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Impact of public health measures in Cardiovascular disease: admissions trends and case-fatality

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Impact of public health measures in Cardio-Vascular disease admissions, trends and case-fatality

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ABSTRACT

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in Europe.

One way to reduce CVD events and mortality are population strategies, which imply altering lifestyle and environmental factors.

Portugal has implemented a set of public health initiatives that tackled CVD, such as the smoking ban in 2008, a salt reduction regulation in 2010 and fast-tracking system (FTS) to coronary care unit in 2007.

Our goal was to analyse the impact of these initiatives in CVD trends in Portugal.

Methods

The data used was obtained from the Diagnosis Related Group data and the National Registry of Acute Coronary Syndrome (ACS) data.

We applied segmented regression analysis to assess how much the initiative studied changed CVD trends, immediately and over time.

Results

- The proportion of ACS admissions declined 5.8% after the smoking ban.
- Both HBP in ACS patients and CVD outcomes trends decreased after the initiative to reduce salt intake. Although no trends were statistically significant.
- The proportion of patients activating the FTS is increasing, although more than half of the patients are not resorting to it.
- Strategies such as the smoking ban and the FTS led to an immediate decrease in ACS case fatality rates.

Conclusions

Our study suggests that population-wide approaches can impact CVD, reducing the number of events and eventually reducing premature death. Considering that CVD constitutes an immense public health problem, even a small improvement in treatment and an increase in population awareness can have important clinical, economic and social gains.

Keywords: Cardiovascular disease, public health, acute coronary syndrome, stroke.

RESUMO

Introdução

A doença cardiovascular (DCV) é a principal causa de morte na Europa. Para reduzir os eventos cardiovasculares e a mortalidade são usadas estratégias populacionais, implicando mudanças no estilo de vida e fatores ambientais.

Portugal implementou um conjunto de iniciativas de saúde pública direcionadas à DCV, como a proibição de fumar em 2008, a redução do sal em 2010 e a via verde coronária (VVC) em 2007.
O objetivo deste estudo foi analisar o impacto destas iniciativas nas tendências de DCV em Portugal.

Métodos

Os dados foram: Grupos de Diagnósticos Homogéneos e o Registro Nacional de Síndrome Coronária Aguda (SCA). Utilizou-se regressão segmentada para avaliar o quanto a iniciativa alterou as tendências de DCV.

Resultados

- A proporção de internamentos por ACS diminuiu 5,8% após a proibição de fumar.
- As tendências no número de doentes com HTA e SCA no número de internamentos por DCV diminuíram após a iniciativa de reduzir o consumo de sal. Embora nenhuma das tendências tenha sido estatisticamente significativa.
- A proporção de doentes que ativam a VVC aumentou, embora mais de metade não recorra à VVC.
- Estratégias como a proibição de fumar e a VVC diminuíram as taxas de letalidade por ACS.

Conclusões

Este estudo sugere que as abordagens populacionais podem afetar as DCV, reduzindo o número de eventos e mortes prematuras. Considerando que a DCV constitui um imenso problema de saúde pública, uma pequena melhoria no tratamento e um aumento na consciencialização da população podem ter importantes ganhos clínicos, económicos e sociais.

Palavras-chave: Doença cardiovascular, saúde pública, síndrome coronária aguda, acidente vascular cerebral.

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ABBREVIATIONS

ACC/AHA- American College of Cardiology/American Heart Association

ACS – Acute Coronary Syndrome

CI – Confidence interval

CVD – Cardiovascular disease

ESC – European Society of Cardiology

PSC – Portuguese Society of Cardiology

FTS – Fast track system

FMC – First medical contact

ITS – interrupted time series

HBP – High blood pressure

CCU – Coronary Care Unit

NCDs – Noncommunicable diseases

WHO – World Health Organization

STEMI – ST-segment elevation myocardial infarction

NSTEMI – non-ST-segment elevation myocardial infarction

UA – Unstable angina

CHD – Coronary heart disease

PCI – Percutaneous coronary intervention

DRG – Diagnosis related group

INEM – Institute of Medical Emergency

CODU – urgent care counselling centre

GLS – Generalized least squares

GLM – Generalized Linear Model

NRACS – National Registry for Acute Coronary Syndrome

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death around the world(1) and is the leading cause of death in Europe and the most common cause of death in Portugal(2). It is estimated that by 2030, ischemic heart disease will be the third leading cause of death worldwide(3). Despite recent decreases in mortality rates in many countries, CVD is still responsible for almost half of all deaths in Europe(4), constituting a major public health challenge in Western Europe(5). However many of the CVD events could be prevented if we focused on the modification of main risk factors(6).

The observed reduction in CVD mortality in the last decades, albeit at a low rate, is the result of a set of changes, mainly by efforts made by most European countries in disease prevention, tackling mainly risk factors, as well as to the improvements made in disease management and treatment. Particularly in Portugal, several improvements in CVD management have been made, with improvements in the availability of drug treatments and, more importantly, in the easiest and fastest access to reperfusion and revascularisation interventions(7).

The evidence-based effectiveness of the health policies is increasing, and we have realized that a variety of policy- and practice-related measures will be necessary to effectively reduce CVD incidence and mortality as well as to promote changes in the healthcare system.

There is a growing consensus about the unmet need for health policy impact analysis(8), namely in Portugal, where there was a need to assess the impact of the different initiatives implemented in the country to reduce both CVD incidence and mortality. With this study, we decided to contribute to the knowledge of how these recent health initiatives are impacting the CVD trends.

RELEVANCE OF THE STUDY

As stated previously, CVD is a leading cause of mortality and morbidity worldwide. The most recent Global Burden of Disease (GBD) study estimated that in 2016, 17.6 million deaths were caused by CVD worldwide, which increased by 14.5% between 2006–2016(9).

The World Health Assembly adopted a global target of reducing mortality from non-communicable diseases by 25% by the year 2025(10). However, over the past 25 years, the absolute number of CVD cases has increased in Europe and in the EU, with increases in the number of new CVD cases found in most countries. Nevertheless, the age-standardised prevalence rate of CVD has fallen in most European countries, with

greater decreases in Northern, Western and Southern European countries compared to those in Central and Eastern Europe.

Nevertheless, each year CVD causes 3.9 million deaths in Europe and over 1.8 million deaths in the European Union, accounting for 45% of all deaths in Europe and 37% of all deaths in the EU.

Overall CVD is estimated to cost the EU economy €210 billion a year. Of the total cost of CVD in the EU, around 53% is due to health care costs, 26% to productivity losses and 21% to the informal care of people with CVD(11).

Studying the trends in the incidence, through the number of admissions, and in-hospital mortality, for both ACS and stroke, provides crucial insights into the determinants of heart disease, which is essential to its treatment and prevention. Within this framework, it is important to recognize that these trends are complex, likely multifactorial and evolve over time.

Three major public health initiatives were chosen to be analysed in this study, due to its complexity, we will explain the relevance for studying each in separate sections.

The relevance of smoking ban

Tobacco is now considered one of the most important public health issues and a major determinant of preventable mortality and morbidity in developed and developing countries (12-13). Diseases associated with tobacco consumption encompass a significant burden on individuals, societies, and healthcare systems.

Smoking affects not only active smokers but also those who are exposed to second-hand smoke in the vicinity of a smoker(14). Passive smoking has been associated with an increased relative risk of coronary heart disease, in some studies the exposure of non-smokers to second-hand smoke was associated with a 25% increased risk of coronary artery disease and myocardial infarction(15). Even in short-term passive smoking appears to cause damages in the endothelial function that could immediately compromise the cardiovascular system(16).

Smoking, including second-hand smoking, was responsible for the death of approximately 12.350 people in Portugal by the year 2013 (around 11%)(17).

Having in mind that the 2013 World Health Assembly called on governments to reduce the prevalence of smoking by about a third by 2025 there is an urgent call to firstly understand the problem, secondly created measures that can lead to those reductions and lastly assess the impact of such measures.

The relevance salt reduction

The association between salt and hypertension has been extensively studied, mainly because hypertension is one of the major risk factor for cardiovascular disease (CVD). The increase salt consumption is estimated to have already caused more than 3 million deaths mostly related to CVD(18). All this evidence led the World Health Organization (WHO) to create a set of recommendations that countries should implement to reduce dietary salt to a minimum of 5g/day, in order to prevent chronic disease and improve health(18). Salt reduction has been a public health priority to the EU, leading to the creation of an initiative called EU Framework for National Salt Initiatives(19). Thanks to this initiative, 26 of the 53 Member States, including Portugal, have implemented operational salt reduction policies(20).

According to the WHO, 15 million people have a stroke worldwide every year, most of whom are in developing countries. High blood pressure is the most important risk factor for stroke and contributes to more than 12·7 million strokes worldwide. In developed countries, the incidence of stroke seems to be declining, largely because of efforts to reduce blood pressure, but the overall incidence of stroke remains high because the population is ageing. To sustain the decline in stroke incidence, it is extremely important to continue with efforts to educate and update health-care providers about management of hypertension.

Although it is known that Portugal is one of the countries with the highest mortality rate by stroke among the Western countries(21) salt consumption levels are approximately twice of the value recommended by the WHO, with a mean salt intake of 10.7 g salt /day(22).

Therefore, studies are needed to understand the potential overall impacts on hypertension and CVD of the public health measures implemented in Portugal.

The relevance of PPCI and the coronary fast track system

Several improvements in coronary heart disease (CHD) management have been made in Portugal, with improvements in the availability of drug treatments and, more importantly, in the easiest and fastest access to reperfusion and revascularisation interventions(7).

As the mortality by ACS, namely by STEMI, is highly influenced by many factors, among them, time delay to treatment, it seems crucial to understand factors associated to this delay in the Portuguese population as well as to understand the measures taken in the country to improve this problem and assess their efficacy.

AIMS OF THE STUDY

To date, there is no study for the Portuguese population to focus on the impact of these three initiatives in CVD trends, which indicates the extreme importance of the present study, aiming to improve the understanding of the problem, besides providing important data for the planning of actions targeting education of both patients and health professionals.

Therefore, this study aims to identify the trends in CVD, acute coronary syndrome and stroke, before and after the implementation of three major public health initiatives, such as the smoking ban, the salt reduction regulation and the implementation of the fast-track system to coronary care unit (CCU).

Specific aims:

1- To evaluate the impact of the smoking ban on the number of admission of ACS in Portugal
2- To evaluate the impact of the salt reduction regulation on the number of hypertensive ACS patients and ACS admissions
3- To assess the impact of the Fast track system to the coronary unit on case fatality rate
4- To assess the impact of the measures previously mentioned, individually and altogether on ACS case fatality rate

Figure 1 illustrates the rationale behind the development of this study, summarizing the objectives proposed to be studied herein.

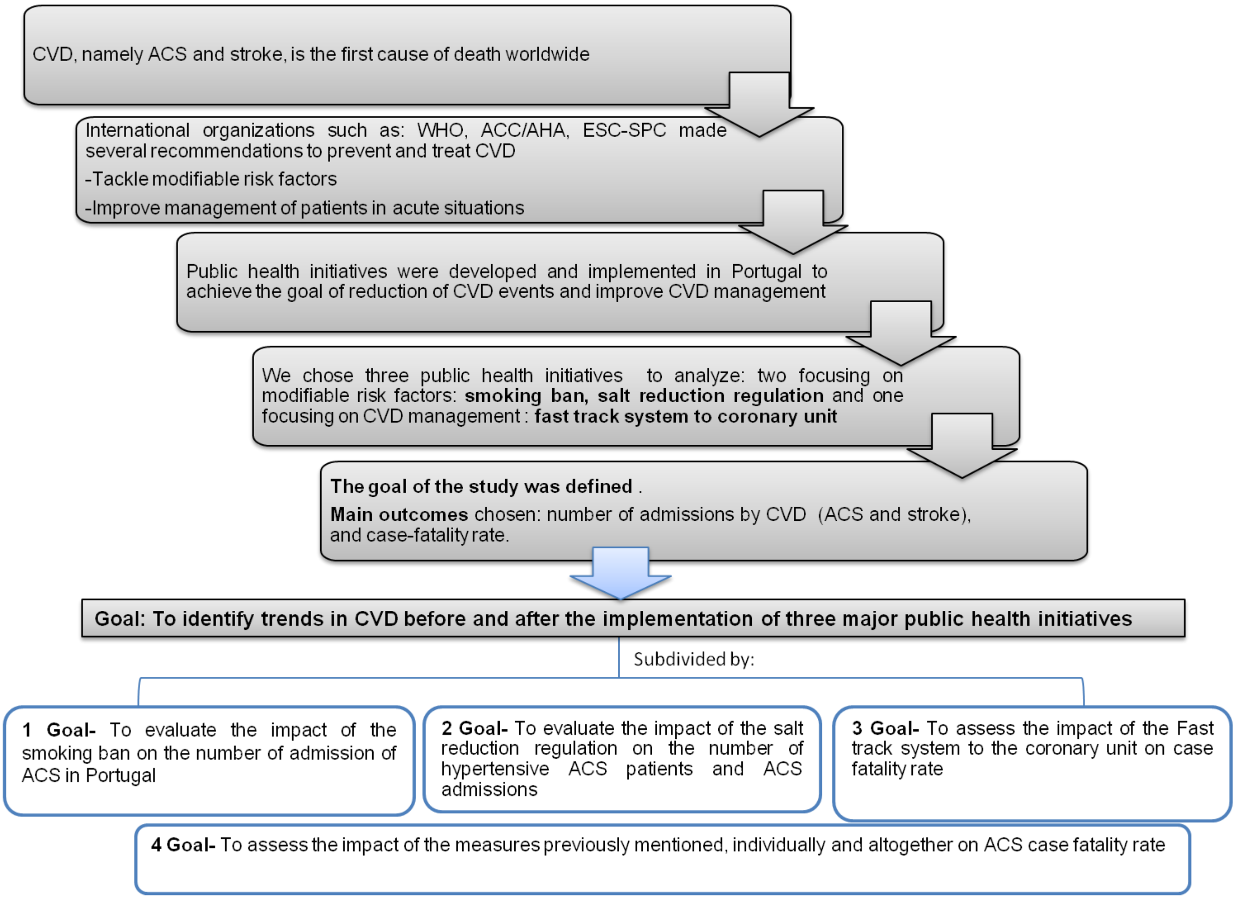

Figure 1: Flowchart summarizing the sequence of the construction of the study.

This study consisted in the elaboration of a total of four scientific manuscripts. Two already published and two submitted waiting for response. The three initial manuscripts focused on assessing the impact of each of the health policies/initiatives, namely the smoking ban, the salt reduction strategy and the coronary fast track system on CVD trends. The first publication, entitled: **"Longitudinal impact of the smoking ban legislation in Acute Coronary Syndrome admissions"** (submitted on December 2017 and accepted on February 2017)**,** focused on the impact of the smoking ban on Acute Coronary Syndrome (ACS) admission trends. The second publication, entitled: **"Cardiovascular disease and high blood pressure trend analyses from 2002 to 2016: after the implementation of a salt reduction strategy"** (submitted on February 2018 and accepted on June 2018) focused on the impact of the salt reduction strategy on High Blood Pressure (HBP) and CVD, namely ACS and stroke, admission trends. The third publication entitled, "**Trends of case-fatality rate by ACS in Portugal: Impact of a fast-track to the coronary unit",** (submitted on November

2018, waiting for feedback) focused on impact of the coronary fast track system on case-fatality rate by ACS.

A more global and integrated manuscript on the effect of all of the policies/initiatives on ACS mortality, entitled "**Impact of public health initiatives on acute coronary syndrome fatality rates in Portugal**" (submitted on December 2018, awaiting for feedback), was also elaborate within the scope of this study.

In parallel, we produced a publication that focused in vascular disease, namely on peripheral arterial occlusive disease, entitled "Global impact of peripheral obstructive arterial disease in Portugal - an eight years study", which is also relevant for the public health community and was included in a project conducted by the ENSP-UNL during the period of elaboration of this work.

To facilitate the organization and presentation of this work, it was divided into 5 chapters. The first chapter, "Conceptual Framework" where we present a literature review, from the pathology to the health policies studied. A second chapter explaining the methodology applied in general and for each of the publications is also included. The results, 3rd chapter, and the discussion, 4th chapter, have also been included and these are divided by each of the manuscripts that are part of this project. The last chapter is the conclusion, where we have listed the main findings in our study, and also added a general comment towards the public health community.

CONCEPTUAL FRAMEWORK

In this chapter, we will address some theoretical concepts needed to understand the relevance of the study as well as to be able to interpret the results found.

1. CARDIOVASCULAR DISEASE: ACS AND STROKE

Noncommunicable diseases (NCDs) are the leading causes of death globally. In 2016, an estimated 41 million deaths occurred due to NCDs, accounting for 71% of the overall total of 57 million deaths, killing more people each year than all other causes combined(23-24).

The World Health Organization (WHO) has established the "4 by 4" principle of 4 core NCDs: cardiovascular disease (17.9 million deaths; accounting for 44% of all NCD deaths); cancer (9.0 million deaths; 22%); chronic respiratory disease (3.8 million deaths; 9%); and diabetes (1.6 million deaths; 4%)(23-24). NCDs are caused, to a large extent, by four behavioural risk factors such as: tobacco use, unhealthy diet, insufficient physical activity and the harmful use of alcohol(23).
As CVD is accountable for almost half of all NCDs the relevance of studying possible ways to control CVD incidence and poor prognostic seems indisputable.

The WHO defines Cardiovascular Disease (CVD) as a group of disorders of the heart and blood vessels and includes: coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease; deep vein thrombosis and pulmonary embolism. Coronary heart disease, cerebrovascular disease, namely Acute Coronary Syndrome (ACS) and stroke, respectively, are considered acute events and are the main responsible for the high mortality rates associated to CVD(25).

CVD remains the leading cause of death among Europeans countries causing more deaths than any other condition and in many countries still causes more than twice as deaths as cancer(4). The burden of CVD in Europe remains high overall, and varies dramatically between countries. More than 4 million Europeans die of CVD every year and many more are hospitalized after acute episodes or treated for chronic cardiovascular disorders(26).

Despite deaths from cardiovascular diseases have been dramatically reduced in many high-income countries, mainly related to the implementation of government policies which facilitate the adoption of healthier lifestyles and provision of equitable health

care, the WHO projected that annual cardiovascular disease mortality will increase from 17.5 million in 2012 to 22.2 million in 2030(27).

1.1. Acute Coronary Syndrome

The largest contributor to CVD is coronary heart disease (CHD). CHD when considered separately, accounts for almost 1.8 million deaths, or 20% of all deaths in Europe annually, its incidence and the prevalence of important risk factors varies greatly according to geographical region, sex, and ethnic background(6).

Acute coronary syndrome (ACS) is part of the wide range of manifestation of CHD and more accurately reflects the diagnostic uncertainty that exists at the time of hospitalization, highlighting the urgency of the problem and its location and providing a starting point for a series of decisions that rapidly determine optimal treatment and definitive diagnosis(28). ACS is high-risk manifestations of coronary atherosclerosis and is an important cause of the use of emergency medical care and hospitalization(29).

Depending on the changes that patients with ACS had on the 12-lead electrocardiography (ECG) and the presence of biomarkers, ACS is classified into subgroups, Acute Myocardial Infarction (AMI) and Unstable Angina (UA). Among the AMI this can be subdivided into patients with no ST-segment elevation myocardial infarction (NSTEMI) and those who have ST-segment elevation myocardial infarction in the ECG (STEMI). Lastly, UA refers to those with severe transient symptoms (28, 30).
The diagnosis of ACS requires a clinical history, a careful objective examination and a 12-lead ECG at rest. It is useful to carry out the electrocardiographic recording both during symptomatology and after its disappearance. With the development of the technology, there are today techniques that associate with clinical history and ECG allow the diagnosis of ACS, such as the specific biomarkers of myocardial necrosis, which correspond to proteins that are released into the blood from myocytes (cells of the heart muscle) that are damaged and are detected by blood tests that allow the identification of myocardial necrosis / lesion(29). The definition of AMI reflects the death of myocardial cells caused by ischemia, this may be the first manifestation of coronary disease or may occur repeatedly in patients with established disease.

The pathophysiological mechanism in the case of STEMI asserts that this phenomenon occurs when coronary blood flow abruptly decreases after thrombotic obstruction of a coronary artery previously affected by the atherosclerotic process (28, 30).

On the other hand, UA and NSTEMI are closely related conditions: their pathophysiologic origins and clinical presentations are similar, but they differ in severity. A diagnosis of NSTEMI can be made when the ischemia is sufficiently severe to cause myocardial damage that result in the release of a biomarker of myocardial necrosis into the circulation (cardiac-specific troponins T or I, or muscle and brain fraction of creatine kinase [CK-MB]). In contrast, the patient is considered to have experienced UA if no such biomarker can be detected in the bloodstream hours after the initial onset of ischemic chest pain. UA exhibits one or more of three principal manifestations: 1) rest angina (usually lasting >20 minutes), 2) new-onset (<2 months previously) severe angina, and 3) a crescendo pattern of occurrence (increasing in intensity, duration, frequency, or any combination of these factors)(29).

