of 10,569,592 inhabitants, with a mean of 528,479 (SD 558,613) inhabitants per district. The less populated district (Portalegre) had 120,581 inhabitants and the more populated (Lisbon) 2,215,319 inhabitants. The majority (95.4%) of the population lives in the continental territory and in the urban and semi-urban areas (86%), which are essentially concentrated along the coast. The climate is Mediterranean temperate with an annual average temperature of 13°C in the north and 18°C in the south.

Data

The mortality data from 1st January 1981 to 31st December 2005 was obtained from the Portuguese Vital Statistics of the National Institute of Statistics (INE – Instituto Nacional de Estatística) and the Portuguese General Health Directorate (DGS – Direcção-Geral de Saúde). In these statistics, deaths from CHD are classified according to the International Classification of Diseases version 9 (ICD9), codes 410-414, covering myocardial infarction, angina pectoris and other forms of ischemic heart disease. Data after 2005 are available only at Nomenclature of Territorial Unit, level III (NUTIII) which is incompatible with the geographic limits of districts, and for that reason they were not used in this study. Mortality and population data were grouped by sex and 10-year age groups at district level and the analysis was restricted to the ages between 35 and 74 years old. CHD deaths below 35 years old were excluded to avoid underestimation of mortality rates, since they are rare at younger ages and usually associated with different causes. The deaths of individuals above 74 years old were also excluded, because the death certificates are less accurate in this age group, which could lead to an overestimation of mortality rates [11-13].

Statistical Analysis

The Age-Standardized Mortality Rates (ASMR) and the 95% Confidence Intervals (95% CI) were calculated for every year during the study period, by the direct method using European Population as standard. Portuguese population from Census was used for 1981, 1991 and 2001. In the inter-census periods from 1992-2000 and 2002-2005, estimates by district, sex and 10-year age groups were obtained from the Demographic Statistics of the INE. For the inter-census period of 1982-1990 the estimates were calculated by interpolation, assuming exponential growth, and that no striking demographic changes had occurred during that decade.

In addition, Standardized Mortality Ratios (SMR) and sex ratios (men:women – m:w) of the ASMR were calculated. Variations (%) between 1981 and 2005 of the ASMR and sex-ratios were calculated by linear regression and georeferenced using Geographic Information System (GIS) tools.

Results

Maps in Figure 1 show the geographical distribution of ASMR among men and women, as well as the sex-ratio of the years 1981 and 2005.

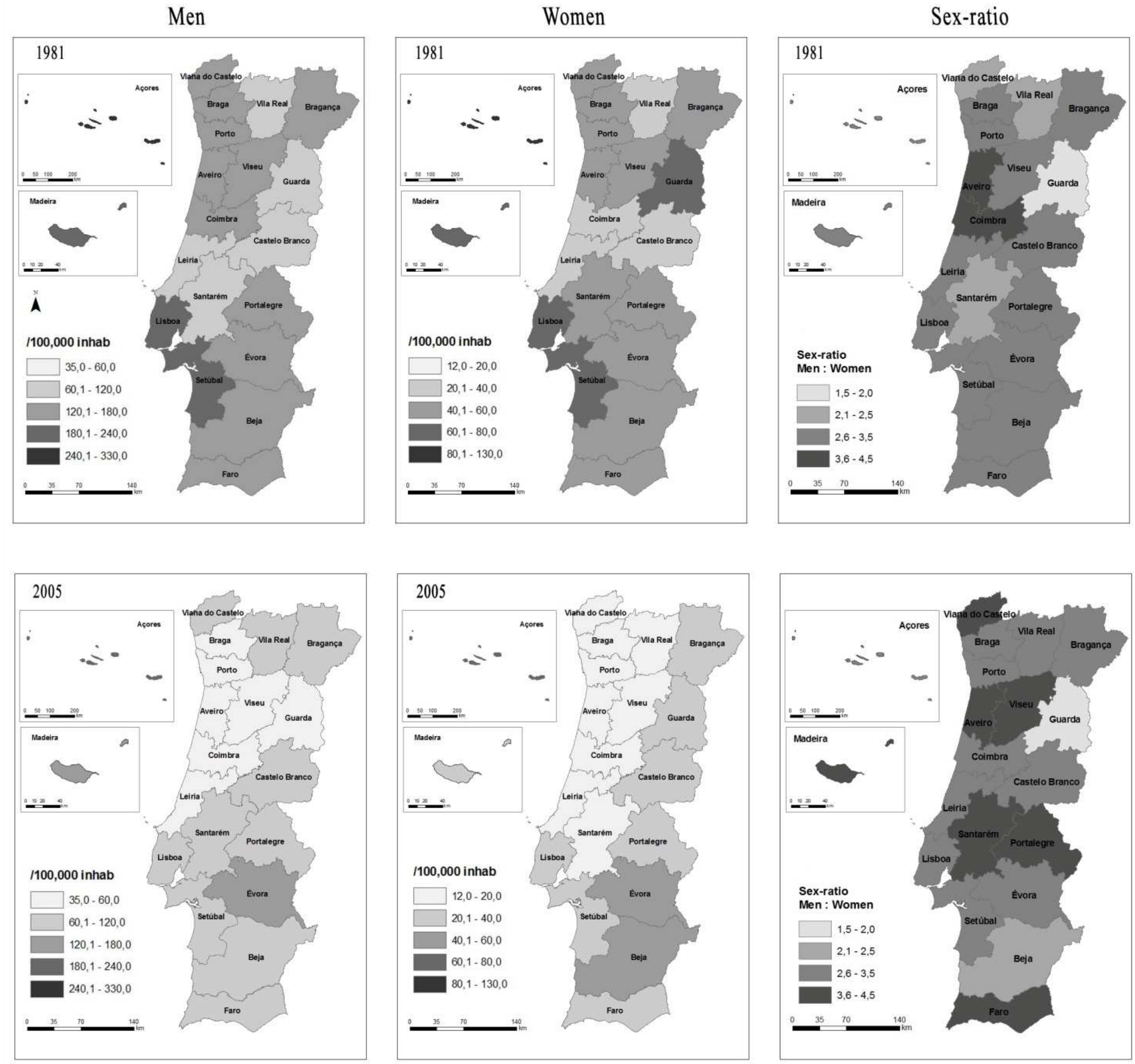

Figure 1– Geographic distribution of ASMR and Sex-ratio of CHD in 1981 and 2005

In 1981, the ASMR (per 100,000 inhabitants: CI 95%) for CHD in Portugal was 103.0: 100.0-106.0 and accentuated geographic patterns were observed.

The archipelagos presented the highest ASMR nationwide, during all the study period, particularly the Azores (222.7: 193.9-251.5), with more than twice the national mortality rates.

In Continental Portugal, the highest ASMR were concentrated in the southern half of the country in the districts of Lisbon (133.1: 125.5-140.6), Setúbal (119.7: 106.4-133.0) and Beja (113.2: 93.5-133.0), whereas the lowest values were observed in the northern half of Portugal, namely Vila Real (54.7: 41.5-67.9), Castelo Branco (68.1: 53.8-82.4), Coimbra (72.3: 61.0-83.6) and Leiria (72.3: 60.3-84.2). The geographical pattern remained similar by sex, although two exceptions must be mentioned: for men, Coimbra was not among the districts with the lowest ASMR and Porto was the fourth district with the highest mortality rates.

A quarter of a century later, the national ASMR almost halved (49.8: 47.9-51.6) but the geographical disparities increased from 4.1 to 5.3 times between the districts with highest and lowest ASMR. The Azores (135.8: 113.3-158.3), Beja (79.7: 62.0-97.4), Setúbal (73.9: 66.0-81.8), Lisbon (68.0: 63.4-72.6) and Madeira (67.8: 52.2-83.4) maintained the ASMR above the average while Leiria (25.4: 19.4-31.5) and Coimbra (30.5: 23.8-37.2) remained districts with lower risk. The district of Évora, in the south (Alentejo region), has worsened its position, being in 2005 among the regions with the highest ASMR.

During the study period the national sex-ratio m:w increased from 2.65 to 3.00 and there were accentuated geographic differences. In 1981, the sex-ratio ranged from 1.85 in Guarda to 4.03 in Coimbra, while in 2005 the variation was from 1.67 in Guarda to 4.13 in Madeira.

The ASMR (95%CI) for each district and AR, as well as the SMR, the position in a rank from the highest (ranked 1) to the lowest ASMR (ranked 20) and the sex ratio are presented in Table 1.

There was a set of districts, within the coastal North and Central Portugal, with the SMR almost constantly below 100 and ranked in the last positions (lower CHD ASMR); and, in contrast, the archipelagos and the Southern districts of the country showed SMR above 100 and were placed in the first positions of the ASMR ranking all along the study period.

Table 1 – Age-standardized mortality rates (ASMR) of CHD and standardized mortality ratios (SMR) in the first and last available years. Age 35-74 years.

DISTRICT		TOTAL		MEN		WOMEN	
		1981	2005	1981	2005	1981	2005
Aveiro	ASMR	95.4 [83.2-107.7]	28.7 [23.4-34.1]	158.2 [134.6-181.7]	46.9 [36.8-57.0]	42.3 [31.7-53.0]	12.6 [7.9-17.3]
	SMR	92.2	58.8	101.7	61.3	70.8	51.6
	Rank*	8	19	8	17	15	20
	Sex-ratio	3.74	3.72				
Beja	ASMR	113.2 [93.5-133.0]	79.7 [62.0-97.4]	170.2 [135.4-205.1]	112.1 [81.0-143.2]	57.8 [38.9-76.7]	49.3 [31.6-67.0]
	SMR	111.5	167.7	111.4	146.6	98.8	211.1