The most frequent mechanism associated to ACS is thrombosis developing on a coronary atherosclerotic plaque. The very rare exceptions to this are spontaneous coronary artery dissection, coronary arteritis, coronary emboli, coronary spasm, and compression by myocardial bridges. Necropsy studies suggest that a new thrombotic coronary event underlies 50–70% of sudden deaths caused by ischaemic heart disease.

The mechanism for thrombus formation is plaque disruption, in this case the plaque cap tears to expose the lipid core to blood in the arterial lumen. The core area is highly thrombogenic, containing tissue factor, fragments of collagen, and crystalline surfaces to accelerate coagulation. Thrombus forms initially in the plaque itself which is expanded and distorted from within; thrombus may then extend into the arterial lumen.

Plaque disruption, like endothelial erosion, is a reflection of enhanced inflammatory activity within the plaque. The cap is a dynamic structure within which the connective tissue matrix, upon which its tensile strength depends, is constantly being replaced and maintained by the smooth muscle cell. The inflammatory process reduces collagen synthesis by inhibiting the smooth muscle cell and causes its death by apoptosis.

The distinction between erosion and disruption is not necessarily of major clinical importance. Both processes depend on enhanced inflammatory activity within the plaque and appear equally responsive to lipid lowering. Disruption has an intraplaque component more resistant to fibrinolytic treatment, while in erosion the thrombus is more accessible(31).

The mechanism explained above describes the pathophysiological process of the development of an ACS. After acknowledging this process, it is equally important to measure the number of ACS events that occurred, this is normally measure through

incidence measures. However, despite its importance, incidence rates and trends for ACS have been poorly address in Portugal. Once incidence of ACS can be used as a measure of quality that can be useful to set health priorities as well as a way to identify high-risk populations, it seems extremely important to study this measure in a Portuguese population(32-33). From the studies performed in Portuguese populations despite the decline observed in mortality trends by ACS, it remains unclear, how much of the this decline is associated to a reduction in the incidence of the disease and how much is associated to improved survival(34) due to novel therapeutic approaches and improved management.

THERAPEUTIC APPROACH TO ACS

Although the basic treatment for managing patients with ACS is mainly pharmacologic, namely by thrombolytic therapy, coronary revascularization procedures achieved by mechanical means such as Percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG), currently present the most beneficial option in the treatment of ACS, allowing for a rapid restoration of the coronary artery blood flow (30). In the case of PCI, since it was first performed it has undergone through a rapid evolution to become one of the most widely performed medical procedures, currently over 3 million annually worldwide. PCI is a highly effective mean of treating acute coronary disease and recent guidelines recommend PCI as a reperfusion strategy, while it is performed by experienced and timeless operators(35).

Briefly, PCI consist in the insertion of a catheter tube and injection of contrast dye, usually iodine-based, into the coronary arteries, through a needle puncture, the catheters are conducted to the heart under the fluoroscopic orientation. The catheter is placed at the ostium of the stenosed coronary artery, allowing a flexible dirigible wire guide passage to a distal part of the artery. A balloon is then passed through this wire and inflated at the place of the stenosis. In acute cases, it is possible to perform a PCI with a 95% higher success rate when compared to pharmacologic treatments, namely fibrinolysis. Some of the advantages of PCI compared to fibrinolysis are: reduced incidence of haemorrhagic strokes, lower incidence of early recurrence, fibrinolytic (28, 30).

PCI is called Primary PCI (PPCI) in case the balloon angioplasty (with or without stenting), is inserted without the previous administration of fibrinolytic therapy or platelet glycoprotein IIb/IIIa inhibitors, to open the infarct-related artery during an acute myocardial infarction with ST-segment elevation. PPCI restores angiographically normal flow in the previously occluded artery in more than 90% of patients, whereas

fibrinolytic therapy does so in only 50 to 60% of such patients(36). In the last years, several studies have been created analysing the benefits of each treatment available for ACS and comparing them. Treatments can go from CABG to pharmacological treatment such as fibrinolysis. The recommendations to choose among treatments available for ACS are well established by both the American College of Cardiology Foundation/American Heart Association (ACCF/AHA)(30) and the European Society of Cardiology (ESC)(28) (adopted by the Portuguese Society of Cardiology). However, PPCI is presented as the less invasive, making hospitalization shorter, has lower economic costs, being effective in symptoms relieve. Nevertheless the recommendations to whether chose one treatment over the other are complex but it is explained in detailed by the European (ESC) and American (ACCF/AHA) guidelines.

The main goal of the PPCI is therefore to minimize total ischemic time, defined as total time between symptom onset to treatment/open vessel(37). Several studies demonstrated that the survival rate decreases drastically after 6 hours, as can be observed in Figure 2. For this reason most authors use the 6 hours as a reference for the best and the worst prognosis (38-40).

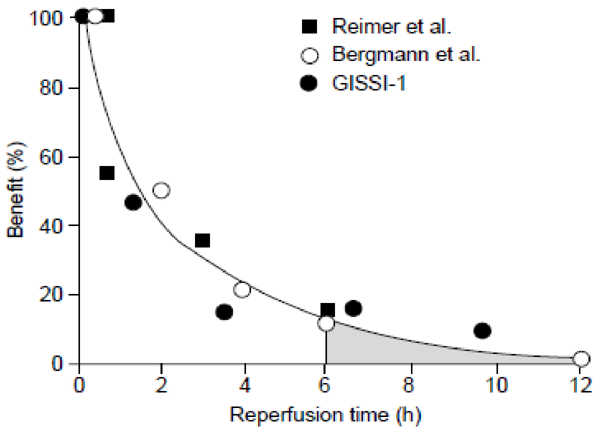

Figure 2: Reperfusion time-benefit curve depicts combined data from several studies.
Adopted from: Williams, W.L., 1998. Guidelines to reducing delays in administration of thrombolytic therapy in acute myocardial infarction.

It is well documented that coronary reperfusion achieved by emergency PPCI may reduce the hospital mortality rate when performed as soon as possible. Unfortunately, it has been verified that over time only a small percentage of patients with STEMI carry out primary PPCI within the stipulated time(39). The fact that some studies have shown

that mortality rates rise with increases in reperfusion time is one of the causes that has led to intensive investigation in order to make PCI available in the shortest possible time (28, 30, 41).

Time between symptom onset to treatment is often divided into time from symptom onset to first medical contact (FMC), and time from FMC to balloon inflation, also known as door to balloon time. Time from symptom onset to FMC, when less than 2 hours has shown better outcomes whereas a relatively stable mortality rate was observed for patients presenting between 2 to 12 hours(42). High mortality rates are observed in the first hours of evolution of the STEMI and may even reach 50% mortality rates in the pre-hospital phase.

On the other hand current American and European guidelines endorse a door-to-balloon time of 90 minutes or less as the target, giving it the highest recommendation level, it is well confirmed that longer door-to-balloon delay, beyond the 90 minutes, in primary percutaneous coronary intervention for STEMI is related to higher risk of adverse outcomes(43-44).

Most studies suggest that an increase in total ischemic time is associated with a worse prognosis (28, 30, 39), assessed by infarct zone size, as well as mortality rate. A recent analysis was proven by each of the 30-minute retrospectives that the time was no more than a 7.5% increase in death risk for one year(45).

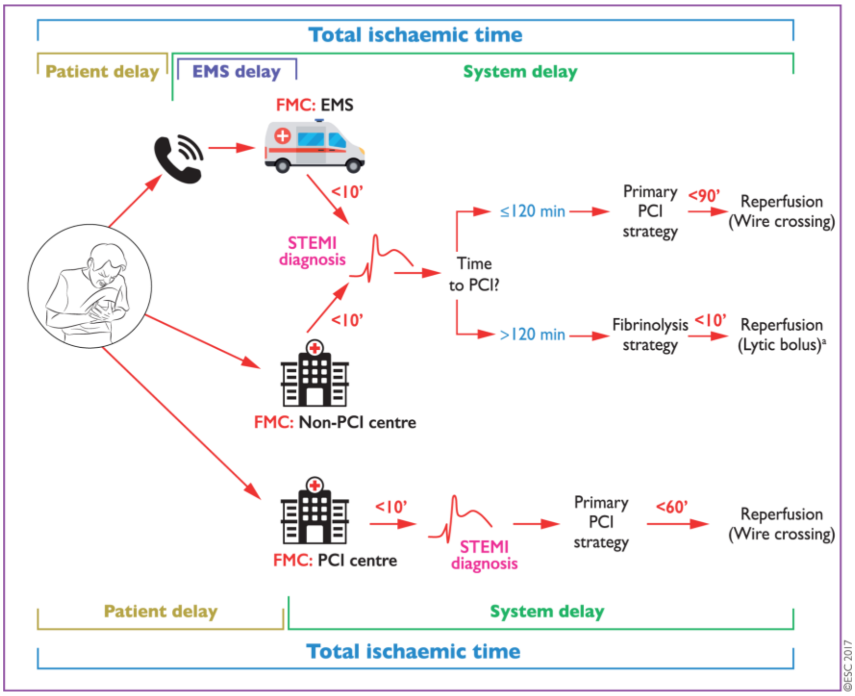

Figure 3: Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation.
Adopted from: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2017; 39(2).

Given the great relevance of reducing both time from symptom onset to FCM and door to balloon time, and following ESC guidelines (Figure 3) a fast track system was implemented in Portugal with the goal of creating a priority system and facilitated access to clinical, therapeutic and complementary diagnostic resources. Direct admission into the CCU is essential not only to improve accessibility but also to allow a more effective treatment, since time between the onset of symptoms and treatment is, in the case of AMI, vital for the reduction of morbidity and mortality. The system is initiated by the patients when calling the emergency number (112 for Portugal). The National Institute of Medical Emergency (INEM) initiates the diagnosis and treatment earlier while referring the person to a hospital unit specializing in ACS treatment(46).
The INEM have the capacity to intervene prematurely, and after the clinical diagnosis and the electrocardiogram, if it is established the diagnosis, decide jointly with the urgent care counselling centre (CODU) the pre-hospital treatment, as well as referral to hospitals increasing the likelihood of therapeutic success. The CODU contacts the hospital unit in order to take the necessary steps for the admission and treatment of the patient(47). The system began to be implemented as a pilot project in the Algarve

region of the country in 2002 but only by 2007 it was implemented as a policy in all Mainland Portugal(48).

1.2. CEREBROVASCULAR DISEASE: STROKE

In 2013, stroke was considered the second most common cause of death (11.8% of all deaths worldwide, after ischemic heart disease (14.8% of all deaths), and the third most common cause of disability (4.5% of DALYs from all cause) after ischemic heart disease(49). Overall, estimates indicate that there is a continuous increase in stroke burden in the world over the last two and half decades. On the other hand the number of stroke survivors and people with incident stroke have also increased 50% to 100%, thus indicating that currently used primary stroke prevention strategies have improved however they are not yet sufficiently effective and require a serious improvements(49).
Across Europe, over the last two decades there has been a reduction in the proportion of people having a stroke, despite this progress, the numbers of strokes are set to rise because the proportion of Europeans over 70 is increasing. The projections indicate that between 2015 and 2035, overall there will be a 34% increase in total number of stroke events in the EU. Stroke prevention should, therefore, be a high priority(50).

Stroke can be defined as a rapidly developing focal (or global) brain dysfunction of vascular origin lasting more than 24h, and depending on the aetiology, strokes can either be ischemic or haemorrhagic. Haemorrhagic strokes include intracerebral haemorrhage and subarachnoid haemorrhage(51-52).
The lesions associated to strokes are mainly caused by the infarction of a specific brain area due to ischaemia or a haemorrhage, which leads to an impairment of the brain function. This infarction is caused by a sudden reduction of the blood flow. Ischemic stroke is by far the most common type of stroke, constituting around 80% of all strokes, of which 60% are attributable to large-artery ischaemia(52).
On the other hand, cerebral haemorrhage, more than ischaemia, is essentially related to arterial hypertension. Chronic increase of pressure in the arteries, especially if it is ignored or untreated, leads to a weakening of the arterial walls, which may result in rupture and consequent haemorrhage(52).

1.3. CARDIOVASCULAR DISEASE RISK FACTORS

Risk factors are conditions or habits that make a person more likely to develop a disease. They can also increase the chances of worst prognosis.

Risk factors for CVD are well known and are divided into 2 main categories, modifiable risk factors and non-modifiable risk factors. Non modifiable risk factors go from age to gender and family history. On the other hand, modifiable risk factors mainly encompass behaviour related factors, such as:

- Smoking
- Diabetes mellitus
- Hypertension
- Hypercholesterolemia
- Unhealthy diet
- Overweight or obesity
- Physically inactivity

It is noteworthy that the first 4 risk factors in this list account for 80% to 90% of the risk of developing CVD(53). In the present study, we will focus mainly on two of the previously major risk factors identified: smoking and hypertension. We will focus here in the relation and the impact between these risk factors on developing CVD. On the following sections, we will address in detail, both the relation between them and the impact of these risk factors on developing CVD.

Smoking and CVD

Smoking and involuntary exposure to cigarette smoke are major causes of ACS and stroke. Smoking was considered the second leading risk factor for early death and disability worldwide in 2015 and it has claimed more than 5 million lives every year since 1990(54). If current smoking patterns persist, tobacco will kill about 1 billion people this century, mostly in low- and middle-income countries. About half of these deaths will occur before 70 years of age(54).
Smoking is clearly one of the main risk factors for CVD and even after adjustment for other risk factors, cigarette smokers have higher risk of CVD and higher mortality from cerebrovascular disease than do lifetime non-smokers, and a dose-response relationship is evident. This has been extensively proven, even resorting to prospective studies with cohorts up to 20-year follow-up which have confirmed the increased risk of death from stroke and other CVD(54). Even low levels of exposure, including exposures to second-hand tobacco smoke, have proven to lead to a rapid and sharp increase in endothelial dysfunction and inflammation, which are implicated in acute cardiovascular events and thrombosis(54).

Studies in Portugal have estimated that 40% of the burden of the most significant smoking related diseases was attributable to smoking, compared to a situation in which the Portuguese population had never smoked(55).

To better understand the way smoking can lead to CVD, the following section has the purpose to give a brief description of the pathophysiology of smoking.

Pathophysiology of smoking leading to CVD

The main mechanism for smoking to lead to an acute CV accident is to produce acute ischemia thus adversely affecting the balance of demand for oxygen and nutrients with blood supply. There is evidence of an increase in demand for oxygen in the myocardium which is a consequence of nicotine stimulation of the sympathetic nervous system and the heart. The same have been observed in brain tissue. Thus, there is impairment between the responses of artery blood flow to an increase in tissue (brain or myocardium) demand for oxygen; that is, smoking reduces the coronary vasodilatory flow reserve(54).

In addition, smoking played a direct role by constricting coronary arteries through nicotine-mediated action on α-adrenergic receptors and by induction of endothelial dysfunction by nicotine and oxidizing chemicals. Other mechanisms have been described in which smoking can lead to inflammation, insulin sensitivity, and lipid abnormalities that most likely contribute to smoking-induced CVD.

Studies demonstrate that cigarette smoking results in a chronic inflammatory state, evidenced by increased counts of circulating leukocytes, CRP, and acute-phase reactants such as fibrinogen. Cigarette smoking also activates monocytes and enhances recruitment and adhesion of leukocytes to blood vessel walls, an integral step in vascular inflammation. Research indicates that inflammation contributes to atherogenesis, because high leukocyte counts and high levels of CRP and fibrinogen are all powerful predictors of future cardiovascular events(54). Dysfunction of the coronary arterial endothelium has also been linked to smoking which associated to the mechanisms explained above which can potentiate an acute CV event.

Hypertension and CVD

High blood pressure (HBP) is one of the most significant risk factors worldwide. Moreover the impact of HBP on mortality among older adults is expected to grow over the coming decades.

Recently, HBP accounts for 90% of the population's attributable risk for myocardial infarction in men and for 94% in women, with approximately 54% of strokes and 47% of coronary heart diseases, worldwide, being attributable to HBP(56). Longitudinal studies indicate that individuals who have high-normal blood pressure have a twofold increased risk for developing heart disease and stroke than those who have blood pressure less than 120/80 mmHg(57).

Therefore HBP represents a major risk factor for developing CVD, especially for stroke. Studies have shown that the risk of stroke increases continuously above blood pressure (BP) levels of approximately 115/75 mm Hg. Since the association is steep, and BP levels are high in most adult populations, almost two thirds of stroke burden globally is attributable to nonoptimal BP (i.e., 115/75 mm Hg)(58).

There is evidence from meta-analyses of randomized controlled trials that confirm an approximate 30% to 40% stroke risk reduction with BP lowering(59). Even small reductions of BP can lead to reductions of the risk of stroke by more than one third and coronary heart disease by one fifth(60). The epidemiological expected benefits from lowering BP are broadly consistent across a range of different population subgroups(58).

The link between salt intake and increased BP has been well established through ecological, population, and prospective cohort studies and intervention trials, yet sodium consumption remains a particular concern in relation to increasing BP in Western populations(61).

One effective way to control BP is through diet, namely by reducing dietary salt intake. A recent metanalysis showed that a modest reduction in salt intake for four or more weeks led to significant and important falls in BP in both hypertensive and normotensive individual(62).

An average reduction of 77 mmol/day in dietary intake of sodium has been shown to reduce systolic blood pressure by 1.9 mmHg and diastolic blood pressure by 1.1 mmHg. Phase 2 of the Trials of Hypertension Prevention Studies has also documented that a reduced sodium intake can prevent hypertension(63).

Besides this, reducing salt intake have also shown as a very cost –effective measure with studies showing that even government "soft regulation" strategies combining targeted industry agreements and public education to reduce dietary sodium is projected to be highly cost effective worldwide, even without accounting for potential healthcare savings(64).

To better understand the way HBP can lead to CVD the following section have the purpose to give a brief description of the pathophysiology of HBP.

Pathophysiology of HBP leading to CVD

The path for which HBP can lead to an acute cardiovascular (CV) event is mainly explained by the endothelial dysfunction, which can exacerbate the atherosclerotic process and contribute to make the atherosclerotic plaque more unstable. The remodelling of coronary arteries and increased resistance at microvascular level, all contributing to a decrease of coronary reserve(65). Moreover, deposition of lipids and the formation of the atherosclerotic plaque may be favoured by the increase of transmural pressure in arterial vessels, with an increase in mechanical stress and endothelial permeability(65).

Another way HBP can lead to CVD is by left ventricular hypertrophy, which is the usual complication of hypertension, and promotes a decrease of 'coronary reserve' and increases myocardial oxygen demand, both mechanisms contributing to myocardial ischemia(65).

2. PUBLIC HEALTH POLICY, ACTION AND INITIATIVES

Projections demonstrate that the NCDs will be increasingly prevalent in the next decades and will reach epidemic proportions, which will seriously influence global public health, and furthermore have substantial effects on social and economic development—unless urgent actions are undertaken(49).
After the Framingham study, a well-defined group of risk factors for CVD were found to be associated with the development of such disease. As the main risk factors have been established there is an urgent need of finding effective means to slow and eventually stop the development of CVD.
One way to achieve this is by these two main approaches that aim to reduce the burden of CVD, namely, population approach, and the "high risk" approach which can also be considered as complementary(6, 66).
The **high-risk approaches** seek to identify and treat intensively only those individuals that present a risk factor, thus targeting "high risk" people, i.e. only persons with high risk of CVD are treated(6). On the other hand the **population approach** is based on the theory that risk-factor reduction can be achieve through population prevention programs, recognizing that small changes in risk among large numbers of people can have a profound effect on the total disease expression of a population.
A simple example to distinguish between these two approaches is given by Nathan D. Wong 2014(6), where he states that the high-risk approach seeks to identify and treat intensively only those individuals with the highest levels of cholesterol, whereas the

population approach reduces overall risk by reducing cholesterol levels in the entire population.
This later strategy assumes that modest reductions in these factors produce graded and often dramatic reductions in disease expression(67). Population-wide interventions have proven to be cost effective and can even be revenue-generating, as is the case with tobacco and alcohol tax increases, for instance(23). In this strategy, governments are the ones considered to have the main responsibility and have the power to influence environmental, social, medical, and lifestyle factors through legislation and taxation of tobacco, alcohol, and food contents (salt, sugar, and saturated fats).
Considering this, the World Heart and Stroke Forum recommends that every country develop a policy on CVD prevention in a global effort to reduce morbidity and mortality from CVD(68).
These national policies should set priorities for public health and clinical interventions appropriate to the country and should also be the foundation for the development of national guidelines on CVD prevention(68).
The health policies implemented should make it easier for healthy people to remain healthy, and for those at high risk will also support lifestyle modification. It should make the case for investment in health and creating societies where health is valued. As it is evident that good health benefits all in society, as good health is vital for economic and social development and supports economic recovery.

Population strategies imply altering, the lifestyle and environmental factors in the entire population, as well as behavioural changes. These strategies require policy and legislative changes that are often not supported by major industries such as dietary salt reduction and smoking and, it can be very difficult to implement.

The goal of these policies that aim to change such habits, as smoking or dietary salt intake, can be difficult not only to implement but to keep the behaviour. Nevertheless, improvements in reducing smoking, obesity, poor-quality diet, and low physical inactivity are feasible and will improve patients' health(69).

In spite of all this evidence in many European countries, the emphasis of current policy for the primary prevention of CVD is placed on high-risk rather than population strategies(70).
For this reason the European Commission's 2014-2020 Health Strategy for Growth Program(71) was created in order to complement, support and add value to Member States' policies aimed at improving the health of citizens and reduce inequalities in health(72).

The WHO has also strengthened its efforts to promote population-wide primary prevention of communicable diseases, through the Framework Convention on Tobacco Control and the Global Strategy for Diet, Physical Activity and Health(73).

In Portugal, the most recent National Health Plan created can be an excellent opportunity to start a different phase in the way health policies are conceived and applied. The fast increase in the stroke burden across all countries of the world suggests that currently used primary stroke and CVD prevention strategies are not sufficiently effective.

The World Health Report 2017 also refers to the importance of not only creating and implementing health policies but also the importance of monitoring, raising awareness, identifying areas for improvement and identifying successful policy actions(24).

Nevertheless, several policies have been implemented, in Portugal, to reduce CVD both incidence and mortality. Polices more focused on disease prevention such as anti-smoking legislation implemented in January 2008(74), as well as legislation targeting reduction in dietary salt intake, in 2010, to achieve the values recommended by the WHO of five 5g/day(18). Also policies directly targeting CVD mortality, such as the implementation of a fast-track system with direct admission to the CCU(75).

Within the scope of this study, only population-wide approaches were considered. Below we included a brief description of each of the population-wide approach studied.

2.1. SMOKING BAN

Portugal was one of the countries that signed the WHO Framework Convention on Tobacco Control(76), leading to the implementation of the most recent anti-smoking measure, the 37/2007 legislation implemented in January 2008(74). This legislation contained new framework to protect individuals from passive smoking and for cutting down/stopping consumption to ensure protection against second-hand smoke(74, 77). This law banned smoking in all enclosed public places, such as hospitals and public transportations, and workplaces. Besides this, it established further regulation for the information provided on tobacco products, packaging and labelling, as well as further restrictions on the advertising(78).

More specifically the legislation imposed limitations to smoking in close spaces intended for collective use. It became forbidden to smoke at:

- Where sovereign bodies, services and bodies of the Public Administration and public corporations are installed;

- At workplace;
- At places of direct service to the public;
- At establishments where health care is provided, namely hospitals, clinics, health centres and homes, doctors' offices, first aid stations and the like, laboratories, pharmacies and places where non-prescription medicines are dispensed;
- At nursing homes and other institutions housing the elderly or disabled;
- At places intended for children, such as day care centres, homes for children and youth, leisure centres, colonies and holiday camps and other similar establishments;
- At educational establishments, regardless of the age of the pupils and the educational level, including, in particular, classrooms, study rooms, teachers and meetings, libraries, gymnasiums, atriums and corridors, bars, restaurants, canteens, playgrounds;
- At vocational training centres;
- At museums, visitable collections and places where classified cultural goods are stored, in cultural centres, archives and libraries, in conference, reading and exhibition rooms;
- At theatres and venues and other venues for the dissemination of the arts and entertainment, including antechambers, entrances and contiguous areas;
- At the playgrounds, in the casinos and in the enclosures destined to shows of non-artistic nature;
- At enclosed areas of sports facilities;
- At the enclosures of the fairs and exhibitions;
- At shops, shops and public places of sale;
- At hotel establishments and other tourist developments where accommodation services are provided;
- At catering or beverage establishments, including those with dance halls or spaces;
- At canteens, cafeterias and bars of public and private entities exclusively for their staff;
- At service areas and fuel stations;
- At airports, at railway stations, at bus stations and at sea and inland waterways;
- At the metropolitan facilities affected by the public, namely in the terminal or intermediate stations, in all their accesses and establishments or contiguous installations;
- At covered car parks;
- At elevators, lifts and the like;
- At closed telephone booths;
- At the enclosures of automatic cash withdrawal networks;

- At any other place where smoking is prohibited by management, administration or other applicable legislation, in particular with regard to the prevention of occupational risks.
- At vehicles used for public urban, suburban and interurban passenger transport, as well as road, rail, air, sea and river transport, express, tourist and rental services, taxis, ambulances, patients transport vehicles and cable cars.

In addition to the ban on smoking in enclosed spaces, the current smoking ban further restricts advertising.

Smoking legislation was implemented in January 2008, providing six years of data before implementation of the legislation (January 2002 through December 2007) and seven years of data after the legislation was implemented (January 2008 through December 2014).

2.2. Salt reduction policy

In light of the evidence that suggested health gains from salt reduction, the EU Framework for National Salt Initiatives was launched in 2008 and since then most EU Member States have made salt reduction a public health priority(19).

Evidence show that increased salt consumption have caused millions of deaths mostly related to CVD, particularly stroke, which is the first cause of death in Portugal(2). The high prevalence of HBP is pointed as one of the main reasons. Bearing in mind that salt intake in Portugal have reach a most recent value of 7.3 g/day in 2016(79), varying from 12g/day(22) in 2007 to 10g/day in 2012(21) and considering that bread is the foodstuff that contributes with about one-sixth of daily salt intake(80-81) as well as the fact that Portugal together with Poland and Japan is one of the countries with the highest levels of salt in bread(82-83) led to the implementation, in mid-2010, of a new legislation in Portugal.

This legislation aim to reduce salt in bread to minimum of 1.4g of salt per 100 grams of final product, also the law foresees mandatory labelling for pre-packed products stating clearly the salt content in the product. Portugal was thus, the first western country to create a law for the delimitation of the quantity of salt contained in bread(84-85).

2.3. Coronary Fast Track System

As time is crucial in ACS, time is muscle, it is essential to create measures that can help reducing time from symptom onset to treatment, thus reducing mortality and morbidity associated with ACS. For this purpose, a Fast Track System (FTS) to CCU was implemented in Portugal in order to reduce this crucial time.

This FTS strategy was created by the Directorate General of Health (DGH) within the framework of the “National Program for Disease Prevention and Control Cardiovascular” included in the Diary of Republic No. 193 of August 22, 2003.

One of the main goals of this National program is to improve CVD management. Bearing in mind that by the time this program was created, Portugal was below average concerning the use of PPCI, which is the main treatment for acute coronary events, there was a need to create strategies that would increase the use of PPCI. In this context, the DGH developed the FTS to promote better patient access to coronary care.

The creation of the FTS is an organized way to reach both, referral to hospitals and appropriate timed treatment, intervening at pre, intra and interhospital stages, of clinical acute situations, as is the case of ACS. The main goals of this strategy are: the promotion of the early recognition of alarm signals, the definition of referral to the appropriate institution and the recommendations and clinical protocols to be followed, of systems of registries and evaluation and monitoring(86).

As not all hospitals in the country have the necessary conditions to conduct a PPCI, namely no catheterization laboratory nor specialized personnel, a Hospital Referral Networks was established. This system intend to regulate complementarity and technical support relationships among all hospital institutions, in order to guarantee access of all patients to health care services and units, supported by an integrated inter-institutional information system.

Thus patients admitted into a hospital where PPCI cannot be conduct are transferred through this referral network to a hospital geographically closer that allows the patients to benefit from the adequate treatment(46).

The FTS was first implemented as a pilot project in the Algarve region of the country in 2002, but only by 2007, it was implemented as a policy throughout Portugal(48).

METHODOLOGY

In order to achieve our goal to identify the trends in CVD, ACS and stroke, before and after the implementation of three major public health initiatives, the smoking ban, the salt reduction legislation and the implementation of the FTS to CCU, we created a methodological and statistical plan that would allow us to provide robust results and conclusions. As it is impossible to do a randomized controlled trial of such a large scale public policy interventions, the methodology applied in our study is the one adequate for ecological studies.

We started by describing the common methods used in the four manuscript included in this study and finally described the Specific Methodology including the particular methods applied in each of the four manuscripts.

The sections 3 and 4 encompass the general methodology as well as the data used through all the manuscripts produced. Details on the methodology applied in each manuscript are included in section 5.

3. TYPE OF STUDY: ECOLOGICAL STUDIES

Ecological studies are observational epidemiological evaluations in which the unit of analysis is populations, or groups of people, rather than individuals(87).

They are frequently used where alternative study designs are not possible (e.g., randomized control trials), such as when investigating the effect of geographical and temporal factors on disease incidence or the effect of a government policy change on health outcomes(88).

Complete ecological studies involve studies where all of the variables are ecological in nature, whereas partial ecological studies involve a mixture of individual-level and ecological variables.

These type of studies are inexpensive and easy to carry out, using routinely collected data. Although some cautions are appropriate for ecological studies regarding causality, it may never be possible to conduct individual-level studies to answer certain questions and that if a strong and biologically plausible effects are observed in an ecological study, the causal inferences may be sufficiently strong to warrant appropriate policy or clinical practice changes(88).

The adoption of a multilevel perspective when thinking about ecological studies, allows integration of theory and observations on all available levels: physiological (which examines exposures and responses of systems within individuals), individual (which examines exposures and responses of individuals), and aggregate or contextual

(which examines exposures and responses of aggregates or clusters of individuals, such as locales or societies).

There are two major types of measurements on aggregates: summaries of distributions of individuals within aggregates, such as mean age and percent female; and purely ecologic (contextual) variables that are defined directly on the aggregate, such as whether there is a needle-exchange program in an area. The causal effects of the latter purely contextual variables are the focus of much social research and ecosocial epidemiology. Nonetheless, most outcome variables of public-health importance are summaries of individual-level distributions, such as prevalence, incidence, mortality, and life expectancy, all of which can be expressed in terms of average individual outcomes(89).

Ecological studies have played an increasingly important role in the field of cardiovascular outcomes research and are increasingly attracting the attention of policy makers, health system managers, clinicians, and the public(88).

4. DATA AND STATISTICAL ANALYSES

Before getting into detail of which statistical techniques were applied in our study it is important to know which data was used as well as which sources where used to obtain these data.
After describing the data, a detailed description of the statistical techniques applied will be provided.

4.1. DATA

Data used in this study were obtained from two different sources, both with National reach, the Diagnosis Related Group (DRG) data and the National Registry of Acute Coronary Syndrome (NRACS) data.

The DRG data allowed us to obtain the number of admission made by ACS and stroke to any public hospital in mainland Portugal, as well as the number of in-hospital deaths by ACS. It also contained variables such as age, sex, country and region which allowed further stratification of the data.

The NRACS provided data such as risk factors for each of the patients included in the study, as well as information on the activation of the FTS, age and sex. This information is crucial as smoking and HBP are the risk factors mainly affected by the policies we aimed to assess. The fact that it contains data on the activation of the FTS

is equally relevant as one of the goals of our study was to assess the impact of this measure.

4.1.1. The Diagnosis Related Group

Diagnosis related group (DRG) is a classification system for patients admitted to acute hospitals that groups patients into clinically coherent and similar groups regarding their resource consumption. It allows defining operationally the set of goods and services that each patient receives according to their needs and the pathology that led to hospitalization and as part of the defined treatment process.

Each group is associated with a relative weight, i.e. a weighting coefficient reflecting the expected cost of treatment of a typical patient grouped in that DRG, expressed in relative terms against the typical average patient cost at the national level. The casemix index of a hospital thus results from the ratio of the number of equivalent patients weighted by the relative weights of the respective GDH and the total number of equivalent patients.

The Central Administration of the Health System (ACSS) are the responsible for centralizing all data related to the hospitalization and outpatient episodes performed in hospitals of the NHS, coded according to the International Classification of Clinical Modification 9th revision (ICD-9-MC) and classified into the DRG(90).

These data are sent by hospitals, monthly, and report to all coded episodes. Thus the DRG database contains, among other data, data on primary diagnosis but also collects some demographic data such as sex and age, as well as the geographic region of the admission(90).

<u>Access to the data</u>

We obtained access to the data by the ENSP-UNL which grant access to these data for the specific use in academic projects. A set of CDs with yearly data were provided in order to select the variables that were required for the study.

All admission cases from 2002 to 2016 were extracted using codes in ICD 9 as 410.00-410.xx to identify admissions diagnosis of Acute Myocardial Infarction (AMI) and 4130 codes, to identify unstable angina, as well as codes for ischemic and haemorrhagic stroke for stroke. Detailed description of each of the codes used can be found in Annex 1 (Annex 1: ICD 9 Codes and description for ACS and stroke).

Demographic variables were also selected such as gender and age. Also variables like date of hospital admission, region of the country and destination after hospital discharge were collected.

4.1.2. The National Registry of Acute Coronary Syndrome

The National Registry of Acute Coronary Syndrome (NRACS) is part of one of the most important initiatives of the Portuguese Society of Cardiology (PSC). In order to stimulate the study and the research of the CVD field the PSC created, in 2001, the National Centre for Data Collection in Cardiology. The main objective of this Centre is the promotion of continuous registries and multicentric studies in the area of cardiovascular diseases.

This NRACS is an observational and prospective clinical registry, with the continuous registered of voluntary membership. The registry started on January 1st, 2002, and initially included 44 Departments of Cardiology distributed all over the country. The main goal of this Registry was to assess the situation in Portugal regarding the clinical profile, diagnostic and therapeutic management and medium-term prognosis of the entire clinical spectrum of ACS, as well as to evaluate compliance with clinical guidelines and to monitor temporal trends and the impact of actions implemented for its improvement(91).

By 2002, around 50% of all coronary events in the country were included in the National Registry, a great effort has been made in order to include all coronary events around the country. In 2002 a total of 7348 patients were included in the registry, by the year 2008 a total 22482 had been included (91-92). In 2008, the distribution of ACS was 45.5% participants with STEMI, 41.4% NSTEMI and 13.1% with UA(92).

The inclusions criteria applied are the following:

- Adult patients (≥18 years of age) diagnosed with ACS with <48 hours of evolution.
- The diagnosis of ACS is defined as the presence of angina at rest in last 48 hours associated with: ischemic electrocardiographic changes - ST segment deviations or negative T waves; and / or Increase biomarker (cardiac troponin or CK-MB).

The exclusions criteria apply are:

- Participants with AMI after revascularization procedures.

All data is submitted to the National Cardiology Data Collection Centre (NCDC), under the responsibility of Principal Investigator. The submission is made through electronic platform, available on the website of Portuguese Cardiology Society. The NCDC receives and manages these data, subsequently validating records.
This data has the advantage of being integrated into the Euro Heart Survey platform and, consequently, uses the Cardiology Audit and Registration Data Standards (CARDS) system. This system ensures that credible and comparable information is collected in several European countries over time as they use standardized information, both in terms of the definition and coding of variables, and in the form of measurement and collection of data. As data is validated and standardize allows for the possibility of applying and validating analysis in other larger populations, thus being able to obtain more robust results(93).

Access to the data

To access the NRACS data a formal request was made to the Executive Direction of Portuguese Cardiology Society and to NCDC as well as to the Central Coordination of the specific registry describing the research objective.
All registries collected from 2002 to 2015 were extracted, as well as all demographic variables, risk factors and information regarding in-hospital death after the ACS.

4.1.3. Variables

Variables from the two different data sources (DRG and NRACS) were extracted and use accordingly to the objective being studied.

As this study consists in four scientific manuscripts thus different variables were used in each paper. Nevertheless, herein we aim to list all variables extracted from the different data sources used. The specific variables used in each scientific manuscript are included in the results sections.

4.1.3.1. Variables from the DRG

Variable directly extracted:

- Date of admission
- Destination after hospital discharge, destination defined as death was selected
- Variables used for stratification:
    - Gender
    - Age
    - Country Region

Variables derived:

- Proportion of hospital admissions
- Case fatality rate
- Variables used for stratification:
    - Age grouped into 2 categories: <65 and >=65
    - Country Region: NUTSII regions for mainland Portugal (Alentejo region, Algarve region, Midlands region, Lisbon and Tagus Valley region and North region)

4.1.3.2. Variables from the NRACS

Variable directly extracted:

- Date of admission
- Destination after hospital discharge, destination defined as death was selected
- Transportation to hospital: activation of the coronary FTS
- Time of symptom onset (hours)
- Time of hospital arrival(hours)
- Presence of risk factors (yes or not)
    - Smoking
    - HBP
    - Diabetes
    - Dyslipidaemia
    - Obesity
- Variables used for stratification:
    - Gender
    - Age
    - Country Region: NUTSII regions for mainland Portugal (Alentejo region, Algarve region, Midlands region, Lisbon and Tagus Valley region and North region)

Variables derived:

- Case fatality rate
- Age grouped into 2 categories: <65 and >=65
- Monthly proportion of ACS patients presenting with previously diagnosed HBP
- Monthly proportion of ACS patients presenting previously as smokers
- Time from symptom onset to FMC (in minutes)

4.1.3.3. Variables used to assess trends

The following two variables were used to assess admissions trends of CVD main outcomes, ACS and stroke admissions. The trends of these two variables were assessed through the monthly proportion of hospital admissions.

Monthly case fatality rate was created to assess trends from ACS in-hospital mortality.

Proportion of hospital admissions

Proportion of hospital admissions (crude rates) were computed for each month for both ACS and stroke, using the population of the country, restricted to adult population resident in mainland Portugal with ages over 20 years as the denominator and the number of ACS or stroke events as the numerator.

Case fatality rate

Monthly case fatality rate was compute using the total of patients admitted into public hospital as the denominator and the number of ACS in-hospital deaths as the numerator.

4.2. STATISTICAL ANALYSES

4.2.1. Interrupted time series design

Time-series designs are a form of longitudinal ecological study, and can provide a dynamic view of a population's health status. Data are collected from a population over time to look for trends and changes. Like other ecological studies, the data are collected at a population level.

Interrupted time series (ITS) design has emerged as a quasi-experimental methodology with the strongest power to infer causality without stripping contextual and temporal factors from the analysis(94-95).

In an ITS study, a series of observations on the same outcome before and after the introduction of an intervention are used to test immediate and gradual effects of the intervention. A major strength of this design is its ability to distinguish the effect of the intervention from secular change, that is, change that would have happened even in the absence of the intervention.

ITS offers a rigorous methodology to determine the effectiveness of complex healthcare interventions on outcomes when Randomized Clinical Trials are not feasible or not applicable(95). ITS is considered the strongest research design in the health

policy evaluation literature. It has been considered rigorous enough for inclusion into Cochrane meta analyses (96).
Estimating the intervention effect is done by comparing the trend in the outcome after the intervention to the existing trend in the pre-intervention period, and is achieved through modifications to the standard regression analysis.

Our goal in this study was to assess both patterns over time and also comparing time periods defined by the implementation of the health policies or initiatives.

4.2.2. Segmented regression

Segmented regression is the most popular statistical method for analysing time series data of healthcare interventions(94).
In a basic segmented regression analysis, the time period is divided into pre- and post-intervention segments, and separate intercepts and slopes are estimated in each segment(97).
To evaluate changes over time, we used an interrupted time series design, implementing a segmented multiple linear regression model.
Segmented regression analysis of interrupted time series data allows us to assess, in statistical terms, how much an intervention changed an outcome of interest, immediately and over time; instantly or with delay; transiently or long-term; and whether factors other than the intervention could explain the change. It requires data on continuous or counted outcome measures, summarized at regular, evenly spaced intervals.
An additional adjustment is usually required to account for serial autocorrelation, which arises because observations taken over time are usually correlated.
When a standard regression analysis is used with time modelled as a single continuous variable, an estimate is obtained for the slope over time, but it is impossible to distinguish the effect of the intervention from the underlying secular trend and to make causal claims about the effects of the intervention(97).
In this type of regression, a change in outcomes is referred to as a level change and is analogous to the difference in mean scores before and after the intervention, with independent data values. The level change is interpreted as the jump between the projected mean based on the pre-change point phase and the estimated mean post-change point(94, 98).
While the level change identifies the size of an intervention's effect, the change in trend quantifies the impact of the intervention on the overall mean.
In a simple way, the model constructed can be specified in the following way:

$$Y_{t=}\beta_0 + \beta_1 time + \beta_2 intervention + \beta_3 postslope + \varepsilon_i$$

Where $Y_{t=}$ is the outcome variable at time *t*; time is a continuous variable indicating time from the start of the study up to the end of the period of observation; intervention is an indicator for time t occurring before (intervention= 0) or after (intervention =1), post-slope is a continuous variable counting the number of months after the intervention at time t, coded 0 before the intervention and coded sequentially from 1 thereafter.

$\beta_0$estimates the baseline level of the outcome (proportion of ACS or stoke), mean proportion of ACS events per month, at time zero; β_1 estimates the change in the mean proportion that occurs with each month before the intervention (i.e. the baseline trend); β_2 estimates the level change in the mean monthly proportion immediately after the intervention, that is, from the end of the preceding segment; and β_3 estimates the change in the trend in the proportion after the intervention, compared with the monthly trend before the intervention. The error term ε_i at time *t* represents the random variability not explained by the model.