	Rank	5	2	6	4	6	2
	Sex-ratio	2.94	2.27				
Braga	**ASMR**	91.7 [79.6-103.8]	29.6 [24.2-35.1]	136.6 [114.3-158.8]	48.1 [37.8-58.4]	53.1 [41.2-65.1]	13.9 [8.9-18.9]
	SMR	89.0	59.7	87.3	61.7	90.1	55.0
	Rank	10	18	9	16	9	19
	Sex-ratio	2.57	3.47				
Bragança	**ASMR**	91.9 [71.8-112.0]	41.8 [28.5-55.2]	134.4 [99.0-169.8]	63.4 [39.8-87.1]	50.5 [30.7-70.3]	22.7 [8.9-36.5]
	SMR	84.4	86.7	80.4	86.7	83.6	83.8
	Rank	9	11	10	12	11	11
	Sex-ratio	2.66	2.79				
Castelo Branco	**ASMR**	68.1 [53.8-82.4]	43.9 [32.2-55.6]	101.2 [75.4-127.1]	64.3 [43.2-85.4]	38.9 [24.6-53.2]	25.3 [14.0-36.5]
	SMR	62.7	89.5	61.9	82.7	61.1	105.2
	Rank	19	9	19	10	18	9
	Sex-ratio	2.60	2.54				
Coimbra	**ASMR**	72.3 [61.0-83.6]	30.5 [23.8-37.2]	122.9 [100.7-145.1]	46.3 [34.1-58.5]	30.5 [21.2-39.8]	17.0 [10.3-23.7]
	SMR	70.1	62.4	78.5	61.1	53.0	65.9
	Rank	17	17	13	18	20	15
	Sex-ratio	4.03	2.73				
Évora	**ASMR**	89.9 [71.5-108.3]	79.1 [61.4-96.7]	133.8 [101.3-166.3]	121.5 [89.9-153.1]	47.2 [29.3-65.1]	41.2 [23.7-58.7]
	SMR	88.1	155.4	87.4	158.6	80.1	146.5
	Rank	11	3	11	2	14	3
	Sex-ratio	2.84	2.95				
Faro	**ASMR**	87.8 [74.0-101.7]	56.1 [46.4-65.8]	129.2 [104.8-153.5]	89.5 [71.8-107.1]	47.5 [34.0-61.1]	23.3 [14.9-31.6]
	SMR	83.8	109.3	81.7	112.1	79.7	92.0
	Rank	12	7	12	8	13	10
	Sex-ratio	2.72	3.84				
Guarda	**ASMR**	85.9 [68.4-103.4]	33.9 [23.1-44.6]	112.1 [82.9-141.4]	43.3 [25.0-61.6]	60.5 [41.0-80.1]	25.9 [13.4-38.4]
	SMR	79.7	72.8	70.4	58.7	95.0	105.8
	Rank	13	15	17	19	4	7
	Sex-ratio	1.85	1.67				
Leiria	**ASMR**	72.3 [60.3-84.2]	25.4 [19.4-31.5]	107.0 [85.7-128.3]	38.2 [27.3-49.0]	39.8 [28.0-51.6]	13.9 [7.9-20.0]
	SMR	69.8	51.3	68.5	49.8	66.8	53.6
	Rank	18	20	18	20	17	18
	Sex-ratio	2.69	2.74				
Lisboa	**ASMR**	133.1 [125.5-140.6]	68.0 [63.4-72.6]	199.2 [185.2-213.2]	105.1 [96.6-113.6]	78.5 [71.0-86.0]	36.4 [31.9-40.9]
	SMR	129.3	135.8	127.0	135.6	131.0	138.4
	Rank	2	5	2	6	2	5
	Sex-ratio	2.54	2.89				
Portalegre	**ASMR**	103.5 [82.7-124.3]	55.5 [39.5-71.6]	161.7 [123.4-200.1]	91.8 [61.2-122.4]	50.9 [31.9-70.0]	25.6 [11.1-40.1]
	SMR	105.1	125.2	107.1	133.4	91.7	107.0
	Rank	7	8	7	7	10	8
	Sex-ratio	3.18	3.59				
Porto	**ASMR**	110.2 [101.5-118.9]	35.0 [31.1-38.9]	174.6 [157.9-191.3]	53.3 [46.3-60.4]	56.8 [48.8-64.8]	19.2 [15.3-23.0]
	SMR	106.8	70.8	111.7	69.1	97.0	75.7
	Rank	6	14	5	14	7	13
	Sex-ratio	3.07	2.78				
Santarém	**ASMR**	79.6 [68.2-91.0]	37.2 [29.9-44.6]	114.2 [94.0-134.5]	60.2 [46.4-74.1]	47.7 [36.2-59.2]	16.9 [10.5-23.4]
	SMR	76.8	73.9	72.4	76.9	81.5	66.9
	Rank	15	13	16	13	12	16
	Sex-ratio	2.40	3.55				
Setúbal	**ASMR**	119.7 [106.4-133.0]	73.9 [66.0-81.8]	182.8 [158.9-206.7]	111.3 [97.2-125.4]	60.4 [47.6-73.2]	39.6 [31.8-47.4]
	SMR	115.8	144.5	116.8	139.9	98.9	151.0
	Rank	4	4	4	5	5	4
	Sex-ratio	3.03	2.81				
Viana do Castelo	**ASMR**	83.7 [67.6-99.9]	42.4 [31.9-53.0]	122.5 [92.1-153.0]	72.0 [51.2-92.7]	54.0 [37.5-70.5]	19.1 [10.0-28.2]
	SMR	81.2	89.0	77.8	96.9	90.7	78.3
	Rank	14	10	14	9	8	14

	Sex-ratio	2.27	3.76				
Vila Real	**ASMR**	54.7 [41.5-67.9]	40.3 [29.0-51-5]	77.6 [54.5-100.7]	64.1 [43.6-84.7]	33.5 [19.7-47.3]	19.9 [8.7-31.1]
	SMR	53.0	79.9	49.8	84.6	56.0	67.8
	Rank	20	12	20	11	19	12
	Sex-ratio	2.32	3.23				
Viseu	**ASMR**	78.7 [66.3-91.1]	32.1 [24.7-39.5]	122.1 [99.0-145.3]	53.1 [39.0-67.1]	41.2 [29.6-52.8]	14.3 [7.7-20.9]
	SMR	73.9	66.9	75.4	71.5	68.3	56.3
	Rank	16	16	15	15	16	17
	Sex-ratio	2.96	3.72				
Azores	**ASMR**	222.7 [193.9-251-5]	135.8 [113.3-158.3]	329.0 [277.6-380.4]	215.6 [173.9-257.2]	126.5 [97.7-155.3]	66.5 [45.2-87.9]
	SMR	216.2	273.9	211.3	279.5	211.6	257.5
	Rank	1	1	1	1	1	1
	Sex-ratio	2.60	3.24				
Madeira	**ASMR**	122.0 [100.2-143.9]	67.8 [52.2-83.4]	197.2 [153.9-240.4]	120.9 [88.5-153.2]	64.9 [44.9-84.9]	29.2 [16.2-42.3]
	SMR	119.2	134.9	125.1	155.6	112.8	114.7
	Rank	3	6	3	3	3	6
	Sex-ratio	3.04	4.13				
Total	**ASMR**	**103.0 [100.0-106.0]**	**49.8 [47.9-51.6]**	**156.0 [150.4-161.5]**	**77.3 [73.9-80.6]**	**58.8 [55.8-61.9]**	**25.8 [24.0-27.5]**
	SMR	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
	Sex-ratio	**2.65**	**3.00**				

**Descending order*

From the linear regression analysis, it was observed that the yearly CHD ASMR had an accentuated decline with 47.4% reduction nationwide from 1981 to 2005, more pronounced in women (52.6%) than in men (46.1%). Figure 2 presents the trends of ASMR (A) and age-specific mortality rates (B and C) by sex.

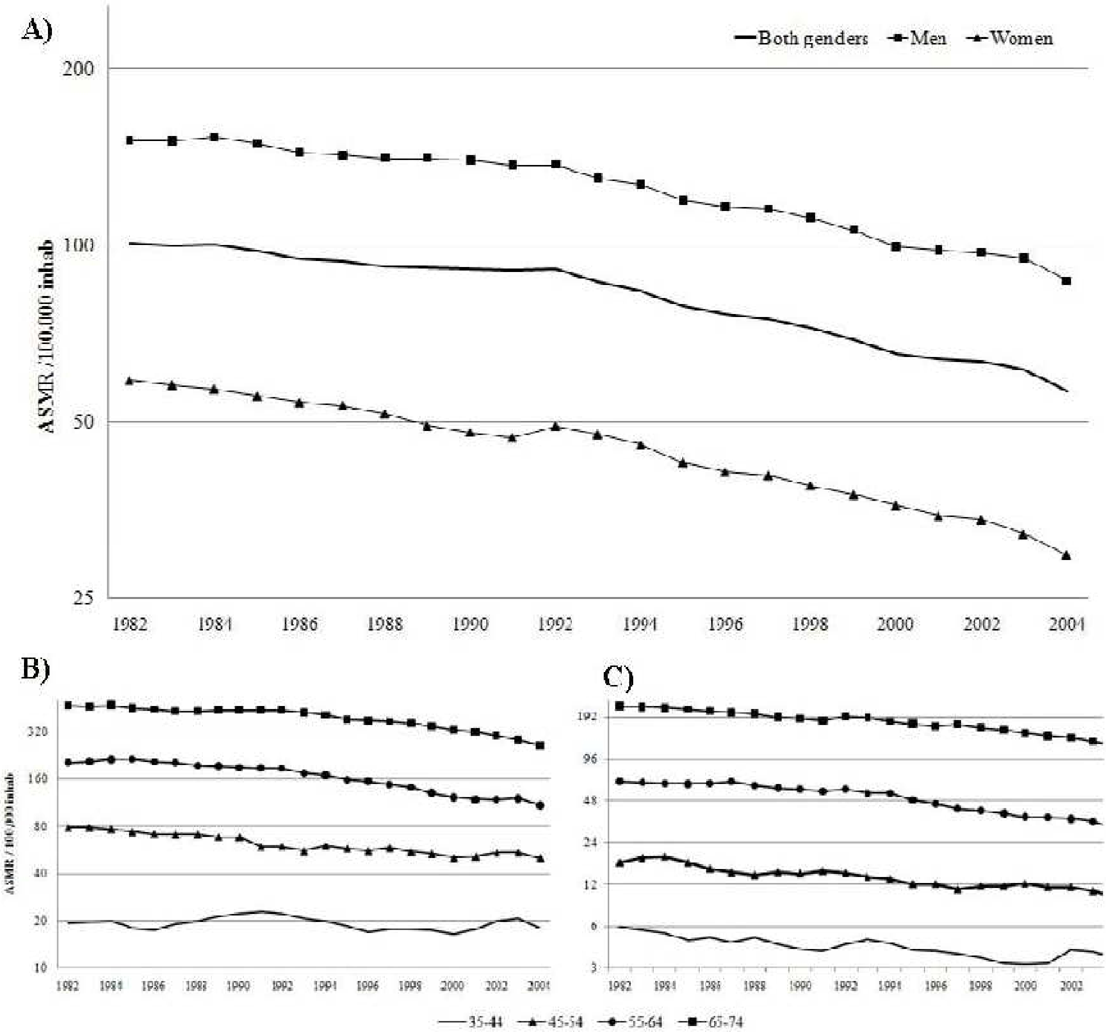

Figure 2 - Evolution (3years smooth, logarithmic scale) of age-standardized mortality rates (A) and age-specific mortality rates for men (B) and women (C) from coronary heart disease in Portugal, 1981-2005.

Some districts in north and central regions of Continental Portugal had a decline in the ASMR above 60%, while in the south; the percentage of decline was much smaller, around 30% (Figure 3). Among women, the decline was steeper, above 70% in some of the northern districts.