5. SPECIFIC METHODOLOGY

Segmented regression was the main statistical method applied in our study. However as the four scientific manuscripts, that are part of this study, were created separately we will assess the statistical section in more detail dividing this section by manuscript.

5.1. IMPACT OF THE SMOKING BAN ON ACS ADMISSIONS TREND

To assess if the smoking ban has caused any impact, namely a reduction, in the proportion of monthly ACS admissions we resorted to a segmented model using R package "segmented".

This Package is aimed to estimate linear and generalized linear models having one or more segmented relationships in the linear predictor.

The algorithm used in this package is an iterative procedure that needs starting values only for the breakpoint parameters and therefore it is quite efficient even with several breakpoints to be estimated. Thus a starting point, in our case a month for a given year was introduced in the algorithm (January 2002) to test for the existence of any breakpoint after that.

This is particularly useful in our study as although we know the month and year of the smoking ban implementation it is impossible to determine when it had any effect, in case there is any.

We then included 2002 as the starting point for the breakpoint search. We used other starting points to test the different results, however the results kept being consistent.

This package allowed us to obtain two different slopes, pre-policy and post-policy, to test if there were significantly different, Davies test was applied. Basically this test evaluated if the difference between the two calculated slopes is not equal to zero returning a p-value to assess the significance.

One of most important assumptions to use this package is that it only allows for linear models or Generalized Linear Models (GLM) to be applied. Thus before implemented a segmented regression a GLM model was created using proportion of monthly admission by ACS as a response variable, using a Gaussian link function, thus assuming the proportion followed a linear behaviour.

In order to exemplify how the package was implemented we have included a few steps taken while running the model: The steps are straightforward with this package. First, a standard GLM is estimated, as explained above, and a broken-line relationship is added afterwards by re-fitting the overall model.

The original GLM accounts for a response variable `(Proportion)`, in this case the proportion of ACS events (more details on how this variable was created can be found in chapter 4.1.3.3) and for two covariables. In this model, the covariables included were time `(Date)` as a continuous variable (year and month, i.e. 200201 stands for January 2002) and also a covariable that indicates the month `(Month)`, in order to account for seasonality.

Code:

```
1 step)fit.glm<-glm (Proportion~Date+Month, data=data,family=gaussian)
2 step)fit.seg<-segmented (fit.glm, seg.Z=~Date, psi=200201)
```

The package takes the original GLM (fit.glm) and fits a new model taking into account the piecewise linear relationship. The argument `seg.Z` is a formula (without response) which specifies the variable, supposed to have a piecewise relationship, in this case the date (year and month) of the event (ACS or stroke) while in the `psi` argument is the initial guess for the breakpoint is included(99).

In the models created with this package we have also included a covariate to adjust for seasonality in the outcome admissions, as the seasonality of ACS admissions have been extensively proven, with higher rates of admission over winter, and lower rates during the summer(100).

In addition, the unit of analysis was monthly admission for ACS rather than an individual patient, so it was possible for a person to be counted more than once, since

changes in the number of admissions were also expected to be affected by the legislation.

Finally, the data was further stratified by sex, age and geographical region and one model was created per each category of the stratification variables.

Autocorrelation between month estimates was incorporated adequately into the model, with the presence of short term autocorrelation applying a first order autoregressive - AR (1) - structure to the residuals.

5.2. IMPACT OF THE SALT REDUCTION INITIATIVE ON CVD (ACS AND STROKE) ADMISSIONS TREND AND HBP TREND

Three main outcomes were analysed in this manuscript:

- Monthly proportion of ACS patients presenting with previously diagnosed HBP.
- Monthly proportion of ACS admissions into public hospitals in the country.
- Monthly proportion of stroke admissions into public hospitals in the country.

The proportion of ACS patients with HBP was obtained by dividing the number of monthly HBP diagnoses by the total ACS patients registered for month, using data from the NRACS.

In order to test for any significant breakpoint in the monthly proportion of ACS patients presenting with previously diagnosed HBP we resort to the “segment” R package, explained in the above section.

However when studying the ACS and CVD monthly proportion, the “segmented” package could not be used as the salt reduction policy was implemented just 1 year after the smoking ban. Thus as the algorithm included in this package needs a starting point to identify a breakpoint even after using several starting points, 2008 (two years before the salt reduction was implemented) was always chosen as the breakpoint.

Considering this limitation, we applied a multiple linear regression model using standard methods for interrupted time series. We created a Generalized least squares (GLS) regression as one of the assumptions underlying ordinary least squares estimation is that the errors should be uncorrelated as in time series uncorrelated errors is very unlikely we decided to use a GLS regression(99).

In this regression, we included one dichotomous variable that accounted for the main effect on hospital admissions (for ACS and stroke, using a different model for each) of the estimated breakpoint and an interaction between the breakpoint estimated and time, to evaluate changes over time following the breakpoint. The breakpoint used in

this regression was the year obtained in the segmented regression for the proportion of HBP patients.

As explained in section 4.2.2, in this regression two parameters define each segment of the time series, namely level and trend. The level is the value of the series at the beginning of a given time interval (i.e. the y-intercept for the first segment and the value immediately following each change point at which successive segments join). The trend is the rate of change of a measure (in other words, the slope) during a segment. In this type of segmented regression analysis, each segment of the series is allowed to exhibit both a level and a trend.

A change in level in the outcome after the intervention constitutes an abrupt intervention effect. A change in trend is defined by an increase or decrease in the slope of the segment after the intervention as compared with the segment preceding the intervention. A change in trend represents a gradual change in the value of the outcome during the segment(98).

This later model was implemented in order to test whether there was a significant change in the proportion of CVD admissions.

5.3. IMPACT OF THE CORONARY FAST TRACK SYSTEM IN ACS CASE FATALITY RATE

The main outcome in this scientific paper was monthly case fatality rate for ACS, later stratified by age and sex.

The same statistical technique as the one mentioned in the above section (section 4.2.2) was applied in this manuscript, namely, multiple linear regression model using standard methods for interrupted time series, thus including one dichotomous variable that accounted for the main effect on case fatality rate of the included breakpoint and an interaction between the breakpoint and time, to evaluate changes over time following the breakpoint.

As the effect of the breakpoint, namely the implementation of the FTS to coronary unit, has been proved to have an immediate effect on ACS mortality there was no need to resort to the segmented package and standard methods for interrupted time series was decided to be implemented.

In this paper, it was also compared case fatality trends for hospitals with the fast-track system in place vs. hospitals with no such system. GLS regression was applied, with a

dichotomous variable distinguishing hospitals with the fast-track system from those without such a system and a month indicator to account for seasonal variations.

In addition, time from symptom onset to FMC was also analysed through GLM with a Gaussian link function, assuming a linear behaviour of time, using as covariates a dichotomous variable before and after the fast-track implementation, demographic variables (sex and age) and risk factors (smoking, hypertension, diabetes, dyslipidaemia, obesity). The variable representing the use of the fast-track system was a "yes" or "no" categorical variable.

5.4. IMPACT OF PUBLIC HEALTH INITIATIVES IN ACS CASE-FATALITY RATE

The impact of the three policies was firstly studied individually, using the standard methods for segmented regression, with a binary covariable indicating the start of the policy (also called the breakpoint), as well as a continuous covariable to account for the effect of the policy after its implementation.

Secondly, we used the segmented model resorting to the "segmented" R package to search for a breakpoint in the ACS case-fatality rates. The segmented package has also been explained in detail in the above chapter (section 5.1).

6. RESULTS FOR EACH MANUSCRIPT

As stated above this work encompasses a total of four manuscripts that were prepared separately. For this reason, we will divide this section highlighting the main results for each specific manuscript.

6.1. ACS ADMISSIONS TREND AND THE IMPACT OF THE SMOKING BAN

A total of 190.974 cases of ACS were registered in the country (Mainland Portugal), from 2002 to 2014, of which 64% were males.

We assessed crude rates (per 100000 adults) of monthly admissions by ACS for the period of 2002 and 2014. Our results show a decline of ACS events by 2008, year of the law implementation, that was used as a breakpoint in the model created (Figure 4).

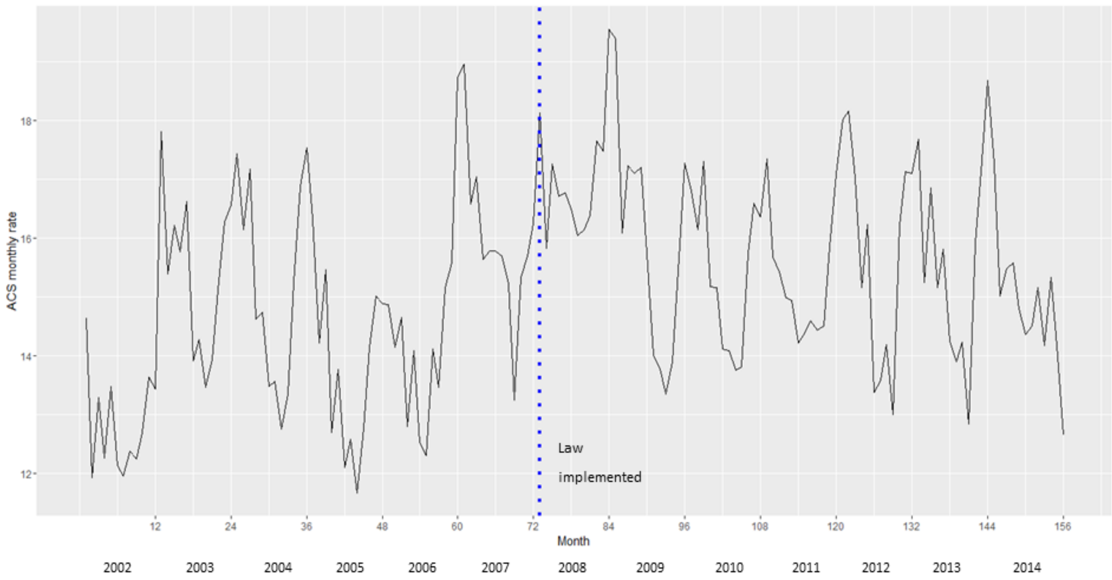

Figure 4 Longitudinal trends for overall monthly crude rates (per 100000 adult population) of ACS admissions from January 2002 to December 2014. Pre-legislation and post-legislation periods

A positive trend was observed for the years preceding the year of the legislation implementation (yearly trend of 0.004 events per 100000; 3.8 %). For the period after the legislation took place, the trend observed for ACS crude rate was negative, with a decreased of 0.0018 events per 100000; -1.7% by year after the legislation (Table 1).

Table 1: Results of multivariate linear regression analyses to detect association between smoke-free legislation and monthly crude rates of ACS admissions per 100000.

	Pre-legislation trend (change per month)	Change in trend in post-legislation period compared to pre-legislation	Post-legislation trend (change per month)
Overall			
β *	0.004	-0.006	-0.0018
IC for β	0.0029;0.0055	p-value<0.001	-0.0033;-0.0004
yearly change %	3.84	-5.76	-1.73
Males			
B*	0.0034	-0.0046	-0.0012
IC for β*	0.0021;0.0047	p-value=0.0002	-0.0028;0.0004
yearly change %	3.26	-4.80	-1.15
Females			
B*	0.0017	-0.0033	-0.0016
IC for β	0.0008;0.0023	p-value=0.0002	-0.0027;-0.0004
yearly change %	1.63	-3.17	-1.54
Age ≥65			
B*	0.0016	-0.01352	-0.0119
IC for β	-0.0018;0.0051	p-value<0.001	-0.01625;-0.0075
yearly change %	1.54	-12.98	-11.42
Age<65			
B*	0.0011	-0.0052	-0.0483
IC for β	0.0008;0.0014	p-value=0.2692	-0.1573;0.0607
yearly change %	1.06	-4.99	-4.64

The difference between the two slopes for the trends before and after the legislation was significant (-0.006 events per 100000, $p<0.001$) in the overall population (Table 1) with a decline of ACS events of -5.8%. We stratified the ACS events by sex, and the trends observed for the pre-legislation and post-legislation periods were similar for both men and women (Table 1). Although the trends were similar, the reduction in ACS event crude rate, was more markedly in men (-0.0046 events per 100000;-4.8%, p-value=0.0002) than women (-0.0033 events per 100000;-3.2% p-value=0.0002). However, the results obtained for males should be interpreted with caution as the confidence interval for the slope after the law implementation is wider than the one obtained for women and zero was included.

The results for age stratification showed a significant reduction in ACS rate after the legislation took place for people over 65 years old (-0.014 events per 100000; -13% p-value<0.001), however this finding was not verified for people under 65 years old.

Results stratified by region, showed that the only region with a significant decrease in ACS events after the law implementation, was Lisbon and Tagus Valley (change in slope of -0.013 events per 100000, p-value<0.001). Although the North region also showed a trend in decrease after the law implementation, this reduction was not significant (change in slope of -0.003 per 100000, p-value=0.1683). The remaining regions did not show any significant changes.

The seasonal pattern observed was consistent with that reported elsewhere (100), with higher rates of admission over winter, and lower rates during the summer.

The analysis of the NRACS data allowed us to assess the proportion of ACS patients that were currently smokers for the period 2002 to 2010. At the time of the registry, the proportion of smokers among ACS patients has been steadily declining over the years, the decrease observed after 2008 was not significant (p-value=0.997, Figure 5).

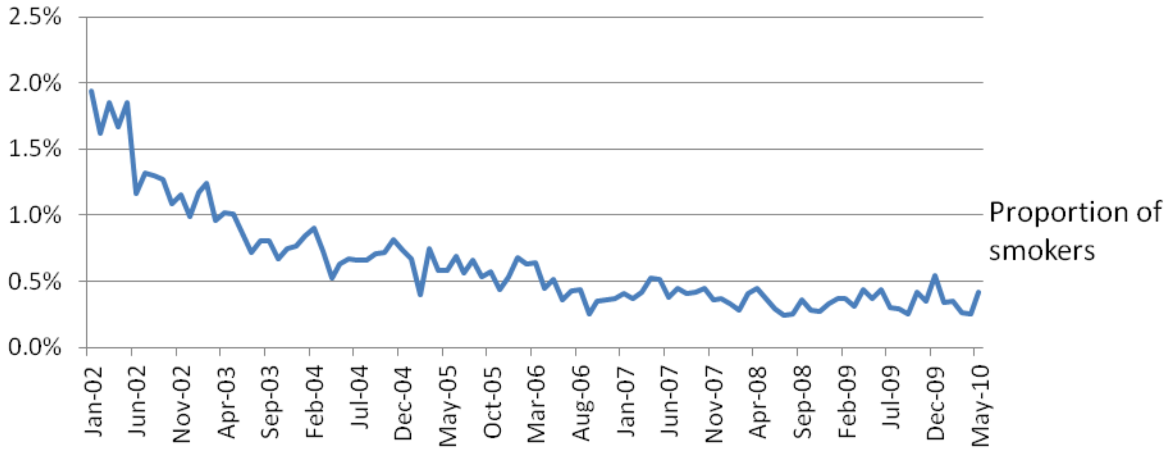

Figure 5 Proportion of ACS patients that are current smokers,

6.2. HBP AND SALT REDUCTION AND CVD (ACS AND STROKE)

ADMISSION TRENDS

A total of 43,271 ACS events were registered in the NRACS over the last 14 years. The proportion of males presenting with ACS has been consistently higher than women, with around 69% of ACS events occurring in males. Mean age through the years of study has also been fairly steady, ranging from 65 to 66 years old (Table 2).

Table 2: Demographic characterization of the data analysed,

	ACS *(DRG data)*	***stroke*** (DRG *data)*	***HBP in ACS patients*** *(NRACS data)*
		Before regulation	
Female %	26,00%	49,43%	35,33%
Age ≥65 %	37,93%	77,15%	65,38%
		After regulation	
Female %	26,36%	49,61%	32,67%
Age ≥65 %	37,85%	78,26%	64,29%

Male/female ratio for HBP patients (Figure 6) has also remained fairly steady through the years in the ACS population.

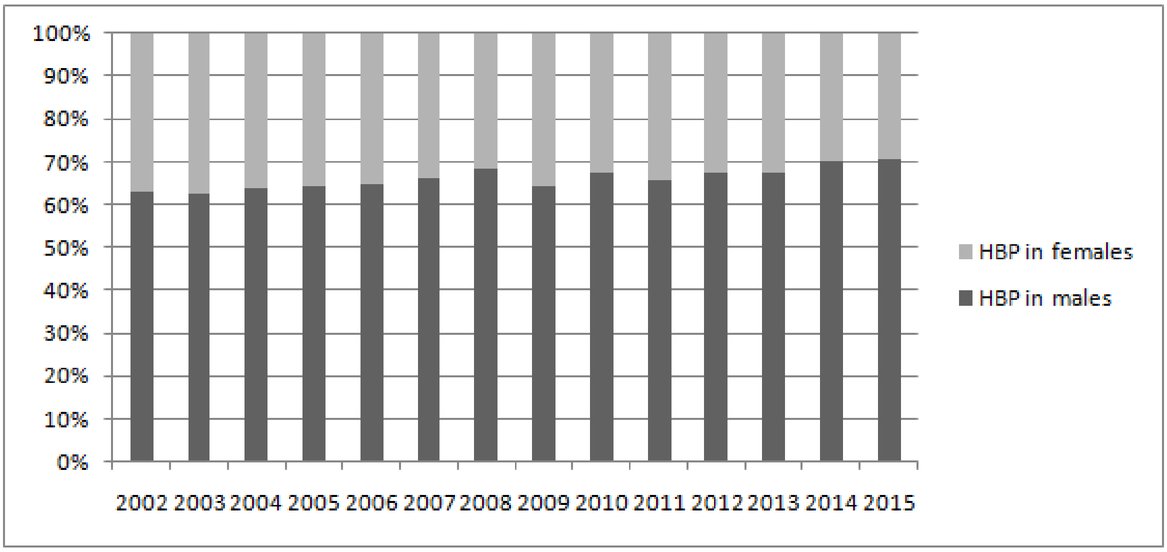

Figure 6: Proportion of patients with HBP in the ACS population. Female/male ratio from years 2002 to 2015.

The proportions of patients with HBP ranged from a minimum proportion of 50.0% to a maximum of 79.2%.

Breakpoint analysis revealed an estimated breakpoint around the year 2013 for the proportion of HBP patients (Figure 7), the year after there is a decreasing trend, however it was not significant (p-value = 0.832).

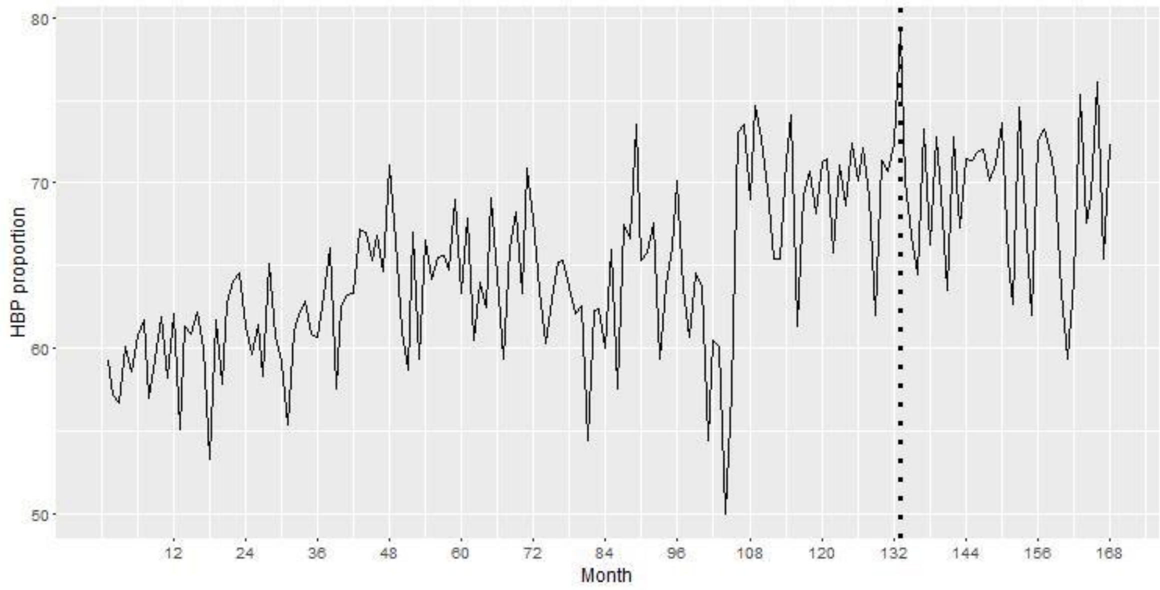

Figure 7: Trends in overall monthly proportion of HBP in ACS patients from January 2002 to December 2015.
Dashed line represents the beginning of 2013, year associated to the estimated decline in trends.

Analyses showed the trend before 2013 was, in fact, increasing and started to decrease after this year (βbefore = 0.009, CI: 0.007, 0.011; βafter = -0.003, CI: -0.037, 0.0302). Although zero is present in the CI for the slope after 2013, the change between both slopes (before and after 2013) is negative with a decrease of -0.012 in the monthly proportion. Thus, the decrease estimated after 2013 is higher than the increase estimated before 2013. This decrease in proportion can be translated into a reduction of 555 people per year presenting with HBP in the ACS population (Table 3).

Table 3: Results from the three regressions applied, segmented multiple linear regression model, for the proportion of HBP patients, and both multiples linear regressions using standard methods for interrupted time series, for the ACS and stroke outcomes.

	β (IC)	**t-value**	**p-value**
HBP proportion			
Overall*			
Pre-breakpoint trend (change per month)	0.009(0.007;0.011)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.012	-	0.832
Post-breakpoint trend (change per month)	-0.003(-0.003;0.0302)	-	-
Male*			
Pre-breakpoint trend (change per month)	-0.003(-0.022;0.022)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.01577	-	0.215
Post-breakpoint trend (change per month)	-0.019(-0.061;0.023)	-	-

Female*			
Pre-breakpoint trend (change per month)	-0.003(-0.028;0.022)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.016	-	0.215
Post-breakpoint trend (change per month)	-0.018(-0.052;0.014)	-	-
Age<65*			
Pre-breakpoint trend (change per month)	-0.022(-0.798;0.754)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	0.011	-	>0.05
Post-breakpoint trend (change per month)	-0.011(-0.039;0.017)	-	-
Age≥65*			
Pre-breakpoint trend (change per month)	0.029(-0.017;0.075)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.018	-	>0.05
Post-breakpoint trend (change per month)	0.011(-0.017;0.039)	-	-
ACS crude rates (per 100000)			
Overall*			
Time of the breakpoint	0.068('-1.974;2.111)	0.065343	0.948
Time of the breakpoint* time interaction	-0.057(-0.154;0.039))	-1.1682	0.2444
Male*			
Time of the breakpoint	0.289(-2.269;2.848)	0.222	0.825
Time of the breakpoint* time interaction	-0.018('-0.108;0.072)	-0.393	0.695
Female*			
Time of the breakpoint	-0.497('-1.927;0.932)	-0.682	0.496
Time of the breakpoint* time interaction	0.013('-0.034;0.060)	0.560	0.576
Age<65*			
Time of the breakpoint	0.151('-0.723;1.024)	0.338	0.736
Time of the breakpoint* time interaction	-0.015(-0.044;0.015)	-0.986	0.325
Age≥65*			
Time of the breakpoint	0.151(-5.159;6.721)	0.258	0.7970
Time of the breakpoint* time interaction	-0.015(-0.358;0.066)	-1.349	0.1792
Stroke crude rates (per 100000)			
Overall*			
Time of the breakpoint	0.351(-1.452;2.154)	0.38177	0.7031
Time of the breakpoint* time interaction	-0.049(-0.128;0.028)	-1.24488	0.2150
Male*			
Time of the breakpoint	0.900(-0.743;2.543)	1.074	0.284
Time of the breakpoint* time interaction	-0.022(-0.074;0.030)	-0.822	0.412
Female*			
Time of the breakpoint	0.999(-1.204;3.202)	0.888	0.376
Time of the breakpoint* time interaction	-0.047(-0.121;0.027)	-1.244	0.215
Age<65*			
Time of the breakpoint	0.448(-0.261;1.157)	1.238	0.217
Time of the breakpoint* time interaction	-0.014(-0.037;0.009)	-1.207	0.229
Age≥65*			
Time of the breakpoint	2.548(-5.351;10.446)	0.632	0.528

Time of the breakpoint* time interaction	-0.238(-0.502;0.026)	-1.764	0.079

*All models were adjusted for seasonality
HBP: High blood pressure
ACS: Acute coronary syndrome
Values not presented in the table (-) are not available for the type of regression
β represents the coefficients in the regression. CI: confidence interval

Figure 8 displays the frequency of ACS and stroke admissions from 2002 to 2016. A total of 115 public hospitals from mainland Portugal registered ACS admissions from 2002 to 2016 and 122 registered stroke admissions. A maximum age of 99 years old was found in the database and the majority of admissions were for both ACS and stroke.

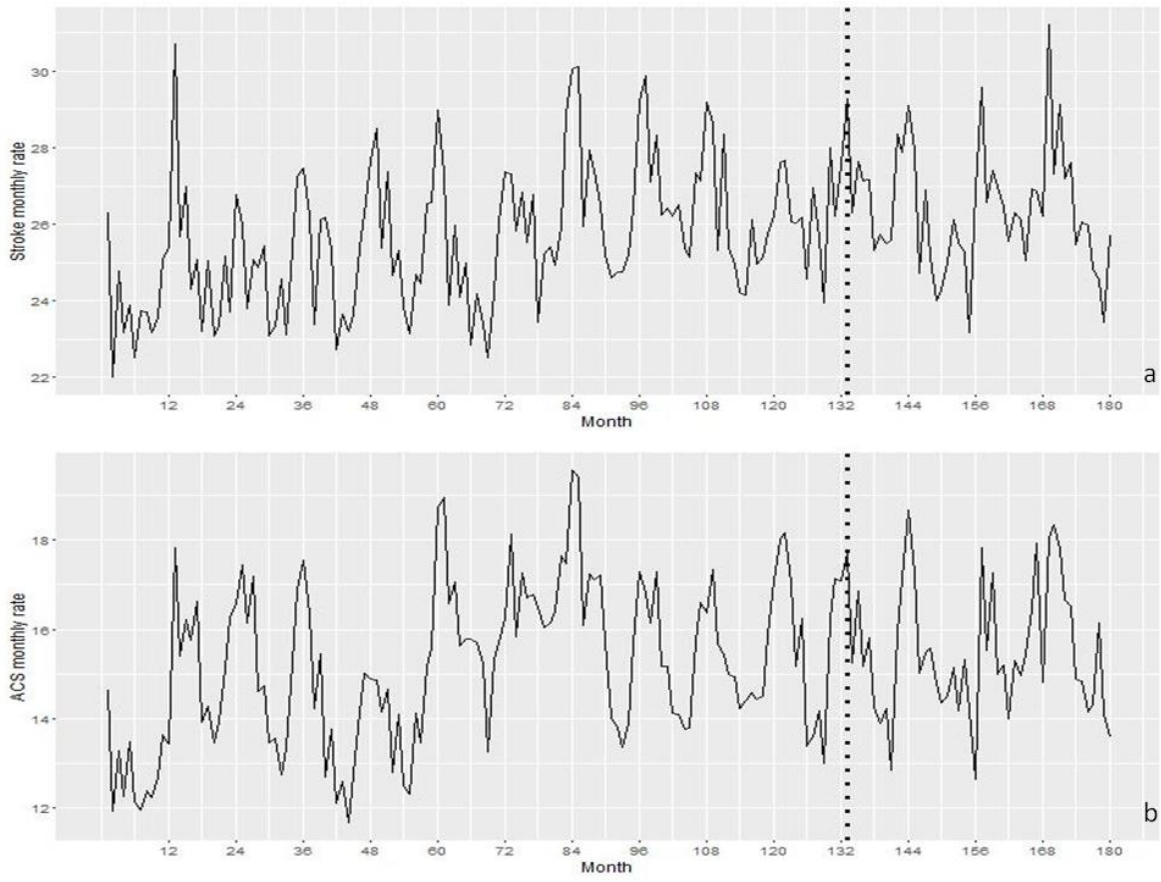

Figure 8: Trends in overall monthly crude rates of CV admissions from January 2002 to December 2016 per 100000 adults.
a) Trends for stroke crude rates admissions. b) Trends for ACS crude rates admissions. Dashed lines represent the beginning of 2013, year associated to the estimated decline in trends.

We analysed trends for ACS and stroke and tested the significance for a breakpoint in the year 2013.

Although none of the remaining trends were significant (Table 3) for ACS crude rates (β = -0.057, CI: - 0.154, 0.039) and stroke crude rate (β = -0.049, CI: -0.128, 0.029), a decreasing trend can be observed.

When further stratified data by sex and age, although no significant trends were observed, a decreasing trend for ACS was found in women but not in men. The largest decrease was found for people over 65 years old for both outcomes. Nevertheless, all these results should be interpreted with caution as none of the coefficients were significant (p-values > 5%), and zero was always included in the confidence interval.

The seasonal pattern observed for ACS and stroke was consistent with that reported elsewhere (100), with higher rates of admission over winter, and lower rates during the summer (Figure 8).

6.3. THE CORONARY FAST TRACK SYSTEM

A total of 20,849 in-hospital deaths by ACS were registered in the country (Mainland Portugal) from 2000 to 2016, out of a total of 203,040 ACS admissions.

We assessed monthly case fatality rates by ACS for the period of 2000 to 2016, and our results show a decline in the number of registered deaths for the period studied. After the year of the implementation of the fast-track system in 2007, the year used as a breakpoint in the model created (Figure 9), there was a steep decrease in case-fatality rate, although there was no significant differences from the rate observed in the period before thus the rate of the decline has remain steady throughout the last 15 years.

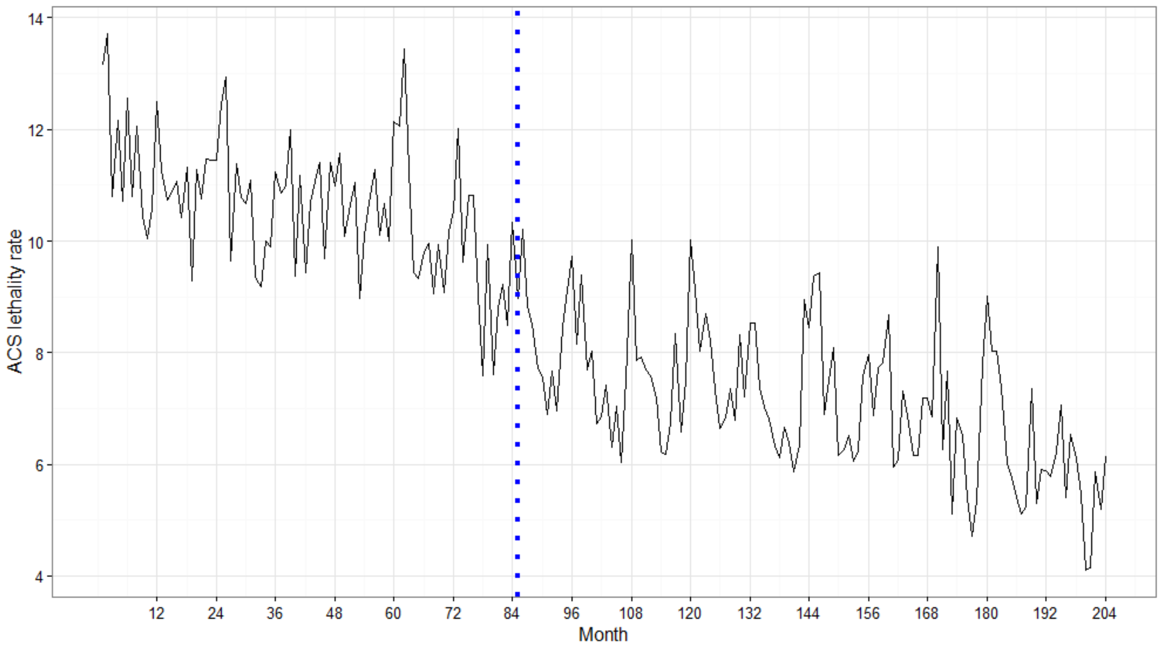

Figure 9: Longitudinal trends for case-fatality rate by ACS (percentage) from January 2000 to December 2016.
The vertical line marks the year 2007 for the full implementation of the fast-track system in the entire country.

There was a significant change in level, i.e. a significant drop in ACS case-fatality rate (β = -1.268 p-value: <0.01) after the fast-track system implementation, representing an abrupt intervention effect(98).

Although the change in trend was not significant, i.e. there was not a significant decrease in the slope after the fast-track implementation, the fact that there was a significant change in level denotes a clear change in ACS case-fatality rate after 2007. On the other hand, it also points out the fact that the rates of decline observed after FTS have remain fairly similar to the rates of decline observed before FTS.

We stratified the ACS case-fatality rate by sex, and the trends observed for the pre-system implementation and the post-system implementation were similar for both men and women (Figure 10, Table 4).

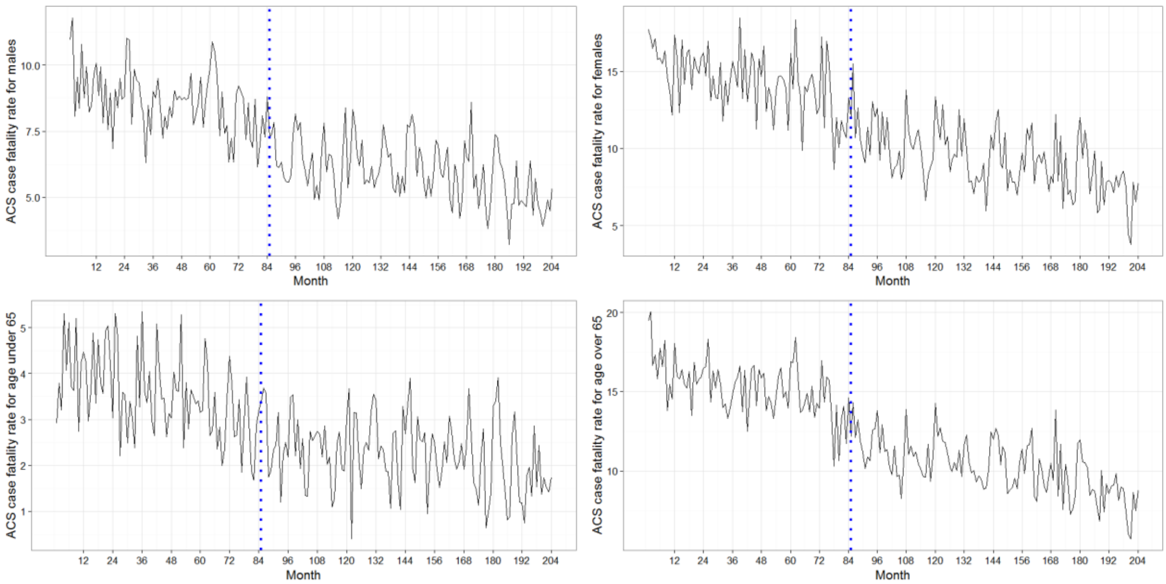

Figure 10: Stratified longitudinal trends for case-fatality rate by ACS (percentage) from January 2000 to December 2016.

The vertical line marks the year 2007 for the full implementation of the fast-track system in the entire country. a) Longitudinal trends for males. b) Longitudinal trends for females. c) Longitudinal trends for patients under 65. d) Longitudinal trends for patients over 65.

Table 4: Results of segmented linear regression analyses to detect association between fast-track system and monthly case-fatality rate ACS and multivariate regression analysis between time from symptom onset and several predictors.

	β (CI)	**t-value**	**p-value**
Impact of the fast-track system on case-fatality rate by ACS			
Overall*			
Fast track implemented	-1.27 (-2.10; -0.436)	-2.99	< 0.01
Fast track implemented* time interaction	0.005 (-0.011; 0.020)	0.58	0.565
Male*			
Fast track implemented	-1.064 (-1.869; -0.258)	-2.59	0.01
Fast track implemented* time interaction	0.006 (-0.009;0.021)	0.74	0.46
Female*			
Fast track implemented	-1.453 (-2.555; -0.352)	-2.59	0.01
Fast track implemented* time interaction	0.009 (-0.011;0.029)	0.89	0.37
Age < 65*			
Fast track implemented	0.184 (-0.302; 0.669)	0.74	0.46
Fast track implemented* time interaction	0.011 (0.003; 0.019)	2.60	0.01
Age ≥ 65*			
Fast track implemented	-0.348 (-1.413; 0.716)	-0.64	0.52
Fast track implemented* time interaction	0.023 (0.004; 0.041)	2.44	0.02
Time from symptom onset to first medical contact			
Fast Track (Yes)	-47.14 (-60.48; -33.79)	-6.92	< 0.01
Age	1.60 (1.28; 1.92)	9.73	< 0.01
Sex (Male)	15.28 (6.91; 23.66)	3.58	< 0.01
Smoker (yes)	-17.58 (-26.92; -8.23)	-3.69	< 0.01
Hypertension (yes)	3.88 (-4.12; 11.88)	0.95	0.34
Diabetes (yes)	15.72 (7.45; 23.98)	3.73	< 0.01
Dyslipidaemia (yes)	-2.84 (-10.22; 4.54)	-0.76	0.45
Obesity (yes)	9.02 (0.12; 17.92)	1.99	0.05

*All regression models were adjusted for seasonal effects

β represents the coefficients of the regression

CI: confidence interval

For both men and women, there was a steep decrease after the system was implemented; however, as for the overall rate, the decreasing trends remained fairly steady. Although the immediate decrease was similar for men and women, the reduction in ACS case-fatality rate was more marked in women (β = -1.45, p-value = 0.01) than in men (β = 1.06, p-value = 0.01) (Figure 10, Table 4).

Interestingly, the results for age stratification showed that for people under 65, there was an increasing trend in case fatality (β = 0.01, p-value = 0.01), although the value of the change trend was significant, it was in fact a minor increase, with less than 0.05%.

However, for patients aged 65 and over, the case fatality trend was also significant (β = 0.02, p-value = 0.02). For younger participants, although the increase trend was significant, it was a minor increase of less than 0.05%.

The seasonal pattern observed was consistent with that reported elsewhere(100), with higher rates of admission over winter and lower rates during the summer.

Analysis of the NRACS data allowed us to assess the actual proportion of patients that activated the FTS over time. Although the proportion of fast-track admission has been increasing over time it has only reached a maximum value of 38% in 2016, it has been a slow increase (Figure 11).

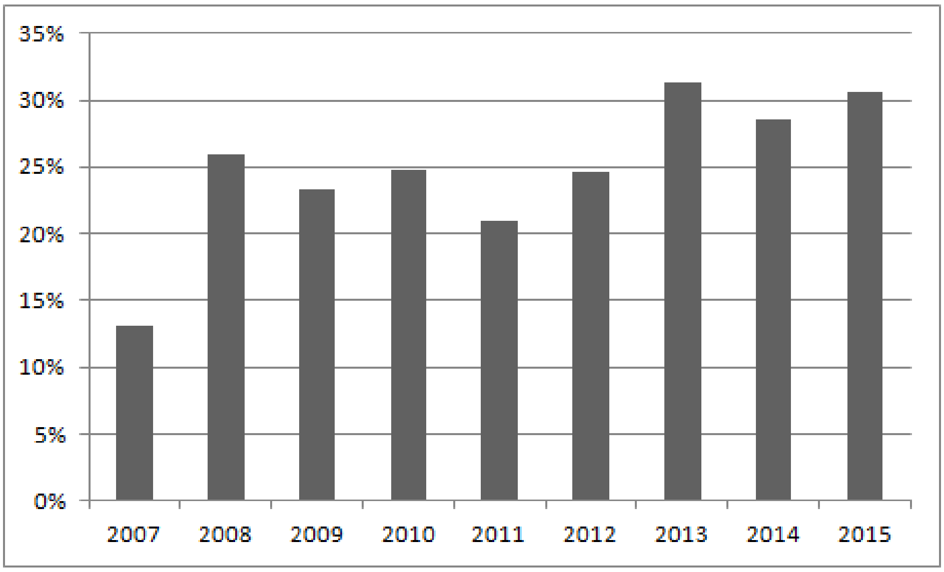

Figure 11: Percentage of annually STEMI patients admitted through the fast-track system.

Furthermore, we compared the ACS case-fatality rate between hospitals with a fast-track system implemented and hospitals with no such system, as a proxy to compare case fatality rates, although we acknowledge the fact that hospitals with the fast-track system can still admit patients that reach the hospital by any other way of transportation. Our results indicate a significantly lower case-fatality rate for hospitals with the FTS implemented (β = -0.67, p-value < 0.01; Figure 12).