Nationwide, a statistically significant (p=0.002) increase was observed in the sex-ratio, but at regional level, the vast majority of districts did not present such significant differences.

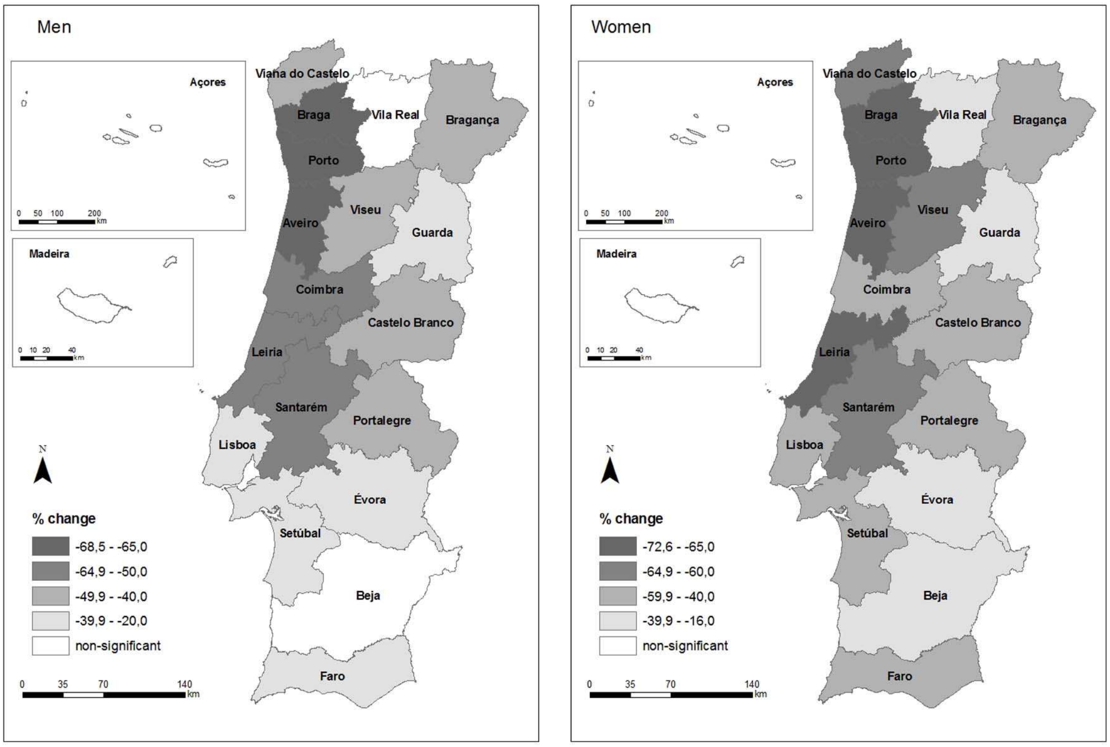

Figure 3 – Geographic distribution of variation (%) in ASMR of CHD in men and women

Discussion

In a quarter of century, Portugal, had a reduction in the mortality of Coronary Heart Disease of nearly 50% for both sexes, but regional differences remained during the study period. The districts along the coast, in the Northern and Central Continental territory presented declines of roughly two thirds, while in the South and in the archipelagos of the Azores and Madeira the reductions were less pronounced, increasing the gap between higher and lower risk regions. Putting in other words, CHD mortality decline was not widespread across Portugal and in some districts no meaningful reduction was assessed. Beyond the regional inequalities in the mortality of CHD, time-trends differed by sex and, as a consequence of a stronger decline among women, the ratio m:w increased nationwide.

It was not the purpose of present study to investigate the reasons for such regional inequalities. However, the geographic distribution of cardiologists, its increase in the last years and recent creation of Acute Coronary Care Units (ACCU), in a first inspection, doesn't seem to explain the regional differences in CHD mortality time-trends.

As in other countries, a combination of changes in lifestyle and in the health care system may explain the majority of the decline observed in mortality for CHD in Portugal, but further analysis is needed to be done to confirm this.

The magnitude of the decline of CHD mortality in Portugal was very similar to what was reported in other studies in the Western Europe and North America, although in those regions the decline began earlier, in the 1970s-1980s, whereas in Portugal the steepest decline seems to have started in the early 1990s.

Pointing in the same direction were the results from a study on mortality by CHD, between 1994 and 2001, in the South European countries [14]. There, a North-South trend in Portugal was also observed; among women the reduction in the CHD mortality was strongest (above 50% nationwide) and was significant in all districts, while among men the observed decline was significant only in Lisbon, Leiria and Coimbra districts. In our study, which involved a longer period, the decline among men was significant for all districts except Beja, Vila Real and the Azores and Madeira.

Attempts have been made to explain these recent and accentuated reductions in CHD mortality rates. In England, 41.8% of the decrease was attributed to treatment (11.2% to secondary prevention, 12.6% to heart failure, 7.7% to acute myocardial infarction, 7.0% to angina, 3.1% to hypertension and 0.2% to statins for primary prevention) and 58.2% to reduction in population risk factors, mainly in tobacco consumption (-48.1%), blood pressure (-9.5%), cholesterol (-9.6%) and deprivation (-3.4%), against an inverse effect in physical inactivity (+4.3%), obesity (+3.4%) and diabetes (+4.7%) [15]. Other studies, although not quantifying the contribution of each determinant, attributed the decline to improved smoking habits among men, better control of hypertension and advances in treatment [3].

In a worldwide study on cardiovascular mortality time-trends, reductions in the ASMR among Portuguese men (27.4%) and women (33.9%) were observed between 1965 and 1998. The smallest magnitude of this decrease, compared to our results, can be explained by the study period, which includes years in which mortality rates increased in the majority of the western countries, including Portugal [3].

In Spain, between 1980 and 1998, CHD mortality rates declined by 12% in men and 11% in women and significant reductions were observed in 27 out of 52 provinces among men, whereas in women only 12 provinces showed significant declines [16]. In other words, and in contrast to what was observed for Portugal, decline was slightly more marked in men than in women.

Concerning the increasing tendency in the sex-ratio detected in this study, nationwide and in some districts of Portugal, few studies analyzed sex-ratio trends for CHD. Even so, secular analyses of differences in the mortality, by sex, for cardiovascular diseases have detected phases in sex-ratio evolution that tend towards an increase, or in some cases stabilization, of the sex-ratio. In England, until 1920s there was no apparent excess in men mortality from CVD; in a second phase, from 1920s to 1960s, mortality from CVD increased intensively among men and sex differences showed up; and, finally in a third phase, from the 1960s to the present, the excess of mortality among men persisted with stabilization of the sex-ratio [17]. Another investigation of CHD mortality, developed in England, confirmed that sex differences started to be identified in the beginning of the 20^{th} century and since 1950s mortality from CHD among men presented a marked increase peeking in the 1970s [18].

A study, covering CVD mortality from 1956 to 1988 in several countries in the world, reported an increase in the sex ratio in all age groups in most of the countries. In Portugal the increase was more accentuated in the younger ages, namely of 54.7%, 40,4% and 24.6% for the age groups of 45-54, 55-64 and 65-74, respectively [19].

One possible explanation for the still ongoing trend of increase in the sex-ratio is the pattern of Portuguese smoking habits, one of the major risk factors for CHD. In 1999-2000, Portugal was still in the transition from the second to the third stage of the smoking epidemic, the prevalence of smoking being higher among men, while among women, especially the younger and more educated, tobacco consumption was becoming more prevalent. Thus, it is expected that the prevalence of smoking in women will reach that among men, increasing the burden of CHD among women and consequently the sex-ratio will invert the actual increasing tendency [20].

The main limitation of this study relates to the quality of statistics of mortality, which are dependent on the quality of death certificates. Nevertheless, to avoid overestimation of mortality rates, the age group above 74 years old, which is more prone to be affected by the lower quality of death certificates, was excluded from the analysis. On the other hand, to avoid the underestimation of mortality rates, since deaths for CHD are rare among the young, the age group under 35 years old was also excluded. In general, official statistics are accurate sources of information for epidemiologic investigation, although, according to some authors, they tend to overrate mortality in comparison with data from clinical records [12, 21]. For that reason, the results must be interpreted with caution. Moreover, the change in disease codification with the introduction of ICD, 10^{th} revision in 1998 could interfere in the quality of data. However, in Portugal the ICD9 was used from 1980 until 2001, which comprises almost all the study period and therefore the variations observed cannot be attributed to the changes in codification.

The present study has the advantage of covering a period of 25 years, which makes the temporal analysis less prone to bias as result of sporadic fluctuations. On the other hand, districts were used, instead of municipalities, to avoid random fluctuations associated with small numbers, which would be the case in some municipalities with small populations and few deaths by CHD, especially among women.

In conclusion, a generalized decline in Portuguese CHD mortality rates was registered between 1981 and 2005, which is in accord with the Western European and North American trends. In Portugal, the geographic and sex inequalities in CHD mortality, however, increased in the study period.

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3.3. The geographic distribution of coronary heart disease hospitalizations in Portugal between 1997 and 2005.

The geographic distribution of coronary heart disease hospitalizations in Portugal between 1997 and 2008

Ana Ribeiro, BS[1,2,3], Maria de Fátima de Pina, PhD[1,2,3]

[1]INEB – Instituto de Engenharia Biomédica; [2]Faculdade de Medicina, Serviço de Higiene e Epidemiologia, Universidade do Porto; [3]ISPUP – Instituto de Saúde Pública da Universidade do Porto

Abstract

Introduction: Geographical differences in coronary heart disease (CHD) mortality have been widely reported in epidemiological studies. In Portugal, the highest CHD mortality rates are located in the districts of Lisboa and Setúbal and in the Azores Archipelago. Little is known about the incidence of such disease. The objective of this study was to identify spatial patterns of CHD hospital admissions in Portugal.

Methods: Hospital admissions due CHD (International Codification of Diseases, version 9 Clinical Modification ICD9-CM: 410-414x, 429.2x) in Continental Portugal were obtained from 1997 until 2008 from the National Hospital Discharge Register. Age-standardized hospitalization rates (ASHR) were computed by periods of three years, for individuals aged 35-74 years old, at municipal and district level. Spatial statistics methods were applied to smooth the ASHR and to identify significant spatial clusters.

Results: There were 266,475 hospital admissions with CHD as primary or secondary diagnosis in the study period. The overall ASHR (/100,000: CI 95%) remained stable during the 12 years but geographic inequalities and spatial clustering were observed. Differences of 2.0-fold (men) and a 2.8-fold (women) in the ASHR per district were observed in the last triennium. Spatial autocorrelation, measured by Moran index showed moderate degree of spatial dependency (0.43 and 0.41 in men and women, respectively, in 2006-2008) and spatial clusters were identified. A Northeast-Southwest trend, (from lowest to highest values) in the ASHR was revealed.

Conclusion: The ASHR of CHD remained stable along the study period, but fatality had a reduction of 25% in both sexes, following the trends of mortality for CHD in the developed countries and suggesting that decrease in mortality observed in the last decades is not associated to a decrease in the incidence of CHD, rather to an increase in survival due to improvements in the health care procedures. The mean length of stay significantly decreased, while the costs of hospitalization increased. Accentuated geographic inequalities of ASHR were observed in Continental Portugal, higher among women. Women were older, had a longer LOS, lower average costs per admission and almost the double fatality, comparing to men.

A Northeast-Southwest trend in the ASHR was coincident with the borderline of the climate regions in Portugal. Reasons for geographical distribution of ASHR must be better investigated. Explanations should not be based only on cardiovascular risk factors, but also on external determinants such as climate diversity.

Introduction

Geographical differences in coronary heart disease (CHD) mortality have been widely described in epidemiological studies [1-3]. In Portugal, reports documented a strong North-South pattern, for both sexes, placing the highest CHD mortality rates in the Lisboa and Setúbal districts and in the Azores Archipelago [4-5]. Additionally, a study carried out for Southern Europe observed roughly the same pattern, being Lisboa district the worst region in terms of mortality and the Center region of Portugal the better one [6].

Reasons for this patterning were not identified yet. One hypothesis is that regional differences of mortality rates for CHD derived from identical spatial inequalities of the incidence of such diseases; other, that they arise from spatial differences in survival. Obviously, geographical differences in CHD mortality can also be due to differences in quality of death certification and international investigations were performed to verify it in particular areas [7]. Despite the majority of the international studies, engaged to interpret the geographic inequalities, investigated only mortality, the importance of using morbidity indicators has been increasingly recognized, either in the study of CHD time-trends or in the investigation of geographical differences [8-11].

The present investigation was undertaken to examine the geographic distribution of hospital admissions (as a proxy of incidence) from 1997 until 2008 in Portugal and to determine the burden of CHD hospital admissions.

Materials and Methods

1. Study area

The study area was Continental Portugal, which is divided into 279 municipalities, forming 18 districts (Figure 1a), the most populated being the district of Lisboa and the less populated Portalegre. The climate in Continental Portugal is influenced by the Northeast-Southwest orientation of the Montejunto-Estrela Mountains creating two major climatic regions: North and South. Figure 1b shows the borderline that divides the North and South major climatic regions [12]. In the north climatic region the mean altitude is higher and the climate is temperate Atlantic, with mild summers and very humid and rainy winters (relief precipitation). On the contrary, the south climatic region is plain and the climate is typically Mediterranean, characterized for the mild winters and very long, dry and hot summers.

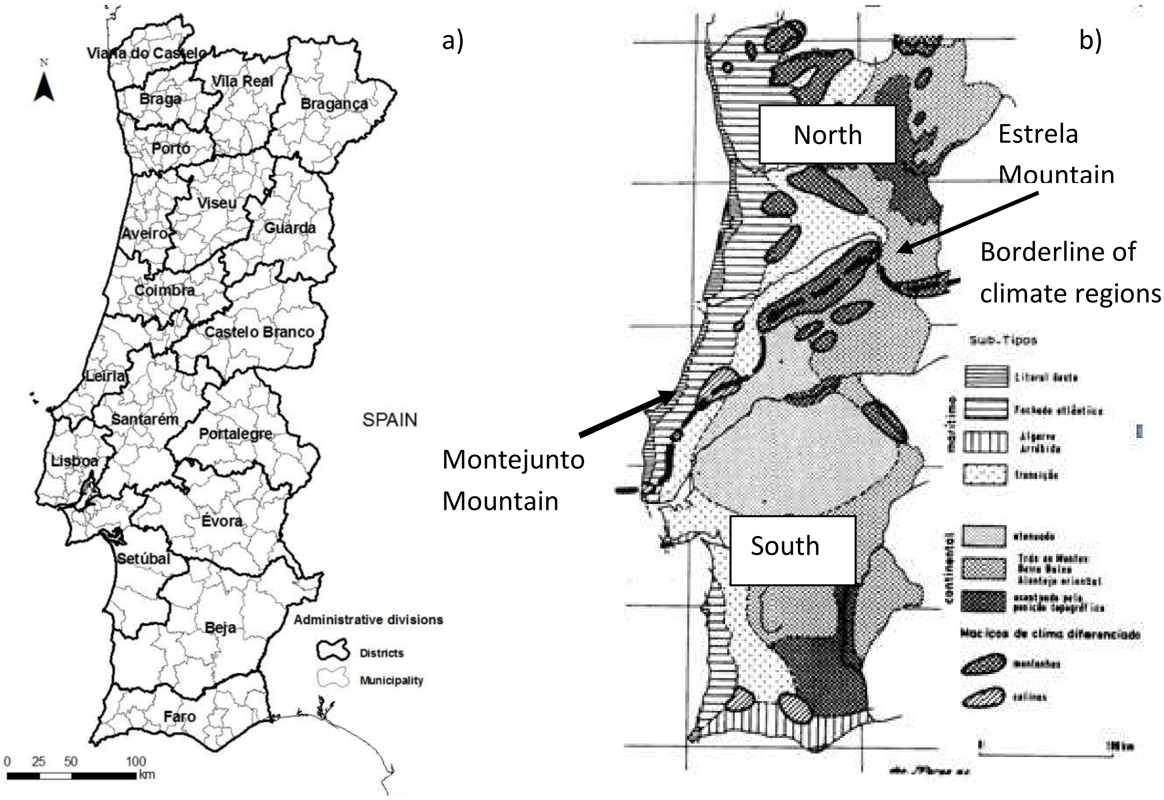

Figure 1 – Portuguese Mainland administrative divisions (a) and main climate regions [12] (b) Obs: In map b) the dashed-line corresponds to the climate transition between North and South.

2. Data

Secondary data from the National Hospital Discharge Register (NHDR) was used. In Portugal the National Health System guarantees universal and free access to all the population from all social groups and ages. Therefore, most of the population is treated in public hospitals, especially with mandatory and severe conditions like acute coronary events, for which treatment is less commonly available in private hospitals. For that reason the admissions for CHD are highly documented and the National Hospital Discharge Register represents the totality of admissions in Continental Portugal.

The NHDR is managed by the Central Administration of the Health System (Administração Central do Sistema de Saúde – ACSS), which centralizes the data monthly sent by all hospitals from the National Health Service (Serviço Nacional de Saúde – SNS). However, this database does not cover hospitals from the Portuguese Autonomous Regions, the archipelagos of Azores and Madeira, where 5% of the population lives, and therefore explaining why the study area was limited to Continental Portugal.

In the NHDR, each record corresponds to one admission and contains information such as sex; age; first cause of admission (and up to 19 secondary causes), coded by the International Classification of Diseases, Version 9, Clinical Modification (ICD9-CM);

main Diagnosis (and up to 19 secondary diagnosis) also coded by the ICD9-CM; Clinical Proceedings (up to 20); surgeries; hospital of provenience, final outcome (death and destiny after discharge); length of stay (LOS); place of the patient residence and hospitalization costs.

For this study, we selected all admissions from 1st January 1997 to 31st December 2008 with a primary or secondary discharge diagnosis of CHD including ICD9-CM codes: 410.x - acute myocardial infarction; 411.x - other acute and subacute forms of ischemic heart disease; 412.x - old myocardial infarction, 413.x - angina pectoris; 414.x - other forms of chronic ischemic heart disease; and 429.2x unspecified cardiovascular disease.

Each hospital admission was georeferenced by municipality of patient's residence, and counted by sex and 5 years age groups, at municipal and district levels.

3. Statistical analysis

The distribution of hospital admissions was analyzed by sex and age group (bellow 35 years old, 35-44, 45-54, 55-64, 65-74 and above 75). Yearly mean length of stay (LOS) per admission, mean cost and mean age of the inpatients were calculated and discharge types were studied. To analyze the burden of CHD hospitalizations in the national healthcare system, the ratio of hospitalizations for CHD by the total number of hospitalizations and by the number of hospitalization by Cardiovascular Diseases (CVD) was calculated.

Temporal trends between 1997 and 2008 were estimated using linear regression. District CHD age-standardized hospitalization rates (ASHR) were calculated, by triennium, by sex and using 5-year age groups, using the direct method and the European Standard Population. The population at risk used was from the Portuguese Demographic Estimates of the National Institute of Statistics (INE).

To calculate ASHR, age groups between 35 and 74 years old were used, to allow future comparability with international studies of mortality by CHD, since the majority of these studies are excluding deaths below 35 years old in order to avoid underestimation of mortality rates, (because they are rare at younger ages) and above 74 years old to avoid an overestimation of mortality rates (because the death certificates are less accurate at these ages). The same methodology was used to calculate the ASHR at a municipality level.

The use of small areas (like municipalities) in spatial epidemiological studies brings important contributions to the knowledge of the disease etiology, by allowing to perceive local risk areas that, otherwise, would not be identified in a national or regional scale. On the other hand, dealing with small areas brings some statistical disadvantages, like the Problem of Small Numbers and the consequent effect of random fluctuations in the rates caused by few cases in small populations, which can lead to artificially high rates [13].

To avoid the Small Numbers Problem, data were aggregated in 3 years periods (1997-1999; 2000-2002; 2003-2005 and 2006-2008) and the Empirical Bayesian (EB) method was used to estimate the ASHR by smoothing the observed rates to the average rates of the neighbors in function of the size of population and variability of the rates in the surround areas. The EB method gives better estimates of the true risk of an area, by adjusting the artificial high rates caused by the small numbers. The magnitude of the adjustments increases as the population of an area decreases. In areas with small population and high variability (consequently with highly unstable rates) the observed rates are shrunk to the average rate of the neighbourhood to produce an estimated rate. In areas with large populations the trust in observed incidence rates is higher and the estimated incidence rates will have similar values to the observed ones [14].

Spatial dependency was computed using Moran-I index which gives a global measure of the ASHR spatial autocorrelation. The interpretation of the Moran I is similar to the regression coefficient although the values can go over the limits of -1 to 1.When Moran I is close to zero, there is no spatial autocorrelation, that is, disease occurs randomly in space; when positive and close to 1 (or over) there is spatial dependency and the disease tend to cluster in the space. When the coefficient is negative and close to -1 (or below) there is an inverse spatial dependency representing a tendency to occurrence of “islands” meaning that regions with high rates are surrounded by regions with low rates or vice-versa.

However, Moran I produces one single value for the whole area, don’t enabling to identify localized disease clusters. So, complementarily, Local Index of Spatial Autocorrelation (LISA) were calculated and clusters of ASHR were mapped according to the classes: high-high (high rate areas surrounded by high rate areas), low-low (low rate areas surrounded by low rate areas), high-low (high rate areas surrounded by low rate areas) and low-high (low rate areas surrounded by high rate areas). Since the available softwares for spatial statistical analysis only allow the calculation of LISA for crude rates, a routine was developed to calculate the mean ASHR of the neighbor areas producing more correct results. Neighbors of areas were considered when sharing a common border. Geographic information systems (GIS) were used to produce neighbor matrix, analyze and visualize the data.