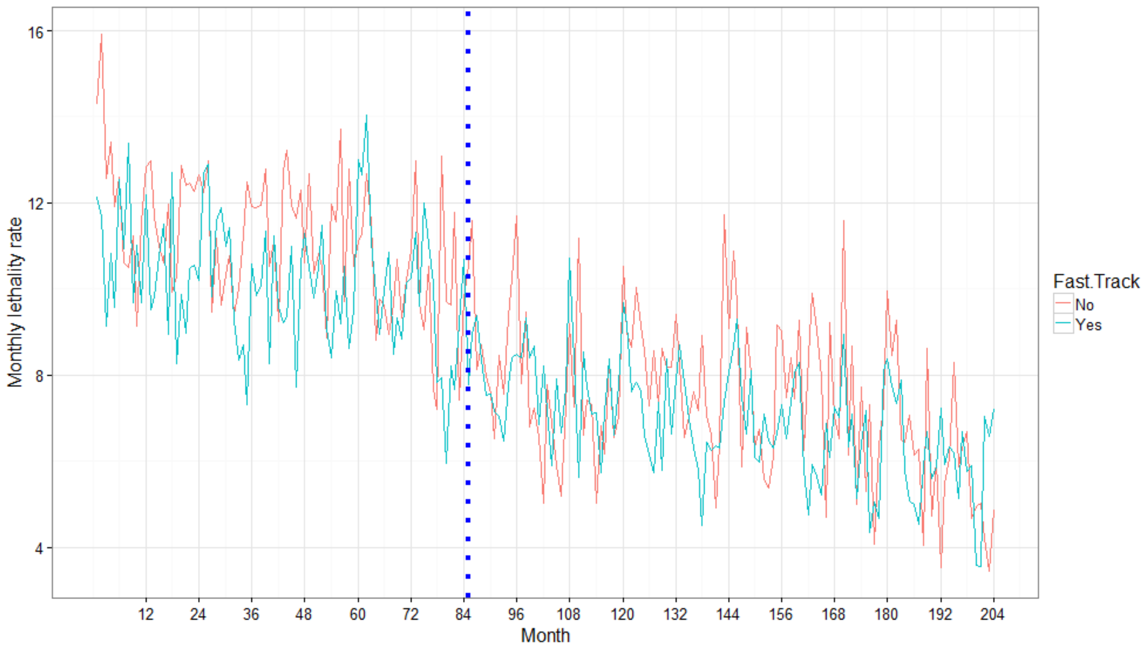

Figure 12: Comparison of longitudinal case fatality trends between hospitals with fast-track system vs. hospitals without the fast-track system.

Mean time from symptom onset to FMC was also analysed. For patients admitted through the fast-track system, the mean time from symptom onset to FMC was 224.20 minutes, approximately 3 hours, while for patients that were not admitted through this system, mean time from symptom onset to FMC was 354 minutes, approximately 6 hours (Figure 13).

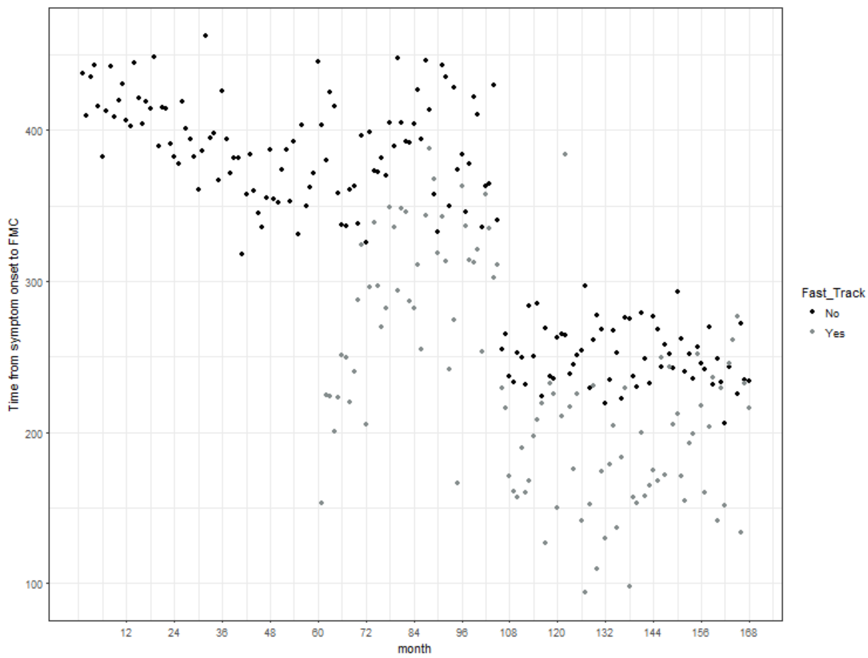

Figure 13: Time from symptom to FMC between patients that activated the fast-track system and patients who did not activate it.

When assessing the results from the multivariate regression (Table 4), time from symptom onset to FMC was significantly lower for participants admitted through the fast-track system, up to around 50 minutes less. Analysis of the demographics and risk factor covariates used in the model denoted that older people and women, as well as patients with diabetes and obesity, had longer delays. Surprisingly, smokers had lower times from symptom onset to FMC.

6.4. IMPACT OF PUBLIC HEALTH INITIATIVES IN ACS CASE-FATALITY RATE

A total of 20,849 in-hospital deaths from ACS were registered in mainland Portugal from 2000 to 2016, out of a total of 203,040 admissions for ACS.

For the models created individually, one for each policy, FTS showed an immediate decrease in case fatalities (β= -1.27, p-value= 0.003); however, it did not impact case fatality trends after 2007, as they remained steady. Similarly, the smoking ban resulted in an immediate decrease in case fatalities after its implementation (β= -0.861, p-value= 0.05); however, no significant decrease in trends was observed after 2008 (Table 5, Figure 14).

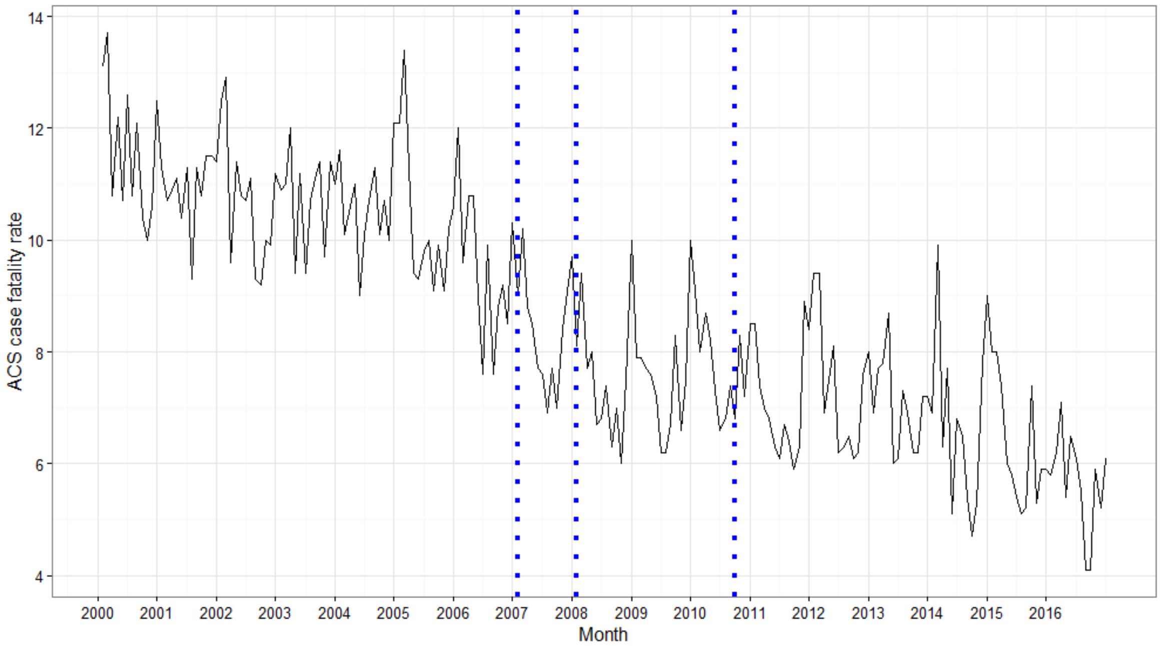

Figure 14: Longitudinal trends for case-fatality rates from ACS (percentage) for January 2000 - December 2016.
The vertical lines mark the year 2007, when FTS was fully implemented in the entire country. The line at 2008 denotes the implementation of the smoking ban, and the line mid-way through 2010 denotes the implementation of the salt reduction regulation.

Table 5: Results of segmented linear regression analyses for each of the models for the individual policies.

		β (CI) *	p-value
Smoking ban			
Overall	Time of the breakpoint	-0.861(-1.72;-0.003)	0.051
	Time of the breakpoint* time interaction	0.013(-0.002;0.028)	0.087
Male	Time of the breakpoint	-0.457(-1.288;0.374)	0.283
	Time of the breakpoint* time interaction	0.013(-0.002;0.027)	0.089
Female	Time of the breakpoint	-1.306(-2.394;-0.217)	0.020
	Time of the breakpoint* time interaction	0.019(0.001;0.038)	0.051
Age<65	Time of the breakpoint	0.141(-0.362;0.645)	0.583
	Time of the breakpoint* time interaction	0.012(0.003;0.020)	0.009
Age>=65	Time of the breakpoint	-1.169(-2.209;-0.129)	0.029
	Time of the breakpoint* time interaction	0.019(0.001;0.037)	0.045
Salt reduction regulation			
Overall	Time of the breakpoint	0.421(-0.488;1.295)	0.365
	Time of the breakpoint* time interaction	0.012(-0.006;0.031)	0.190
Male	Time of the breakpoint	0.538(-0.319;1.395)	0.220
	Time of the breakpoint* time interaction	0.008(-0.009;0.026)	0.341
Female	Time of the breakpoint	0.243(-0.921;1.408)	0.683
	Time of the breakpoint* time interaction	0.023(0.0001;0.046)	0.052
Age<65	Time of the breakpoint	0.557(0.061;1.053)	0.029
	Time of the breakpoint* time interaction	0.005(-0.005;0.015)	0.320
Age>=65	Time of the breakpoint	0.711(-0.404;1.826)	0.213
	Time of the breakpoint* time interaction	0.016(-0.007;0.039)	0.170

*All regression models were adjusted for seasonal effects.

By contrast, the salt reduction policy did not produce any significant impact on case fatalities (β= 0.012, p-value = 0.189), or any immediate impact after its implementation (β = 0.421, p-value = 0.365; Table 5).

Using a model where segmented regression was applied, end 2008, more accurately September 2008, was identified as a year where a difference in rates of case fatalities existed. Both slope before (β = -0.004; CI= -0.005; -0.004) and after (β= -0.003; CI=-0.003;-0.002) end 2008 showed a decrease; however, after end 2008 it was less pronounced (β = 0.002, p-value = 0.004; Table 6).

Table 6: Results of segmented linear regression analyses where end 2008 was found as the breakpoint for differences in slopes.
Stratified results, by gender and age group, are also included.

		β (CI)*	p-value
All	FTS- breakpoint	-1.236(-2.379;-0.092)	0.035
	FTS breakpoint* time interaction	-0.004(-0.052;0.044)	0.861
	Salt reduction regulation- breakpoint	0.329(-0.757;1.415)	0.554
	Salt reduction regulation breakpoint* time interaction	-0.006(-0.044;0.033)	0.774
Male	FTS- breakpoint	-1.271(-2.314;-0.228)	0.018
	FTS breakpoint* time interaction	0.012(-0.024;0.048)	0.527
	Salt reduction regulation- breakpoint	0.328(-0.717;1.372)	0.539
	Salt reduction regulation breakpoint* time interaction	-0.014(-0.051;0.023)	0.472
Female	FTS- breakpoint	-1.256(-2.726;0.214)	0.096
	FTS breakpoint* time interaction	-0.001(-0.051;0.049)	0.968
	Salt reduction regulation- breakpoint	0.245(-1.228;1.718)	0.745
	Salt reduction regulation breakpoint* time interaction	0.011(-0.041;0.062)	0.687
Age<65	FTS- breakpoint	-0.212(-0.858;0.434)	0.520
	FTS breakpoint* time interaction	0.004(-0.018;0.026)	0.699
	Salt reduction regulation- breakpoint	0.473(-0.175;1.121)	0.154
	Salt reduction regulation breakpoint* time interaction	0.0003(-0.023;0.022)	0.974
Age>=65	FTS- breakpoint	-1.803(-3.128;-0.477)	0.008
	FTS breakpoint* time interaction	0.007(-0.038;0.051)	0.765
	Salt reduction regulation- breakpoint	0.541(-0.792;1.873)	0.427
	Salt reduction regulation breakpoint* time interaction	-0.008(-0.054;0.038)	0.731

*All regression models were adjusted for seasonal effects.

All four models were stratified for ACS case-fatality rates by gender. For females (β =-1.306, p-value = 0.020) and people older than 65 years old (β = -1.169, p-value = 0.029), there was a significant decrease in case fatality rates after the smoking ban. For the FTS both genders presented with a significant decrease in case fatality rates; however, there was no difference in trends between age groups (Figure 15).

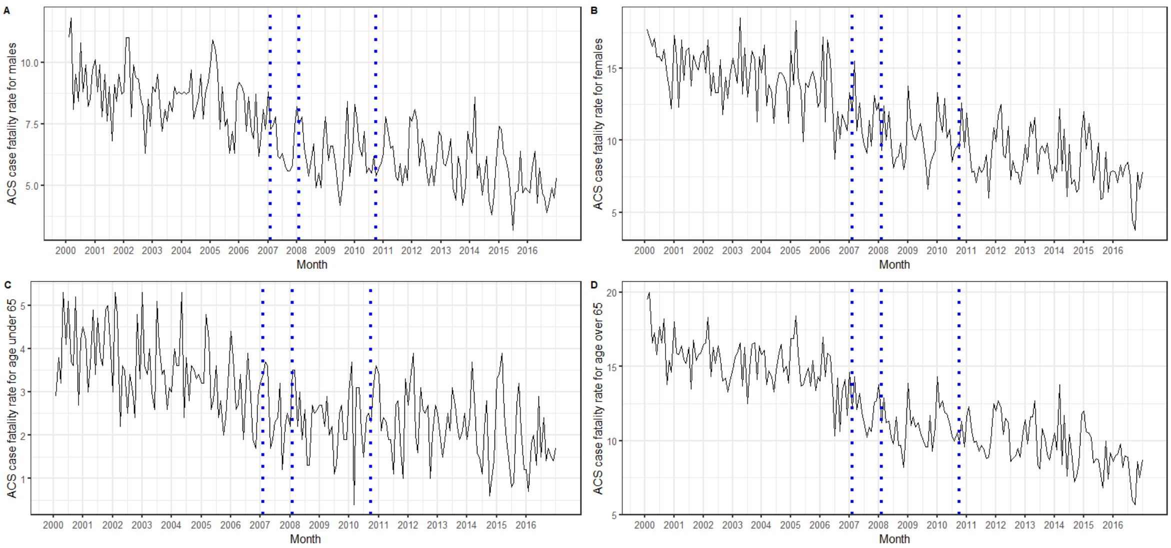

Figure 15: Stratified longitudinal trends for case-fatality rate from ACS (percentage) for January 2000 - December 2016.
The vertical lines mark the years the policies were implemented. A) Longitudinal trends for males. B) Longitudinal trends for females. C) Longitudinal trends for patients under 65. D) Longitudinal trends for patients over 65.

In the segmented model, the year found to have a differential rate of case fatalities was consistent with the model including all the data, end 2008. Both trends, before and after end 2008, were decreasing, though after end 2008 the decrease was not as pronounced as for the period before end 2008, as observed for the model including all the patients.

The differences in rates of case fatalities before and after end 2008 were higher for women (β = 0.003, p-value = 0.029) than for men, and for individuals older than 65 years old (β = 0.003, p-value = 0. 0.008; Table 6).

The seasonal pattern was consistent with that reported elsewhere(100), with higher rates of admission in winter and lower rates during the summer.

DISCUSSION

A detailed discussion for each of the manuscripts found in the previous sections can be found in this chapter. The discussion herein is divided by each of the manuscript developed. Figure 16 illustrates the connection between each of the specific goals in this study and each of the manuscripts that were developed.

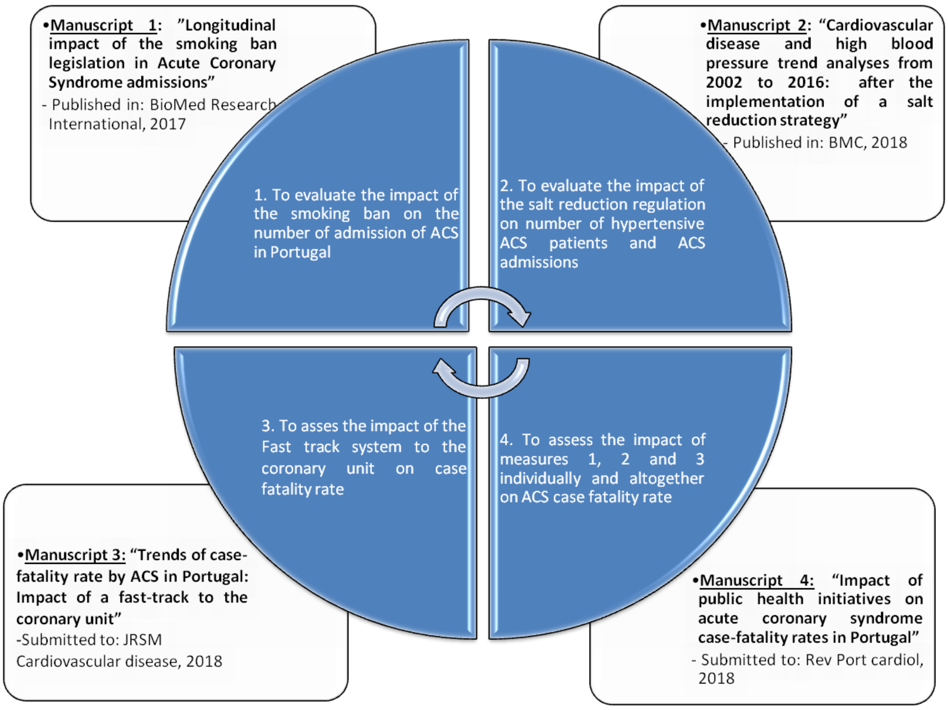

Figure 16: Relation between the specific goals and each of the manuscripts developed.

A detailed section on limitations and future recommendations can also be found in this chapter.

7. DISCUSSION FOR EACH MANUSCRIPT

7.1. ACS ADMISSIONS TREND AND THE IMPACT OF THE SMOKING BAN

The mechanism by which tobacco smoke is associated to ACS has been highly studied, proving that small exposures seem to increase platelet aggregation and alter endothelial function causing other hemodynamic changes that can increase or trigger ACS events(101).

The magnitude of the effect of smoke regulations on ACS events has been found to be very broad, from studies that found no significant reduction after the law had been implemented(102-103), to studies that found very large effects from 27% to 40%

reductions(104-105). However, these two last studies had very small sample sizes and had a very limited time after the ban (6-month).

The pooled estimate, obtained from meta-analysis, of the reduction in ACS events after the smoking ban included more than 30 studies, showed a risk reduction of 10% (95% CI 6 to 14, $p<0.001$)(106). Another meta-analysis study showed a pooled reduction up to 15% in ACS events after the law implementation(107).

Our results show that the implementation of a law to regulate smoking was associated with a decline of hospital admissions by ACS. The change in trend of ACS events from the period before the legislation to the period after the legislation was of 5.8% decrease, moreover the trend of ACS events for the period before the smoke legislation was increasing.

Although the effect of the reduction is not as high as some other studies, this could be explained by the fact that Portugal is among the countries with the lowest proportions of smokers in Europe (around 23%)(17, 108). However, according to the report from the Directorate-General of Health and the National Health Institute, constituting a partnership called InfoTabac, the proportion of smokers decreased by 1% in 2009, compared to 2006, but between 2009 and 2012, the smoking rate has remained stable in Portugal(76, 109), as well as for the period between 1995 to 2006 by which the smokers prevalence was also stable(110).

On the other hand, inconsistent compliance with the smoking law has been reported in few studies. The irregularities in the compliance with the law may be due to some ambiguities/gaps in the law; lack of practical definitions and absence or delay in the effective application of penalties in case of law violations(111-112).

A study published using Portuguese data on asthma(77) demonstrated that at least 39.6% of the sample described positive changes such as improvement of daily life activities performance, decrease in symptoms or lesser recourse to SOS medication, after the law implementation. From this group, 81.6% reported that since the law implementation, they were no longer exposed to second-hand smoke. This reinforces the hypothesis of an association between smoking ban regulation and positive health outcomes.

The seasonal pattern observed in Figure 1, was consistent with that reported in other studies(113-114), higher rates of admission during the winter, (especially around December and January), and lower rates in the summer. The higher rates of ACS during the winter could be explained by increases in blood pressure and in fibrinogen on cold days as well as the increase in infectious diseases, which are more common in industrialized countries during colder weather(115).

In January 2009, the year after the law being implemented, a cold wave was experienced in Portugal explaining the spike in ACS rates presented in Figure 1(116).
Bearing in mind that most of the meta-analysis studies(106, 117-118) evidenced that longer follow-up times were needed to assess later effects of the legislation, as in fact, the longer smoke-free policies are in place, the more pronounced their effects on smoking behaviour(119). Thus the reduction in ACS rates observed over time in our study, suggests that the effect of the legislation was sustained over time. One possible explanation for later effects is that they are due to less rapidly mediated effects on atherosclerosis severity and prevalence(120).
Due to the longer duration of our study compared to most studies and the fact that hospital admissions were captured through a large, well-validated population database, allowed for better delineation of trends(106, 117).
Our results show that males were associated with a greater reduction of ACS events after the legislation in declination of women. Several studies confirm these results showing more effects in male population, than in female population(113, 121-124). According to the Directorate-General of Health there is a higher rate of ACS events among men than among women, this could potentially increase power to detect an effect in men(120, 123, 125). The fact that women present lower prevalence of tobacco consumption than men(126) could lead to lower the impact of the law, although this would not affect second-hand smoking.