Results

The database contained 356,119 hospitalizations, being 74.8% (266,475) of individuals aged 35-74 years old, with CHD as primary or secondary diagnosis. On average, there were 2043 readmissions per year. The total number of hospitalizations represented 3.3% of all hospital admissions (10,872,947) registered in the hospitals of Continental Portugal and 23.8% of the hospitalizations for CVD (1,496,480). Table 1 summarizes some variables for each of the diagnoses (ICD9-CM) included in the group of CHD.

Table 1 – Summary statistics on CHD hospital admissions and its national burden. 1997-2008.

ICD9	Admissions* (% of total CHD)	Mean % of readmissions per year	Burden (% of the total admissions)	
			All causes	Circulatory system
410 – Acute myocardial infarction	131,838 (33.8)	3.7	1.1	8.0
411 - Other acute and subacute forms of CHD	48,619 (12.5)	5.6	0.4	3.0
412 - Old myocardial infarction	7486 (1.9)	3.8	0.06	0.5
413 – Angina pectoris	34,218 (8.8)	3.7	0.3	2.1
414 - Other forms of chronic CHD	166,729 (42.7)	9.2	1.4	10.2
429.2 - Unspecified CVD	1518 (0.4)	2.3	0.01	0.1
Total	356,119 (100.0)	6.9	3.3	23.8

** Sum exceed total of admissions given that both primary and secondary diagnoses were included.*

The major individual contributor for the total hospital admissions was acute myocardial infarction (33.8%), although the category entitled “other forms of chronic CHD” covered almost half (42.7%) of all CHD admissions. Most of the CHD admissions occurred in men (66.7%) with a mean age (Standard Deviation-SD) of 64.0 (±12.0) years old, while among women the mean age was 71.1 (±11.5). Overall sex-ratio (men:women) was 2.15, considering crude hospitalization rates.

The age-specific hospitalization rates for men surpassed those for women in all age groups, although the difference became more attenuated in the elderly (Figure 2). Among women, more than in men, the hospitalizations occur mainly in the elderly

In the study period, mean (SD) LOS was 7.5 (±8.1) days in men and 8.2 (±8.5) days in women. Acute myocardial infarction and unspecified forms of CVD led to the longest period of hospitalization (8.9 in men and 9.2 in women) while angina required the shortest LOS (2.8 in men and 2.7 in women).

The mean cost per hospitalization was 3906.00€ (±3496.00€) in men and 3499.00€ (±3012.00€) in women. Hospitalizations due to myocardial infarction, old myocardial infarction and other forms of chronic CHD were the most expensive (above 4000.00€ per admission) and angina pectoris the less expensive (nearly 2000.00€ per admission).

Concerning destinies after discharge, the majority of the inpatients went home (84.0% in men and 81.6% in women), followed by those that went to another institution with interment service (10.5% and 9.1% respectively for men and women). The percentage of patients receiving domestic care or who left against medical advice was residual.

The fatality was higher among women (8.8%) than in men (4.8%) in all diagnosis and widely varied between diagnoses, being higher among patients with myocardial infarction (9.7% in men and 16.9% in women) and other unspecified forms of CVD (19.8% and 24.7%) and residual among patients diagnosed with angina (0.4% and 0.5%). Table 2 summarizes the mean LOS, cost and age, as well as the destiny after discharge of patients per each of the diagnosis studied.

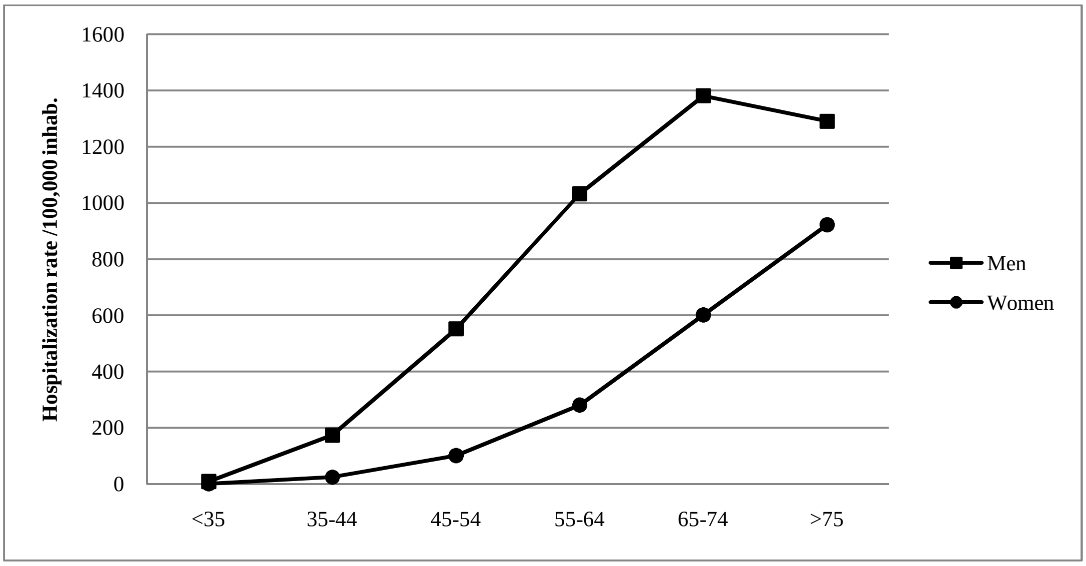

Figure 2 – Distribution of CHD hospitalizations by gender and age group. 1997-2008.

Table 2 - Characteristics of the admissions per ICD9-CM, 1997-2008.

ICD9-CM	MLOS (SD), days		Mean Cost (SD), euros		Mean Age (SD), years		Discharge status (%): Home		Other institution with internment		Domestic care		Left against medical advice		Death	
	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W
410	9.7 (8.4)	10.3 (9.1)	4673 (2776)	4543 (2540)	64.4 (13.1)	73.5 (11.6)	75.8	71.1	12.0	9.8	0.1	0.2	0.6	0.3	9.7	16.9
411	7.5 (7.0)	8.1 (6.6)	2835 (2358)	2484 (2059)	64.0 (11.7)	69.9 (11.2)	81.9	83.0	14.5	12.4	0.1	0.3	0.8	0.5	1.7	2.8
412	7.3 (8.6)	7.7 (6.9)	4072 (4443)	3351 (3181)	63.2 (11.8)	70.9 (11.1)	87.7	84.8	8.1	8.0	0.2	0.3	0.4	0.4	2.7	5.1
413	2.8 (4.7)	2.7 (4.8)	2.020 (1946)	1790 (1523)	63.8 (11.3)	66.8 (11.0)	90.0	90.9	7.9	6.6	0.1	0.3	0.5	0.3	0.4	0.5
414	6.4 (8.1)	7.4 (8.7)	4042 (4131)	3455 (3602)	63.8 (11.2)	70.0 (11.2)	87.8	86.1	8.9	8.0	0.2	0.2	0.3	0.2	2.6	5.2
429.2	8.9 (6.8)	9.2 (7.8)	2585 (1652)	2628 (1809)	78.3 (9.4)	81.2 (9.6)	74.4	71.7	2.1	1.4	0.0	0.4	0.7	0.1	19.8	24.7
410-414, 429.2	**7.5 (8.1)**	**8.2 (8.5)**	**3906 (3496)**	**3499 (3012)**	**64.0 (12.0)**	**71.0 (11.5)**	**84.0**	**81.6**	**10.5**	**9.1**	**0.2**	**0.2**	**0.5**	**0.3**	**4.8**	**8.8**

TIME-SERIES ANALYSIS

Although the absolute number de hospitalizations grew (25.0% in men and 28.0% in women), the overall three ASHR (/100,000 per 3 years: CI 95%) remained stable during the 12 years, varying from 666.9 (660.7-673.1) in the 1997-1999 triennium to 660.0 (654.5-665.6) in the last triennium among men (Tables 3 and 4). The same steadiness was observed in women, whose ASHR ranged from 194.8 (191.2-198.4) to 193.7 (190.9-196.6), respectively in the first and last triennium.

Table 3 – Time-trends (12-years % variation) in hospital admissions. Results from linear regression. 1997-2008.

ICD9-CM	Number of Hospitalizations		Costs		MLOS		Mean age		Fatality	
	M	W	M	W	M	W	M	W	M	W
410	55.2*	94.3*	39.9*	30.3*	-21.6*	-14.7*	4.8*	3.1*	-27.6*	-37.0*
411	-55.2*	-46.6*	31.6*	32.8*	-11.5*	-10.2*	5.9*	7.9*	151.1*	495.3*
412	-55.9*	-49.8*	69.4*	54.5*	-25.0*	-31.2*	2.8*	1.0	-8.6	-29.6
413	96.4*	84.5*	-37.8*	-30.5*	-49.2*	-49.0*	5.1*	2.3*	-83.6*	-83.9*
414	27.5*	14.1*	-3.7	-1.9	-33.1*	-40.5*	4.0*	-0.1	-45.2*	-52.9*
429.2	-69.4*	-72.9*	-6.5	1.8	-12.0	-7.7	5.0	7.5*	-53.1	30.6
410-414, 429.2	**25.0***	**28.0***	**13.2**	**17.0**	**-26.4***	**-25.3***	**4.5***	**2.9***	**-24.5***	**-22.2***

** significant at the 0.05 level (2-tailed).*

Overall, mean LOS strongly decreased, nearly 25%; for unspecified forms of CVD, the declining trend was non-significant, due to the small number of patients. Angina presented a particularly strong variation, with a decrease of about 50% in the MLOS. Similarly, fatality significantly diminished during the study period, over 20%, but not for “other acute and sub-acute forms of CHD”, where a significant and impressive augment (particularly among women) was registered, and old myocardial infarction and unspecified forms of CVD, for which the small number of cases didn’t allow to detect significant trends.

Trends in costs were less clear: there was a significant increase in costs related with myocardial infarction, other acute and sub-acute forms of CHD and old myocardial infarction, but also a significant shrinkage in costs due to angina (more than 30%); the other causes of hospitalization, as well the whole CHD showed no significant changes.

The mean age of the hospitalized patients showed a positive and significant trend, in almost every diagnoses, grossly corresponding to a three years aging for men and two years for women which can be a consequence of the increase in the life expectancy in Portugal, during the study period.

GEOGRAPHICAL DISTRIBUTION OF ASHR

Of the total admissions, 9608 (3.6%) could not be georeferenced at municipality level and from those, 8649 (3.2%) at district level, because of the lesser quality of the information regarding the place of residence of the patient in the first triennium Almost three quarters of those non-georeferenced admissions are related to the period 1997-1999, and reflects less quality of the database in that period, when the hospitals were not obliged to report the admissions to the national register.

The ASHR in the 18 districts, for men and women, in the four time periods presented strong regional differences as can be observed in Table 4.

Table 4 – District ASHR (/100,000 persons per 3years) for CHD, by sex.

District	1997-1999		2000-2002		2003-2005		2006-2008	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Aveiro	431.0	128.1	488.2	120.5	459.5	112.4	601.1	137.0
Beja	602.4	151.1	676.5	185.4	614.9	221.7	848.0	332.4
Braga	607.6	160.2	697.5	160.1	506.1	123.9	561.9	116.8
Bragança	450.5	155.4	522.4	151.1	578.9	142.2	649.1	174.4
Castelo Branco	467.0	148.1	800.7	228.7	767.7	320.0	914.7	285.1
Coimbra	240.3	59.8	515.7	135.9	569.7	140.0	564.3	158.3
Évora	479.8	160.8	614.3	190.1	644.6	229.6	793.3	274.8
Faro	549.8	143.5	552.3	162.5	532.7	164.7	633.9	222.0
Guarda	404.1	115.1	528.9	128.8	622.9	202.0	774.0	223.6
Leiria	422.1	118.0	532.6	164.0	489.5	142.1	548.3	162.3
Lisboa	847.7	278.2	855.0	292.1	766.1	264.0	682.5	208.7
Portalegre	599.0	147.8	806.5	260.1	657.7	191.7	786.0	232.3
Porto	573.8	164.8	626.3	177.7	542.0	171.7	597.0	172.7
Santarém	571.3	187.5	591.5	194.7	567.0	175.7	719.2	202.3
Setúbal	833.1	264.3	810.8	270.7	740.7	231.0	806.4	274.8
Viana do Castelo	420.1	106.7	630.7	139.9	520.3	117.3	611.3	145.5
Vila Real	659.1	188.6	564.6	169.2	448.1	151.4	597.5	176.4
Viseu	339.1	91.7	473.2	119.8	444.4	132.3	464.1	138.0
Portugal	**666.9**	**194.8**	**675.0**	**202.9**	**609.6**	**189.6**	**660.0**	**193.7**
Rate Ratio (higher:lower)	**3.5**	**4.7**	**1.8**	**2.4**	**1.7**	**2.8**	**2.0**	**2.8**

Geographic differences, both for men and women, were more accentuated in the period 1997 to 1999, with a rate ratio between the districts (higher:lower) of 3.5 for men and 4.7 for women. In the subsequent periods the rate ratios were reduced to 1.8, 1.7 and 2.0 among men and 2.4, 2.8 and 2.8 among women. However, because quality of data before 2000 was poor, data for the first period must be analyzed with caution.

Confirming the geographic differences at district level, a moderate degree of spatial autocorrelation in the municipal ASHR was detected. The ASHR per triennium among men presented a Moran Index of +0.48, +0.36, +0.33 and +0.43, respectively in 1997-1999, 2000-2002, 2003-2005 and 2006-2008; in women, the corresponding values were +0.43, +0.35, +0.33 and +0.41. This pattern was very similar to the results supported by the district figures: initially, a stronger clustering, diminishing subsequently to increase in the last triennium.

Despite the overall values of ASHR remained constant along the study period, some districts presented an ASHR much lower in the first period than those computed in the subsequent trienniums. This is, particularly, the case of the districts of Castelo Branco, Coimbra, Évora, Guarda, Portalegre and Viseu.

The most plausible explanation for these odd discrepancies is the already mentioned significant number of non georeferenced patients in the first triennium. The non-georeferenced admissions account for 7.6% of the total hospitalizations in 1997-1999, becoming irrelevant (0.8%) in the 2000-2008 period.

After the computation of EB ASHR and LISA statistics for each triennium, several clusters of high and low ASHR were identified as can be visualized in Figures 3 and 4. The borderline of the two climatic regions (of Portugal was overlaid in the maps to help in the discussion of results [12].

Among men, there were two regions characterized by persistent low ASHR rates: one comprises the northern half of the Leiria district and parts of the adjacent Coimbra district; the other, the northern half of the Viseu district. The high ASHR clusters are far more extended and comprise four distinct areas: the eastern part of the Guarda and Castelo Branco districts; the eastern border between the Portalegre and Évora districts; part of the Beja district; finally, the capital, Lisbon, and its surroundings.

Among women, the two lower ASHR clusters are almost coincident with those identified in men, and a third area was identified, situated in the extreme northwest of Portugal, comprising municipalities of the contiguous Viana do Castelo and Braga districts. In what concerns the regions with high hospitalization rates they were quite similar with those presented by men.

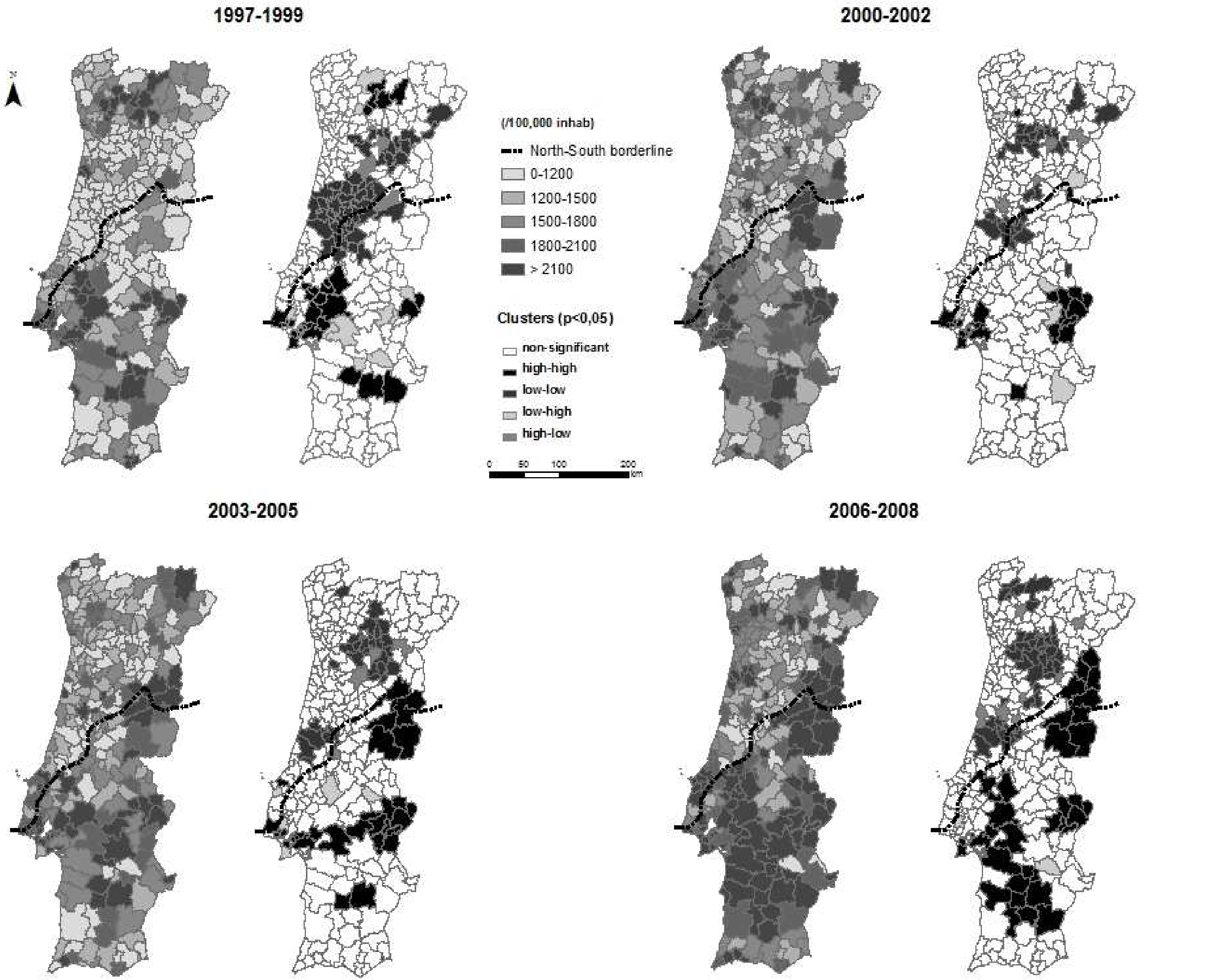

Figure 3 – Coropleth maps of smoothed ASHR among men (left maps) and spatial clusters by municipality (right maps).