The results stratified by age show a significant reduction of ACS events for older people, age over 65 years old, however no significant effect was found for people under 65 years old. The fact that older people are more vulnerable to exposure to second-hand smoking may trigger ACS events. Also it is known that arterial wall stiffness increases in subjects over 55 years. Studies performed in Mediterranean populations such as Spain and Italy showed similar effects in older subjects(124-125, 127). Although one of the main purposes of smoking bans is to decrease exposure to second-hand smoke, we assessed the proportion of ACS patients that reported to be current smokers using the NRACS (Figure 2). Although the ACS rates have decreased from 2002 there is not a marked decrease after 2008. The proportion of smokers remained very stable between 2006 and 2010, this is consistent with the other studies. Barone-Adesi and colleagues calculated that the contribution of reduced active smoking to the reduction found in ACS was less than 1%(103). In addition, the study from D. Ferrante and colleagues reported that the implementation of the law did not impact smoking prevalence(128).

The findings for each region show a significant decrease only for Lisbon and Tagus Valley region. As Lisbon is the capital of country, one could argue that people on bigger cities are more likely to frequent cafes, restaurants and bars, benefiting most from any reductions in second-hand smoking even at low levels(102). The North region of the country also includes big cities, so although it was no significant there was a decreasing trend in ACS events.

Although the Alentejo region is the region with higher rate in male regular smokers in mainland Portugal (108) the fact that no reduction in ACS rate was found after the law implementation could be related to the fact that changes in smoking behaviours may be more difficult in regions with more rural areas(129).

There are encouraging indications suggesting the effects of smoking law regulation in reducing the number of ACS events in the Portuguese population. However, we recognize some limitations to the study. Like any ecological study is not possible to prove directly the association between the implementation of smoking law and the decline in the number of ACS events. On the other hand, by 2010 a law aiming to reduce salt in bread as well as making mandatory to included information on salt content in packed food was implemented in Portugal. Although the effect of this law may be related to the declining in ACS events after 2010, the reduction in ACS rate was significant by the beginning of 2008, year when the smoking law was implemented. Furthermore, more studies are needed to assess the effect of salt reduction legislation on ACS events.

Moreover, our study has some strengths as the availability of information on gender, age and region which allowed us to assess the robustness of our findings among different subgroups. Also the time series method is preferred over the simpler pre and post proportion comparison method that does not take the pre-intervention trend into account and also allows to correct for autocorrelation(130). The fact that we used two well validated and standardized databases is also a major strength as this allows for an easy comparison with other international studies mainly those developed in other European countries.

7.2. HBP AND SALT REDUCTION AND CVD (ACS AND STROKE) ADMISSION TRENDS

Our results showed increasing trends in the proportion of HBP comorbidity in the ACS population until 2013, the following years the trends appear to decrease. This year was used as a breakpoint to test for differences in trends for ACS and stroke. Decreasing trends for both outcomes were also found, but were not significant.

Although our results were not statistically significant, and thus must be interpreted with caution, it is encouraging to find decreasing trends, especially in the proportion of HBP patients in the ACS population, with a reduction of nearly 600 people per year, after the implementation of a major public health measure that was meant to reduce salt intake.

Even a small reduction in the proportion of HBP in the ACS population, as the one observed in our study of 555 persons per year achieved through a population-wide approach, can have huge impacts(66, 131). These impacts has effectively slowed down the development of atherosclerosis in young people, thereby reducing the likelihood of future epidemics of CVD(132).

The decreasing trend for ACS was observed for women but not in men, in fact salt intake have been previously link to higher risk of CV events in women but not in men(61), more particularly studies have found that women could benefit more, concerning stroke reduction, from dietary salt reduction than men(133).

As salt sensitivity is known to be greater in the elderly we hypothesized that if the salt reduction law could have some effect it would be greater for the elderly(22, 134). In fact, our results suggest a decreasing trend for all outcomes in the older group.

Results from this type of population-wide approach were seen in the UK, where salt reduction campaigns showed significant results, achieving a 15% salt reduction from 2003 to 2011, which translated into about 6000 fewer deaths from CVD, saving about 1.5 billion pounds a year(62).

The decreasing trends for all of our outcomes were not as great as we expected however the fact that the starting of the decrease takes place after the implementation of these approaches, and the trend of HBP in ACS patients was steadily increasing before that, supports our hypothesis that this approach of reducing salt in bread and making pre-packed salt labelling mandatory can influence HBP prevalence in ACS patients as well as CVD trends.

The fact that, salt intake levels have been decreasing in Portugal to the most recent value of 7.3 g/day in 2016(79) also supports our hypothesis of the potentially effect of the regulation applied in the country. Although this value was obtained by a 24 hour dietary recall questionnaire, these values were validated against urinary sodium excretion(135) for a sub-sample of 100 subjects and the values were highly correlated

In addition, BP levels have been declining in the Portuguese population, from a mean BP of 134.7/80.5 mmHg in 2003(136) to a mean BP of 127/74.6 mmHg in 2012(21).

Furthermore, several studies showed that bread is one important source of salt in Portugal(80), and contributes to about one-sixth of daily salt intake(80). Results from the National Food, Nutrition and Physical Activity Survey suggest most of the salt consumed by the population comes directly from bread and toast, charcuterie products,

and soups(79). It was all this evidence that led to the creation of the regulation to reduce salt in bread to a minimum of 1.4 g of salt per 100 g of final product(85) and mandatory labelling for pre-packed products stating clearly the salt content of the product. Portugal was, thus, the first western country to create a law for the clear definition of the quantity of salt contained in bread.

Besides the legislation in 2010, several initiatives have been carried in Portugal to reduce salt intake, such as: electronic tools, such as websites included in the National Program for the Promotion of Healthy Eating, to free distribution of books and brochures, by the creation of an animated series, and the creation of the National Food, Nutrition and Physical Activity Survey, aiming to collect nationwide data on dietary intake and physical activity(79).

There is already evidence that reducing salt intake could reduce BP in the Portuguese population. One community intervention trial conducted in Portugal demonstrated that reducing salt intake in an entire village, including cooking and processed food, led to a significant reduction in the BP of the population(137).

Policy interventions to reduce national sodium consumption have demonstrated to be highly cost effective in nearly every country in the world. These interventions could reduce millions of disability adjusted life years at low cost and be more cost-effective than pharmacological interventions(64, 133).

Policy and system changes are critical to reduce HBP in populations, including legislation and public education to reduce dietary sodium and food pricing policies, to support prevention and management of CVD(138).

Alternative public health approaches, such as reducing salt in processed foods and bread, and labelling of processed food along with the use of multiple fiscal and educational policies, have already been proposed by the WHO as the first-line approach for CVD reduction, when implemented on a wide scale(132, 138).

Despite of several efforts being made in the country to reduce salt intake, there is still room for improvement, namely in food labelling(139), adjusting it to the level of health literacy in the country. Once the level of health literacy in Portugal was slightly lower than the rest of European countries(140), this might have prevented the population from fully benefiting from the labelling, as the interpretation of salt content in each food can be difficult.

Simpler labelling systems already exist in other countries, such as labels that rely on the use of front-of-pack information such as logos with information on the overall healthiness of the food and traffic light and colour coding systems, which might help citizens make healthier choices. Countries such as Finland and the UK have already implemented some of these labelling systems. In Finland, food products with salt

contents below the designated levels display a low-salt label to emphasize their lower-than-conventional salt levels (20). In the UK, a traffic light system to distinguish between high, medium, and low salt content in food products was implemented. These strategies proved to be efficient in reducing salt intake in the population(141). The traffic light labelling system has been proposed by the Portuguese Hypertension Society to help the population choose products regardless of their level of literacy.

More restrictions are being planned in Portugal to further reduce salt intake, such as a taxes on products with more than 1g of salt per 100g of finished product such as: pre-packaged crackers and biscuits; pre-packaged cereal flakes and pressed cereals; and pre-packaged, dehydrated potato chips. A rate of 0.80 Euros per kilogram of finished product will be applied to these products.

On the other hand, further reduction of salt content in bread, to a minimum of one g per 100 g of final product, was proposed to be achieved by 2020, with continuous reductions each year after 2018.

Our study presents encouraging indications suggesting there have been reductions in the proportion of hypertensives among ACS patients after 2013, along with an annual decrease in the rates of ACS and stroke.

Nevertheless, it might be too soon to notice great effects from salt reduction on CVD trends. The fact that until 2013, the trend for the proportion of hypertensives was continuously increasing, and right after 2013 a decrease in trend can be observed, suggests that the lack of statistical significance could result from the time period being analysed being too short to capture further reductions.

7.3. THE CORONARY FAST TRACK SYSTEM

Trends in mortality in mortality by AMI have been decreasing steadily in Europe. In Portugal mortality by ACS has been studied up to 2008 and showed around 3,760 fewer deaths in 2008 compared to the expected number if the rates observed in 1995 had persisted(142). More recently, a set of health policies tackling not only disease prevention, but also decrease in mortality, were implemented in the country, namely the fast-track system in 2007, the smoking ban in 2008 and a salt reduction regulation in mid-2010. Although in our study, we focused on the impact of the FTS on case-fatality rates, all these policies can affect CVD mortality.

Although CHD mortality rates in Portugal decreased by more than 25% between 1995 and 2008, we found a significant decrease immediately after the implementation of the FTS up to 2016. Although we cannot attribute this directly to the FTS, the reductions found up to 2008 were attributable to better care and treatments, explaining half of the overall decline in CHD deaths. Furthermore, by 2008, the FTS was already

implemented, and also there was an increased in the number of centres with a catheterisation laboratory. Also, by 2008, approximately 42% of the decrease could be attributed to an improvement in major risk factors(142); therefore, regulations such as the smoking ban and mandatory salt reduction probably had a greater influence on mortality rates.

Our study also shows there was a steep decrease in case fatality rate the year of the implementation of the FTS however the rate of decline observed after that was similar to the years previous to the policy. This is most likely to low proportion of patients activating the system. By 2016, only a total of 38% of the STEMI patients have activated the system thus more than half of the patients are not beneficiating from the fast-track policy.

We found similar decreasing case-fatality rates for men and women, which has previously been observed in other studies where the rate of decrease in CHD mortality appeared to be stable across both sexes(7).

Surprisingly, our results for age stratification were not consistent with the overall case-fatality rate. Either for the youngest or older patients, we observed no immediate change in case-fatality rate after the FTS was implemented. For both groups, there were significant changes in trend; however, the trends observed were increasing. The prevalence of obesity and therefore diabetes(143) is in fact increasing in the country, which can be attenuating the reductions for the younger groups. This fact has also been observed in other studies(7, 144) where the increase of obesity led to lower decrements of mortality for the younger groups. A similar pattern was observed for the older group, which has already been found in other datasets and indicates that older persons benefit the least from the decline in CVD mortality(144). Other studies have also reported a persistently high case-fatality rate among the elderly(145).

Furthermore, when we compared ACS case-fatality rates between hospitals with a FTS implemented and hospitals without such a system, the rates were significantly different, and lower case-fatality rates were observed for hospitals that had the FTS. Although the trends were decreasing for both groups, hospitals with vs. hospitals without the system, the decrease was more accentuated in the group with the FTS. This kind of system allows earlier diagnosis and direct communication between the ambulance team and the CCU, bypassing the ER, thus minimising time to treatment, which leads to better prognosis and, consequently, less case fatality rates.

Previous studies have shown that minimising time to treatment using the FTS can directly lead to diminished case-fatality rates(146-147).

The observed mean time (3 hours), even for patients admitted through the FTS, was longer than the recommended time(44), which is 1.5 to 2 hours after symptom onset.

These type of results have already been reported in other studies where the average delay time from symptom onset to FMC remained at around 2 hours and did not decrease despite multiple public education campaigns(148).

A decrease of 50 minutes was observed for patients admitted through the FTS when compared to patients not admitted through this system, and similar reductions in time have been observed in other studies(149).

The variables affecting symptom onset to FMC were not surprising, as most were found in other studies and associated with longer delays

Although there is clear evidence, in our study as well as in previous studies, of the effectiveness of a FTS, more than half of the patients are not using this system. As this is a patient-initiated process, even when proven to be the best way of admission if patients and the community at risk do not have either sufficient health literacy to acknowledge their symptoms or the process is not widespread enough, the impacts of these health policies will not reach full capacity.

Moreover, Portugal was one of the countries to participate in a global initiative that aims to improve the delivery of facilities by increasing timely access to primary percutaneous coronary intervention, thus reducing mortality and morbidity in STEMI patients. The project was responsible for the launch of a national public campaign to raise public awareness of the symptoms of MI, among other objectives.

The OCDE recently revealed that the use of primary PCI increased dramatically in countries that had been participating in the "Stent for Life" initiative. In fact, 1 year after implementation of the initiative in Portugal, a positive impact was observed, with greater use of the 112 emergency call service and a smaller number of patients arriving by their own means at local hospitals without PCI facilities(150). This suggests that health campaigns, such as the "stent for life" campaign, can have an impact on the health community and the general community.

7.4. IMPACT OF PUBLIC HEALTH INITIATIVES IN ACS CASE-FATALITY RATE

In the last 11 years, a set of health policies have been implemented in Portugal to help decrease CVD mortality. The first initiative was the FTS in 2007, followed by the smoking ban in 2008 and a salt reduction regulation in mid-2010.

We created a set of statistical models; firstly, models to assess the individual impact of each of the policies. Finally, a model was created to assess if there was any year during the study that could indicate a difference between trends, suggesting a possible impact of the policies in the country.

FTS and the smoking ban led to an immediate decrease in case-fatality rate. Previous national and international studies have shown that FTS, substantially shortening the time between symptom onset and treatment, directly impacts survival. It has been demonstrated that time between symptom onset and treatment above 120 min translates into increased in-hospital mortality in an almost linear fashion (147, 151-152).

The relationship between smoking and CVD mortality has been extensively proven, since smoking increases atherosclerotic changes with narrowing of the vascular lumen and induction of a hypercoagulable state. Such changes increase the risk of acute thrombosis leading to death(54). The results of this current study were very encouraging regarding the smoking ban, as an immediate decrease in case fatality was found once the ban was implemented. Since the ban target both smokers and second-hand smokers, case fatality rates should decrease for both groups. Smoking cessation, or even small reductions in consumption, has been previously linked to a decrease in the number of CVD events and also a fall in the mortality risk(153).

There are not many studies analysing the effect of the smoking regulations on CVD mortality. Of those available, most focused on how regulations affected hospital admissions(154); however, the impact on mortality is equally important. Nevertheless, we are not the first to analyse the impact on mortality. A recent study similarly found a reduction of up to 11% in acute myocardial infarction (AMI) mortality 1 year after a smoking regulation was implemented(155). Another study also found a 13% decrease in all-cause mortality, with up to a 26% decrease in ischaemic heart disease (IHD) mortality.

In this current study, we found that end 2008 was a breakpoint in our observed trends, which supported the results from the individual models. Up to 2009, the trends were significantly impacted by the policies, leading to a significant decrease in case-fatality rates. After this year, although the trend continued to decrease it was less pronounced. The impact of the salt regulation in mid-2010 showed a similar effect, with no change in trends after this year. A similar pattern was observed when analysing the impact of this policy on ACS admissions(156).

We hypothesised that although the salt regulation was an important initiative, it was very dependent on an individual's adherence. The way the regulation was implemented might not have produced the desired effect on the population, perhaps due to the low level of health literacy observed in Portugal.

When stratified by sex and age, our results showed that the smoking ban led to an immediate decrease in case-fatality rates for women and individuals older than 65

years old. Although the number of women smoking has increased in recent years, the number of men smoking was even larger and their length of time smoking was also greater. As a consequence, men will have increased mortality from CVD, even if they quit smoking or reduce their smoking habit. Older people are more vulnerable to exposure from second-hand smoking, thus reducing it could lead to a decrease in case fatalities in this group. Our findings were also consistent with another study, where post-ban reductions in IHD mortalities were seen in ages ≥ 65 years, but not in younger subjects(157).

Analysing FTS by groups, we found similar decreasing case-fatality rates for men and women, an effect previously observed in other studies where the rate of decrease in CHD mortality was stable across both sexes(7). In addition, no immediate change in case-fatality rate after the FTS was observed for either the youngest or the older patients. For both groups, there were significant changes in trend; however, the trends observed were increasing. The prevalence of obesity and diabetes(143) is increasing in Portugal, which could have attenuated any reduction for the younger group. This effect has been observed in other studies(7, 144) where an increase of obesity leads to lower reductions in mortality for the younger groups. A similar pattern was observed for the older group, which has previously been found in other datasets(144).

Our results for age stratification when using segmented regression showed significant differences between the trends before and after end 2008, for females and older subjects. As for the non-stratify model, the decrease in trends observed before end 2008 was steeper than the decrease observed after. These results were consistent with those observed when studying the smoking ban with age stratification, where a significant decrease in case fatality was observed for older people, but not for younger. For the sex stratification, although the FTS analysis showed a significant decrease after 2007 for men, this was related to an immediate effect and not a trend.

8. LIMITATIONS AND FUTURE RECOMMENDATIONS

8.1. LIMITATIONS

Although we found some interesting and relevant results, we recognise some limitations of our study. Like any ecological study, it is not possible to prove causal relations, i.e. direct association between the initiatives to reduce CVD and the observed CVD trends. However, our methodology (ITS using segmented regression) has the ability to distinguish the effect of the intervention from secular changes, that is, change that would have happened even in the absence of the intervention. This methodology also has the strongest power to infer causality without stripping contextual and

temporal factors from the analysis of this type of data. The ITS method is preferred over simpler pre and post proportion comparisons that does not take the pre-intervention trend into account and also allows to correct for autocorrelation(130)

8.2. RECOMMENDED FUTURE STUDIES

Public health is a very broad area thus it is impossible to assess all initiatives/policies in one study. Herein we propose future studies for both the policies assessed in this project and initiatives/policies that we did not have the chance to assess.

Mainly, we propose future studies that: I) Assess the impact of the public health measures studied herein in other pathologies besides CVD; II)) Assess the impact of further public health measures on CVD; III) Expand the study presented here to other European countries, using similar type of data, namely using DRG´s data and National Cardiovascular Registries; IV) Apply the same methodology used in this study in other high burden pathologies, such as cancer or respiratory diseases.

Some examples for future studies are presented below.

I. <u>Assess the impact of the public health measures studied herein in other pathologies besides CVD</u>

a) Impact of the salt reduction legislation in non CVD, namely renal disease.

It has been demonstrated that high salt intake may have detrimental effects on glomerular hemodynamic, inducing hyperfiltration and increasing the filtration fraction and glomerular pressure. Furthermore salt intake plays a critical role in the progressive glomerular filtration rate loss of established renal disease(158). Moreover, salt intake can lead to HBP, as already discussed, thus salt intake can also lead to renal disease through a secondary mechanism which is HBP(158).

On the other hand, further studies are planned in the country to study the effect of this legislation in urinary salt excretion that could potentially lead to create further restrictions on salt reductions, mainly tackling the salt content in pre-package food.

b) Assess the impact of the smoking ban in other diseases

There is strong and consistent evidence of the impact of the smoking ban in other disease beyond ACS, namely, ischemic stroke and acute exacerbation of chronic obstructive pulmonary disease (COPD).

Recent studies found that the implementation of a legislative smoking ban was in fact associated with a strong reduction in hospitalizations for acute exacerbations of COPD. This effect was even greater than the known reduction of admissions for ACS(159). Another study provided evidence that the smoking ban reduced the incidence of hospital admissions not only for AMI but also for stroke, asthma(160).

c) Assess the impact of other fast track system created in the country: stroke fast track system

The stroke FTS was implemented in Portugal in 2005, around the same time the coronary FTS.

The impact of the FTS for stroke has already been proven, studies have shown that, fast endovascular treatment (groin puncture within <4 h) significantly improves patients' outcomes. The earlier the patient is presenting, the more important is the fast track, offering chance for full neurologic recovery(161).

However, the impact of this FTS in stroke mortality has been scarcely studied in Portugal. Hence it is highly relevant that more studies are performed in order to study the impact on mortality and also if time from onset to puncture in being shorten.

d) Assess the impact of other fast track system created in the country: sepsis fast track system

As for stroke and ACS a fast track system has been recently implemented in Portugal for sepsis, the goal is to identify patients with sepsis as early as possible and treat them aggressively during the first 24 hours. Treatments ranges from mechanical ventilation, cardiac pacing drugs to dialysis because in case the patient state deteriorates and does not respond to standard treatment. This is in fact a time-dependent situation thus it is necessary to improve the organization and the process in order to reduce time to treatment(162).