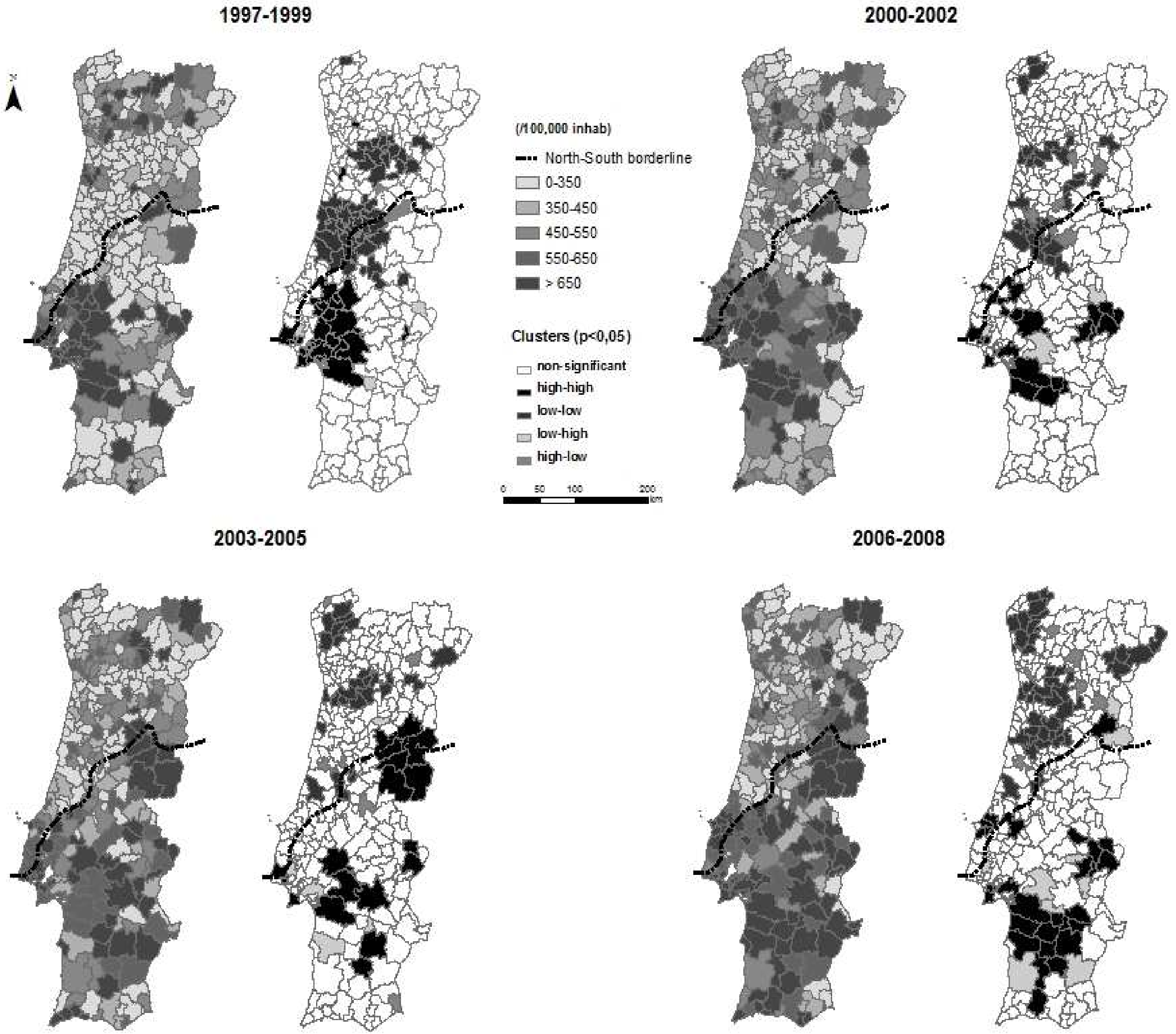

Figure 4 – Coropleth maps of smoothed ASHR among women (left maps) and spatial clusters by municipality (right maps).

Discussion

The present study identified geographic inequalities in CHD hospitalizations, more accentuated among women. In the last triennium, 2.0 and 2.8-fold differences were present at district level (3.8 and 6.0-fold at municipal level), respectively in men and women. Contrary to the international diminishing trends reported for CHD mortality the overall ASHR remained stable during the 12 years of study [15].

In Portugal, the spatial pattern of CHD hospitalizations didn't match the typical North-South trend reported in Europe, with higher values at higher latitudes. In Portugal, similar to Spain, both CHD incidence and mortality were higher at south [10]. Although hospitalization rates did not show exactly the same distribution (Northwest-Southeast instead of North-South division), there seem to be a certain resemblance between the spatial epidemiology of CHD mortality across the Iberian Peninsula, whose populations also share some characteristics of history and geography.

The geographic pattern of ASHR observed in Continental Portugal, for both sexes, showed a clear Northeast-Southwest trend, which seems to perfectly match the Montejunto-Estrela mountain chain and the borderline between the two major climatic regions in Continental Portugal (Figure 1b).

Most of the municipalities with higher ASHR are localized in the southern climatic region, a typical Mediterranean climate with mild winters and long, dry and hot summers. On the contrary, the northern region, with temperate Atlantic climate, with mild summers and very humid and rainy winters has the majority of the municipalities with the lower ASHR (Figures 3 and 4). These results can be reinforced by observing the position of the clusters of high ASHR: almost all are localized in the Southern portion of the climatic regions, either for men and women, suggesting an association between environmental climatic conditions and incidence of CHD in Portugal. However, more studies need to be done to confirm these hypotheses.

Studies had pointed climate, altitude or water hardness as potential determinants [16-17]. In Continental Portugal, the climatic differences between the two climatic regions could also play a role in the ASHR of CHD. A systematic review about the effects of temperature on the incidence of myocardial infarction concluded that the studies conducted in areas with higher mean temperature reported more frequently detrimental effects of cold, but not the contrary (stronger effects of heat in cold regions) [18]. Putting in other terms, it is possible that the Portuguese areas within Mediterranean climate are more susceptible to cold surges, which matches well with the patterns of ASHR of CHD found in this study.

Other studies found that the regions with higher CHD incidence rates share a particular feature – low water hardness, either measured as total hardness, or as calcium (Ca) and magnesium (Mg) concentrations. For instance, in Finland, the high acute myocardial incidence in the East was associated with soft ground water [16]. In most of the Portuguese territory the water hardness is low. However according with the data of the official Drinking Water National Reports (1999-2002), there are higher concentrations of minerals in the South, which apparently contradicts their potential effects as relevant risk factors for CHD, although more detailed studies need to be conducted [19-22].

When trying to justify the strong geographic variability in CHD incidence, some studies included socioeconomic variables, often successfully, but also without significant results [23-24]. In Portugal, differences in socioeconomic conditions could also contribute for the regional disparities in ASHR, but their effect need to be clarified in future studies.

All over the world, geographical differences in CHD incidence were documented. In Europe, a broad North-South gradient was observed, with higher incidence rates in Northern countries than in the Mediterranean basin [25-26]. This North-South pattern was also visible within countries like Great Britain, Sweden, France and Italy [24, 27-29]. However, in Spain and Belgium an inverse North-South division was registered and the highest values of incidence where found at South [10, 30]. The geographical clustering of CHD incidence is not confined to Europe. Also USA seems to be divided into an east region, more susceptible to CHD, and a western region, with the lowest incidence of CHD [23]. In China, as in the majority of the European countries, the Northern provinces presented the highest incidence rates [11].

Some important healthcare indicators showed significant improvements in the hospital admissions, during the study period: fatality declined, as well as mean LOS, but despite this reduction, costs didn’t show the same trend, probably due to the use of more sophisticated and expensive procedures in the treatment of the patients. Therefore, the reduction of deaths for CHD (the contrasting fatality augment observed in “other acute and sub-acute forms of CHD” is probably a consequence of a more-than-average increase of the mean age of those patients), seems to be associated with the improvement of health care conditions, since the reduction trend was not observed in the ASHR (which remained stable) and the costs increased despite the accentuated reduction of mean LOS.

Geographic differences of CHD could also be a consequence of spatial differences in risk factors prevalence. In Portugal, information about the prevalence of cardiovascular risk factors like smoking, physical activity, alcohol intake, chronic diseases, hypertension, obesity and the dietary habits is acquired periodically by the National Health Surveys (NHS), but is not enough geographically disaggregated (only by 5 NUT II regions: Norte, Centro, Lisboa e Vale do Tejo, Alentejo and Algarve, corresponding the last three regions grossly to South Portugal) to allow the association with results from this study [31]. Nevertheless, it is possible to draw some hypothesis using the geographic units presented in the NHS:

1) The highest prevalence of hypertension was found in Alentejo (22.8% in 2005/06 and 17.3% in 1998/99) NUT II, followed by Lisboa e Vale do Tejo (21.4% and 15.7%) and Centro (20.5% and 16.3%). The other regions are below the national average.

2) In 2005/06, the prevalence of present and ex-smokers among persons aged 10 or more was higher in Algarve (40.3%), followed by Alentejo (38.2%) and Lisboa e Vale do Tejo (38.1%). The last positions were occupied by Centro (29.2%) and Norte (33.5%).

3) In 2005/0, the highest proportion of diabetics (7.4%) was located in the Norte NUT II, followed by Alentejo (7.1%).

4) Obesity in persons aged 18 or more has an higher prevalence in Lisboa e Vale do Tejo (17.1% in 2005/06 and 13.1 in 1998/99) and in Alentejo (16.0% and 14.1%). In the opposite side, are situated Algarve (12.2% and 10.6%), Centro (13.3% and 11.9%) and Norte (15.0% and 11.3%).

5) The prevalence of depression in 2005/2006 was higher in Centro (8.9%) and in Lisboa e Vale do Tejo (8.6%) than in Norte (8.2%), Alentejo (7.4%) and Algarve (6.0%).

The southern regions, which have the higher ASHR of CHD, presented also the highest prevalence of most of the traditional cardiovascular risk factors. However, because the borderline that divides the two climatic regions was consistently coincident with the geographic patterns of ASHR, in all periods and for both sexes, the climate conditions might also play an important role in the incidence of CHD. Further studies need to be conducted to test this hypothesis.

The ASHR remained stable along the study period and the geographic inequalities persisted higher among women than among men.

The present study presents also some limitations. The first is the fact that patient´s unique codes were not available because of confidentiality restrictions and the readmissions of the same patients in different years or hospitals could not be identified. Although, when the patient was readmitted within the same calendar year, and in the same hospital, the registers for readmissions could be identified and were eliminated. Studies, comparing hospital registers with linked registers, found that NHDR overestimates the incidence of AMI by roughly 20-30%, in the so-called level bias. However, time-trends, either using first or recurrent events were very similar indicating that no trend bias occurred [32-33].

Moreover, although data was analyzed with caution, the NHDR database has poor quality until 2000 hampering to draw trustful conclusions on data between 1997 and 2000. As mentioned before, the most severe restriction was the percentage of non-georeferenced patients in the first triennium, included in the overall rates, but not in the district and municipal ASHR.

The NHDR is the only source of data about the occurrence of non-fatal coronary events in Portugal and the quality of this database after 1999 is in general very good. Studies examined the accuracy of NHDR diagnosis for CHD and found that it is usually good, especially for acute coronary events like a myocardial infarction [34]. However, in Finland, authors found that the diagnosis were not standardized, varying over time, between regions and types of care, being more accurate in central and district hospitals [35].

Many of the results found in this study were only achieved because of the availability of data at a small scale, which allowed perceiving local risk areas from the spatial statistical analysis, suggesting that underlying patterns can be hidden when epidemiological data are analyzed in aggregated areas. This reinforces the importance of using disaggregated data and developing more spatial epidemiological studies.

Mapping the hospitalizations for CHD and identifying significant geographical clusters through GIS techniques, allowed to spot communities with high risk of suffering from CHD and gives clues for a better understanding of the environmental determinants – normally ignored – of such common and lethal disease. Additionally, by knowing the geographical distribution of health events, one can achieve a better allocation of the health resources and more community-oriented prevention measures.

Further investigations using spatial modeling techniques should be carried out to clarify the geographic variability of CHD, introducing as explaining variables not only classic risk factors, but also environmental determinants.

Conclusions

The ASHR analyzed by municipalities showed the identical pattern of the major climatic regions in Portugal, with warmer and drier areas of the south presenting the higher ASHR and areas with a more severe winter presenting lower ASHR. However, the southern areas of Portugal also present the highest prevalence of most of the traditional cardiovascular risk factors.

Yet, because the borderline that divides the two climatic regions was consistently coincident with the geographic patterns of ASHR, in all periods and for both sexes, we believe that climate conditions play an important role in the incidence of CHD.

The ASHR remained stable along the study period and the geographic inequalities persisted higher among women than among men.

Fatality had a reduction of about 25%, following the trends of mortality rates in developed countries. The reduction of deaths for CHD seems to be associated with the improvement of health care conditions, since this pattern was not observed in the ASHR (which remained stable) and the costs increased despite the accentuated reduction in the mean LOS.

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4. Conclusions

CONCLUSIONS

Systematic review:

- In Europe, a North-South gradient was predominant, with incidence rates of CHD increasing with the increase of latitude. However, the same was not true for North America, where an East-West decreasing trend was found.

- Several studies have reported strong geographic patterns in CHD incidence, but no unambiguous explanation for international and intra-national inequalities was yet found. For a better understanding, studies should extent to other continents.

Mortality trends and geographical distribution:

- A decline of nearly 50% in the age-standardized mortality rate from CHD in Portugal was observed between 1981 and 2005, likewise in the Western European and North America trends.

- However, the regional spatial pattern remained - Azores and southern half of Portugal with the highest values and Northern and Centro coast with the lowest ones. Furthermore, geographic (from fourfold, to above fivefold) as well as sex inequalities increased.

Spatial distribution of hospitalizations:

- The number of CHD hospitalizations has been increasing since 1990s, accompanying the trends showed by the majority of diseases, so its relative burden didn’t change. Age of admission also increased, but length of stay and lethality experienced a decline.

- Age-standardized hospitalization rates remained stable between 1997 and 2008 but revealed strong geographic inequalities, more accentuated among women. The rate ratio was 2.0 (men) and a 2.8-fold (women).

- In the same period, Moran indexes showed moderate degree of spatial dependency – around +0.40 – and specific spatial clusters were identified.

- The ASHR were distributed in a Nortwest-Southeast orientation, with highest risk in the Southeast part, particularly in clusters situated in the Castelo Branco, Lisboa, Beja, Évora and Portalegre districts.

4. Abstract

ABSTRACT

The central purpose of the present study was to contribute to a better understanding of the coronary heart disease (CHD) epidemiology in Portugal during the last decades. A particular focus was made in the geographical distribution of the disease, at distinct levels: national, district and municipality.

First, a systematic review was done of the scientific literature about the geographic patterns of CHD incidence. The main results were the following: in Europe, predominates a North-South gradient, with incidence rates of CHD increasing with latitude; nevertheless, other geographical patterns seem to exist in North America and in a few European countries; the interpretation of these gradients was not straightforward, but often rely on blood lipids and fat intake, other classic risk factors and water hardness.

In a subsequent step, the geographic and sex disparities in the time trends of CHD mortality in Portugal, from 1981 to 2005, were investigated, based on the mortality data obtained from the Portuguese Vital Statistics of the National Institute of Statistics (INE – Instituto Nacional de Estatística) and the Portuguese General Health Directorate (DGS – Direcção-Geral de Saúde). The analysis was performed at national and district level and restricted to ages 35-74 years old. The most relevant results were: nationwide, a 47.4% decline (46% in men and 52% in women) in the age-standardized mortality rates was observed in 1981-2005; simultaneously, the regional spatial pattern (highest values in the Azores and a North-South increasing gradient in Mainland Portugal) remained almost unchanged, although the geographic and sex inequalities increase.

Finally, the study of the spatial patterns was extended to the CHD hospital admissions in Mainland Portugal, obtained from 1997 until 2008 from the National Hospital Discharge Register. Age-standardized hospitalization rates (ASHR) were computed by municipality and district to ages 35-74 years old, empirical Bayes estimators were applied to smooth the municipality ASHR and spatial statistics methods, to identify spatial clusters. The main results were the following: although the absolute number of hospitalizations grew, the national ASHR (contrasting with the ASMR) remained quite stable; strong geographic inequalities, more accentuated among women, and spatial clustering were found. The ASHR were distributed in a Nortwest-Southeast direction, with the highest risk in the Southeast part, particularly in clusters situated in the Castelo Branco, Lisboa, Beja, Évora and Portalegre districts. This pattern matched with the climatic zones which half the country into a warm and dry region and a mild and wet region, suggesting that climate might play an important role (together with the classic cardiovascular risk factors) in the incidence of CHD.

5. Resumo

RESUMO

O objectivo principal do estudo foi contribuir para a compreensão da epidemiologia da doença coronária (DC) em Portugal, durante as últimas décadas. Uma atenção particular mereceu a distribuição geográfica da doença, a nível nacional, distrital e concelhio.

Numa primeira fase, foi realizada uma revisão sistemática dos trabalhos publicados acerca da distribuição geográfica da incidência da DC. Foram obtidos os seguintes resultados: na Europa é predominante um gradiente Norte-Sul, aumentando as taxas de incidência da DC com a latitude, embora outros padrões geográficos pareçam existir na América do Norte e mesmo em alguns países europeus; a interpretação dos padrões não é clara, embora se baseie principalmente em factores de risco como os níveis de lípidos no sangue, consumo de gorduras, outros factores de risco clássicos e a dureza da água.

Em fase posterior, foram investigadas eventuais desigualdades, a nível de sexo e geográficas, nas tendências temporais da mortalidade por DC, entre 1981 e 2005, tendo por base as Estatísticas Demográficas do INE (Instituto Nacional de Estatística) e da Direcção-Geral de Saúde (DGS). A análise foi desenvolvida a nível nacional e distrital, incidindo apenas nas idades compreendidas entre 35 e 74 anos. Os resultados mais relevantes foram: a nível nacional, uma diminuição de 47,4% (46% nos homens e 52% nas mulheres) nas taxas de mortalidade padronizadas pela idade (TMP) foi registada entre 1981 e 2005; ao mesmo tempo, foi mantido praticamente inalterado o padrão geográfico (valor máximo nos Açores e tendência crescente Norte-Sul no Continente), embora com uma acentuação das desigualdades geográficas e por sexo.

A terminar, o estudo foi alargado às admissões hospitalares por DC no Continente, cujos dados para 1997-2008 foram obtidos do Registo Nacional de Altas Hospitalares. Foram calculadas taxas de hospitalização padronizadas por idade (THP), por distrito e município, para o grupo etário dos 35 aos 74 anos, aplicaram-se estimadores empíricos Bayesianos para suavizar as taxas concelhias e métodos de análise espacial, para identificar clusters espaciais. Os resultados principais foram os seguintes: embora o número absoluto de hospitalizações tenha aumentado, a THP nacional (ao contrário do que sucedera com a TMP) manteve-se praticamente constante, tendo sido encontrados grandes desigualdades geográficas e identificados diversos clusters espaciais. As THP distribuem-se segundo um padrão Noroeste-Sudoeste, situando-se o maior risco de sofrer uma DC na zona Sudoeste, em especial em clusters localizados nos distritos de Castelo Branco, Lisboa, Beja, Évora e Portalegre. Este padrão coincide com as zonas climáticas que dividem o país numa região mais quente e seca a sul e numa região mais amena e húmida a norte, sugerindo que o clima (conjuntamente com os factores de risco cardiovasculares tradicionais) desempenha um papel importante na incidência de DC.

Annexes

ANNEX 1 – Insights about Hospital Discharge Register in Portugal

In the present investigation, secondary data from the National Hospital Discharge Register (HDR) was used, which organized discharges according to DRG classification. The DRGs (Diagnosis Related Groups) were born in United States in 1960s to classify the patients into categories with similar clinical characteristics and, consequently, similar medical procedures and resource consumptions. Since the first DGRs classification in 1980s in New Jersey, several updates and changes have been done. Presently, to guarantee homogeneity and increased precision in DRG, diagnoses are classified according to the International Classification of Diseases, 9th Revision Clinical Modification, ICD-9-CM.

Portuguese DRG classification was introduced in 1984 and was inspired in the US arrangement. The National HDR is managed by the Central Administration of the Health System (Administração Central do Sistema de Saúde – ACSS), which centralize all data monthly sent by all hospitals from the National Health Service (Serviço Nacional de Saúde – SNS). Individuals included in this database spent at least one night in the hospital and, because of that, the records comprise only relatively acute and severe cases.

DRG give us information on the following topics: date of discharge, the primary diagnosis and up to 19 diagnoses, demographic information of inpatients (age and sex), place of residence (district, municipality and parish), hospital of internment, length of stay, medical procedures (up to 20, classified according to ICD-9-CM), discharge status (destiny or death), costs of internment, DRG, MDC (Major Diagnostic Categories), between other meaningful information.

Table 1 – ICD-9-CM codes for Coronary heart disease

410	**Acute Myocardial infarction**
410.0	Of anterolateral wall
410.1	Of other anterior wall
410.2	Of inferolateral wall
410.3	Of inferoposterior wall
410.4	Of other inferior wall
410.5	Of other lateral wall
410.6	True posterior wall infarction
410.7	Subendocardial infarction
410.8	Of other specified sites
410.9	Unspecified site
411	**Other acute and subacute forms of ischemic heart disease**
411.0	Postmyocardial infarction syndrome
411.1	Intermediate coronary syndrome
411.8	Other
411.81	Acute coronary occlusion without myocardial infarction
411.89	Other

412	**Old myocardial infarction**
413	**Angina pectoris**
413.0	Angina decubitus
413.1	Prinzmetal angina
413.9	Other and unspecified angina pectoris
414	**Other forms of chronic ischemic heart disease**
414.0	Coronary atherosclerosis
414.00	Of unspecified type of vessel, native or graft
414.01	Of native coronary artery
414.02	Of autologous biological bypass graft
414.03	Of nonautologous biological bypass graft
414.04	Of artery bypass graft
414.05	Of unspecified type of bypass graft
414.06	Of native coronary artery of transplanted heart
414.07	Of bypass graft (artery) (vein) of transplanted heart
414.1	Aneurysm and dissection of heart
414.10	Aneurysm of heart (wall)
414.11	Aneurysm of coronary vessels
414.12	Dissection of coronary artery
414.19	Other aneurysm of heart
414.2	Chronic total occlusion of coronary artery
414.3	Coronary atherosclerosis due to lipid rich plaque
414.8	Other specified forms of chronic ischemic heart disease
414.9	Chronic ischemic heart disease, unspecified
429.2	**Cardiovascular disease, unspecified**

ANNEX 2 – Preparation of the database and selection process

It was compulsory to correct data, which could lead to erroneous conclusions. A large amount of dates of admission and discharge were unformatted and, therefore, they were converted in calendar data. In another group of dates, month was in the place of day and vice-versa and this problem was also needed to be corrected. Birth dates showed the same problems and similar amendments were done. After that, length of stay and age were recalculated and used instead the source information.

Secondly, repeated admission codes were eliminated by using the following criteria: 1) those whose fields were exactly the same; 2) those with death as discharge destiny; 3) those having the same birth date and entering at the same day in the same institution. These were considered to be the same admission. Following these criteria, 7276 repeated admission codes were retrieved and the option was to eliminate the repeated occurrences in a random way by keeping always the first register.