II. Assess the impact of further public health measures on CVD

e) Taxation of beverages with added to sugar and effect on obesity, diabetes and CVD

Following the Framingham Heart Study, which played an important role in elucidating the factors that predispose to CVD and highlighted opportunities for prevention, there are more risk factors that need to be tackled and other that are currently being tackled through the creation of new health policies, such is the case of diabetes and obesity.

In order to tackle these two major risk factors for CVD and to support the goals of the National Health Plan, a new legislation has recently been implemented in Portugal, aiming mainly for the promotion of healthy eating habits.

In 2016, an agreement was signed between the Portuguese Ministry of Health and representative associations of the food industry that aimed at reducing the volume of sugar packages available in commercial establishments. At the same time, through Order No. 7516-A / 2016, published in the Diário da República, 2nd series, no. 108, of June 6, 2016, measures were adopted regarding the installation and operation of vending machines in the various institutions of the National Health Service (SNS), prohibiting a set of food products with excess sugar or added salt, and replacing it with a range of healthier foods that should be made available. Through Law 42/2016, approved by 2017, the Government approved the taxation of beverages with added to sugar, in order to contribute to the relevant reduction of consumption, especially in young people and adolescents(163).

Following these policies, it is further intended to apply limitations of the supply of some less healthy products at bars, cafeterias and buffets of the NHS institutions, in order to obtain a significant and sustainable reduction of the excessive consumption of sugar and salt, promoting the availability of foods in a healthy food pattern.

f) Impact of further salt reduction regulation on Gastric Carcinogenesis

More restrictions are being planned in Portugal to further reduce salt intake, such as a taxes on products with more than 1g of salt per 100g of finished product such as: pre-packaged crackers and biscuits; pre-packaged cereal flakes and pressed cereals; and pre-packaged, dehydrated potato chips. A rate of 0.80 Euros per kilogram of finished product will be applied to these products. On the other hand, further reduction of salt

content in bread, to a minimum of one g per 100 g of final product, was proposed to be achieved by 2020, with continuous reductions each year after 2018.

Regardless of which mechanism is operative, there is a large body of epidemiologic evidence indicating that a high-salt diet is a risk factor for gastric cancer in humans(25–30). Potentially, reductions in dietary salt intake could lead to a reduction in the risk of gastric adenocarcinoma in populations who have a high risk for this malignancy(164).

All this recent health policies are in line with the recommendations made by the WHO, as well as the main scientific cardiology societies as the American Heart Association (AHA) and the European Society of Cardiology (ESC), and National scientific associations as the Portuguese Society of Cardiology and are highly relevant to achieve a healthier population, however it is equally important to follow closely the impact of these initiatives, not only in CVD trends but also in other diseases, as previously mentioned.

CONCLUSION

We believe to have added a small contribution to the knowledge of the impact of public health measures in pathologies with high clinical and social economic burden, such as CVD in general and ACS and stroke in particular, to the possible ways public health initiatives can influenced the trends of one of the diseases with most burden worldwide.

There has been an increasing concern with diseases with an important burden in Portugal, in the last decades, which has led to the implementation of important public health initiatives in the country. However, the analyses of the impact of these initiatives have been very scarce. This type of evidence is crucial for policy makers, providers, and health professionals once it has implications not only in terms of policy definition and implementation but also in terms of clinical decision-making.

In addition, some of the strengths of our study is the fact that we used two well validated and standardized databases which is allows for an easy comparison with other international studies mainly those developed in other European countries, allowing to apply our methodology in countries that have identically systematized information such as the DRG database and national registries on CVD.

As the data we used is also available by gender, age category and geographical region, which allowed us to assess the robustness of our findings across different subgroups, it also possible to run this international comparison by this subgroups.

The present study allowed us to reach the main goal established in the beginning of in this project, namely to assess the impact of three major public health initiatives chosen to be studied, and finally assess the impact of these three major public health initiatives on case-fatality rate by ACS.

Our main findings can be summarized into:

- There was a decline of 5.8% in the proportion of ACS admissions after the smoking ban, the fact that we found an increasing trend in ACS before the implementation of the ban suggests that the decline in the number of ACS events is not related to long term trends but to the ban itself.
- We found a decreasing trend for both HBP in ACS patients and CVD outcomes after major initiative to reduce salt intake was implemented. Although none of the trends we found were statistically significant, the decreasing trend suggests that this type of approaches, although hard to measure, could potentially impact the trends of major public health outcomes.

- Our study suggests that policies such as the fast-track system are related to a decline in ACS case fatality, supporting the importance of this type of policies in achieving health gains.
- The proportion of patients activating the fast-track system is increasing, however more than half of the patients are not using the system. This highlights the importance of continuous education to the general community in terms of guideline adherence, regarding the importance of rapid reperfusion therapy, which can directly affect case-fatality rates.
- Strategies such as the smoking ban and the FTS led to an immediate decrease in case fatality rates; however, after 2009 no major decreases in ACS trends were found.

Undoubtedly, more studies are needed to assess the impact of such measures, not only for other diseases beside CVD, but also adding more years to the study would allow analysis of long terms effects of the public health initiatives.

In conclusion, this research is relevant to the public health community because it provides an indication about the impact that population-wide approaches can have in such relevant public health aspects, as CVD risk factors, and CVD trends themselves. Our results suggest that population-wide approaches can have an impact on the prevention and improvement of CVD control, reducing the number of CVD events, eventually reducing premature death, and potentially reducing morbidity, and disability by CVD, thus maximizing health gains in a group of diseases with such economic weight and burden such.

Considering that CVD, namely ACS and stroke is the number one cause of death in the Western world, including in Portugal, and as such constitutes an immense public health problem(6), even a small improvement in treatment and an increase in patient awareness on avoiding CVD modifiable risk factors, such as life-style risk factors, can have important clinical, economic and social gains.

Our results provide encouragement for different stakeholders, such as decision makers, public health authorities and professionals, legislators, scientific societies and the cardiology community to keep the efforts to ensure law compliance and to create new normative instruments, clinical and policy strategies to reduce the mortality and burden of CVD, in order to obtain the maximum health gains in such a high-impact disease as CVD.

LIST OF MANUSCRIPTS

Longitudinal impact of the smoking ban legislation in Acute Coronary Syndrome admissions

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Abstract

Background and purpose

The association between smoking and CVD, in general and with ACS in particularly, has been extensively proved, however smoking is still the first preventable cause of death in the EU. A smoking-free legislation was implemented in Portugal in 2008. We aim to evaluate the potential impacts of the smoke legislation on the number of ACS events in the Portuguese population, as well as the longitudinal effects of the smoking ban several years after its implementation and investigate trends by age, sex, and region.

Methods

We analyzed the admission rates for ACS before and after the ban (2002-2007 vs 2008-2014) using data from hospital admission. Monthly crude rate was computed using the Portuguese population as the denominator and the total ACS monthly events as the numerator. Data concerning the proportion of current smokers among ACS patients was obtained from the NRACS. Data was stratified by sex, age and region. Interrupted time series were used to assess changes over time.

Results

A total decline of -5.8% was found for the ACS crude event rate after the ban implementation of the smoking legislation. The decreasing trend continued to be observed even after seven years since the law implementation. The effect of the legislation was higher in men than in women, and also in individuals over 65 years old. The most significant reduction of ACS crude rate was found in Lisbon and no significant reduction in other regions of Portugal.

Conclusions

Our results suggest that smoking legislation is related to a decline in ACS admissions, supporting the importance of smoke legislation as a public health measure, contributing to reduce the ACS crude event rate.

Introduction

Tobacco is now considered one of the most important public health issues and a major determinant of preventable mortality and morbidity in developed and developing countries (12-13). Diseases associated with tobacco consumption encompass a significant burden on individuals, societies, and healthcare systems.

Smoking affects not only active smokers but also those who are exposed to secondhand smoke in the vicinity of a smoker (14). Passive smoking has been associated with an increased relative risk of coronary heart disease, in some studies the exposure of non-smokers to secondhand smoke was associated with a 25% increased risk of coronary artery disease and myocardial infarction (15). Even in short-term passive smoking appears to cause damages in the endothelial function that could immediately compromise the cardiovascular system (16).

By 2013 smoking, including secondhand smoking, was responsible for the death of approximately 12.350 people (around 11%) in Portugal (17).

The association between smoking and cardiovascular disease (CVD) has been extensively proved, however smoking is still the first preventable cause of death in the European Union (165). Several meta-analysis showed a reduction on coronary events after the implementation of smoke-free legislation, it suggests potential to achieve vast public health benefits (106). However fewer studies have demonstrated if the reduction effect lasted after the law implementation (106). Furthermore smoking bans benefit non-smokers and smokers, non-smokers as they are exposed to significantly less secondhand smoke, while smokers tend to smoke less, have greater cessation success, and experience increased confidence in their ability to quit (166).

Portugal was one of the countries that signed the WHO Framework Convention on Tobacco Control (76), leading to the implementation of the most recent anti-smoking measure, the 37/2007 legislation implemented in January 2008 (74). This legislation contained new framework to protect individuals from passive smoking and for cutting down/stopping consumption to ensure protection against secondhand smoke (74, 77). This law banned smoking in all enclosed public places, such as hospitals and public transportations, and workplaces. Besides this, it established further regulation for the information provided on tobacco products, packaging and labelling, as well as further restrictions on the of advertising (78).

Within the context of the growing body of consistent evidence from studies in other countries that support the assumption that the implementation of a public smoking ban was the leading cause for the decrease in the number of Acute Coronary Syndrome (ACS) events, we aim to evaluate the potential impacts of the smoke legislation on the number of ACS events in the Portuguese population. In addition we aim to analyze the

longitudinal effects of the smoking ban several years after its implementation and investigate trends by age, sex, and region.

Methods

Data

Data was obtained from the Diagnosis Related Group (DRG) National Database that collects data from all admissions into Portuguese public hospitals (Mainland Portugal), holding data on primary diagnosis and some demographic variables such as sex and age, as well as the geographic region of the admission (90).

All admission cases from 2002 to 2014 were extracted and only participants with ages over 20 years old and with primary diagnosis of ACS coded in ICD 9 (international classification of disease, 9th revision) as 410.00-410.xx to identify admissions diagnosis of Acute Myocardial Infarction (AMI) and 4130 codes, to identify unstable angina, were analyzed.

Data from the National Registry of Acute Coronary Syndrome (NRACS), that gathers information on the diagnosis and treatment of ACS, being considered a surpassing source of information in Portugal (167), was used from the period of 2002 to 2010, in order to obtain the proportion of ACS patients that were current smokers. This dataset has the advantage of being integrated into the Euro Heart Survey platform and, consequently, uses the Cardiology Audit and Registration Data Standards (CARDS) system. This system ensures that credible and comparable information is collected in several European countries over time as they use standardized information, both in terms of the definition and coding of variables, and in the form of measurement and collection of data. As data is validated and standardize allows for the possibility of applying and validating analysis in other larger populations, thus being able to obtain more robust results (93).

Smoking legislation was implemented in January 2008, providing six years of data before implementation of the legislation (January 2002 through December 2007) and seven years of data after the legislation was implemented (January 2008 through December 2014).

The unit of analysis was monthly admission for ACS rather than an individual patient, so it was possible for a person to be counted more than once, since changes in the number of admissions were also expected to be affected by the legislation.

All data analyzed were de-identified.

Statistical analysis

In order to estimate ACS crude event rates population estimates, by age and sex were obtained from the National Institute of Statistics for each year and were used as denominators.

ACS crude event rates (per 100000 adults) were computed for each month, using the population of the country, restricted to adult population resident in mainland Portugal with ages over 20 years. Crude rates were calculated as the number of ACS events divided by the population for that month.

To evaluate changes over time, we used an interrupted time series design, implementing a segmented multiple linear regression model. These models are useful when the relationship between the response and the independent variables are piecewise linear, namely represented by two or more straight lines connected at unknown values, which are usually referred as breakpoints (99). In this study, the segmented model was implemented in order to test whether there was a significant change in the number of ACS events after the introduction of smoke-free legislation.

The response variable was the monthly crude event rate of ACS. The impact of smoke-free legislation, defined as a change in the rate of admissions for ACS after the legislation, was assessed by including January 2008 as breakpoint in the regression. Difference between slopes, before and after the legislation, was assessed through Davies test. A month indicator variable was introduced to adjust for seasonality in ACS admissions.

All analyses were stratified by sex, age and region. Age was grouped into two categories <65 and ≥65 years old. We further stratify data per NUTSII regions for mainland Portugal (Alentejo region, Algarve region, Midlands region, Lisbon and Tagus Valley region and North region) in order to check for any marked reduction in regions with big cities, such as Lisbon and some cities in the North region.

Autocorrelation between month estimates was incorporated adequately into the model, with the presence of short term autocorrelation applying a first order autoregressive - AR (1) - structure to the residuals.

Using data from the NRACS, we computed the monthly proportion of patients with ACS diagnosis that were current smokers for the period of 2002 to 2010. The proportion was obtained by dividing the number of monthly smokers by the total smokers included in the database for the study period. In order to asses if there was a significant decrease in the proportion of smokers after 2008 another segmented multiple linear regression model was implemented and Davies test was used to asses for significant changes in slopes.

Models were fitted in R version 2.3.2 software using the library segmented (168).

Results and Discussion

Results

A total of 190.974 cases of ACS were registered in the country (Mainland Portugal), from 2002 to 2014, of which 64% were males.

We assessed crude rates (per 100000 adults) of monthly admission by ACS for the period of 2002 and 2014. Our results show a decline of ACS events by 2008, year of the law implementation, that was used as a breakpoint in the model created (Figure 1). A positive trend was observed for the years preceding the year of the legislation implementation (yearly trend of 0.004 events per 100000; 3.8 %). For the period after the legislation took place, the trend observed for ACS crude rate was negative, with a decreased of 0.0018 events per 100000; -1.7% by year after the legislation (Table 1). The difference between the two slopes for the trends before and after the legislation was significant (-0.006 events per 100000, p<0.001) in the overall population (Table 1) with a decline of ACS events of -5.8%. We stratified the ACS events by sex, and the trends observed for the pre-legislation and post-legislation periods were similar for both men and women (Table1). Although the trends were similar, the reduction in ACS event crude rate, was more markedly in men (-0.0046 events per 100000;-4.8%, p-value=0.0002) than women (-0.0033 events per 100000;-3.2% p-value=0.0002). However, the results obtained for males should be interpreted with caution as the confidence interval for the slope after the law implementation is wider than the one obtained for women and zero was included.

The results for age stratification showed a significant reduction in ACS rate after the legislation took place for people over 65 years old (-0.014 events per 100000; -13% p-value<0.001), however this finding was not verified for people under 65 years old.

Results stratified by region showed that the only region with a significant decrease in ACS events after the law implementation, was Lisbon and Tagus Valley (change in slope of -0.013 events per 100000, p-value<0.001) .Although the North region also showed a trend in decrease after the law implementation this reduction was not significant (change in slope of -0.003 per 100000, p-value=0.1683). The remaining regions did not show any significant changes.

The seasonal pattern observed was consistent with that reported elsewhere (100), with higher rates of admission over winter, and lower rates during the summer.

The analysis of the NRACS data allowed us to assess the proportion of ACS patients that were currently smokers for the period 2002 to 2010. At the time of the registry, the proportion of smokers among ACS patients has been steadily declining over the years, the decrease observed after 2008 was not significant (p-value=0.997, Figure 2).

Discussion

The mechanism by which tobacco smoke is associated to ACS has been highly studied, proving that small exposures seem to increase platelet aggregation and alter endothelial function causing other hemodynamic changes that can increase or trigger ACS events (101).

The magnitude of the effect of smoke regulations on ACS events has been found to be very broad, from studies that found no significant reduction after the law had been implemented (102) (103), to studies that found very large effects from 27% to 40% reductions (104-105). However, these two last studies had very small sample sizes and had a very limited time after the ban (6-month).

The pooled estimate, obtained from meta-analysis, of the reduction in ACS events after the smoking ban included more than 30 studies, showed a risk reduction of 10% (95% CI 6 to 14, $p<0.001$)(106). Another meta-analysis study showed a pooled reduction up to 15% in ACS events after the law implementation (107).

Our results show that the implementation of a law to regulate smoking was associated with a decline of hospital admissions by ACS. The change in trend of ACS events from the period before the legislation to the period after the legislation was of 5.8% decrease, moreover the trend of ACS events for the period before the smoke legislation was increasing.

Although the effect of the reduction is not as high as some other studies, this could be explained by the fact that Portugal is among the countries with the lowest proportions of smokers in Europe (around 23%) (17, 108). However according to the report from the Directorate-General of Health and the National Health Institute, constituting a partnership called InfoTabac, the proportion of smokers decreased by 1% in 2009, compared to 2006, but between 2009 and 2012, the smoking rate has remained stable in Portugal (76, 109), as well as for the period between 1995 to 2006 by which the smokers prevalence was also stable (110).

On the other hand inconsistent compliance with the smoking law has been reported in few studies. The irregularities in the compliance with the law may be due to some ambiguities/gaps in the law; lack of practical definitions and absence or delay in the effective application of penalties in case of law violations (111-112).

A study published using Portuguese data on asthma (77) demonstrated that at least 39.6% of the sample described positive changes such as improvement of daily life activities performance, decrease in symptoms or lesser recourse to SOS medication, after the law implementation. From this group, 81.6% reported that since the law implementation, they were no longer exposed to secondhand smoke. This reinforces

the hypothesis of an association between smoking ban regulation and positive health outcomes.

The seasonal pattern observed in Figure 1, was consistent with that reported in other studies (113-114), higher rates of admission during the winter, (especially around December and January), and lower rates in the summer. The higher rates of ACS during the winter could be explained by increases in blood pressure and in fibrinogen on cold days as well as the increase in infectious diseases, which are more common in industrialized countries during colder weather (115).

In January 2009, the year after the law being implemented, a cold wave was experienced in Portugal explaining the spike in ACS rates presented in Figure 1 (116).

Bearing in mind that most of the meta-analysis studies (106, 117-118) evidenced that longer follow-up times were needed to assess later effects of the legislation, as in fact, the longer smoke-free policies are in place, the more pronounced their effects on smoking behaviour (119). Thus the reduction in ACS rates observed over time in our study, suggests that the effect of the legislation was sustained over time. One possible explanation for later effects is that they are due to less rapidly mediated effects on atherosclerosis severity and prevalence (120).

Due to the longer duration of our study compared to most studies and the fact that hospital admissions were captured through a large, well-validated population database, allowed for better delineation of trends (106, 117).

Our results show that males were associated with a greater reduction of ACS events after the legislation in declination of women. Several studies confirm these results showing more effects in male population, than in female population (113, 121-124). According to the Directorate-General of Health there is a higher rate of ACS events among men than among women, this could potentially increase power to detect an effect in men (120, 123, 125). The fact that women present lower prevalence of tobacco consumption than men (126) could lead to lower the impact of the law, although this would not affect secondhand smoking.

The results stratified by age show a significant reduction of ACS events for older people, age over 65 years old, however no significant effect was found for people under 65 years old. The fact that older people are more vulnerable to exposure to secondhand smoking may trigger ACS events. Also it is known that arterial wall stiffness increases in subjects over 55 years. Studies performed in Mediterranean populations such as Spain and Italy showed similar effects in older subjects (124-125, 127).Although one of the main purposes of smoking bans is to decrease exposure to secondhand smoke, we assessed the proportion of ACS patients that reported to be

current smokers using the NRACS (Figure 2). Although the ACS rates have decreased from 2002 there is not a marked decrease after 2008. The proportion of smokers remained very stable between 2006 and 2010, this is consistent with the other studies. Barone-Adesi and colleagues calculated that the contribution of reduced active smoking to the reduction found in ACS was less than 1% (103). In addition the study from D. Ferrante and colleagues reported that the implementation of the law did not impact smoking prevalence (128).

The findings for each region show a significant decrease only for Lisbon and Tagus Valley region. As Lisbon is the capital of country one could argue that people on bigger cities are more likely to frequent cafes, restaurants and bars, benefiting most from any reductions in secondhand smoking even at low levels (102). The North region of the country also includes big cities, so although it was no significant there was a decreasing trend in ACS events.

Although the Alentejo region is the region with higher rate in male regular smokers in mainland Portugal (108) the fact that no reduction in ACS rate was found after the law implementation could be related to the fact that changes in smoking behaviours may be more difficult in regions with more rural areas (129).

There are encouraging indications suggesting the effects of smoking law regulation in reducing the number of ACS events in the Portuguese population. However we recognize some limitations of the study. Like any ecological study is not possible to prove directly the association between the implementation of smoking law and the decline in the number of ACS events. On the other hand, by 2010 a law aiming to reduce salt in bread as well as making mandatory to included information on salt content in packed food was implemented in Portugal. Although the effect of this law may be related to the declining in ACS events after 2010, the reduction in ACS rate was significant by the beginning of 2008, year when the smoking law was implemented. Furthermore, more studies are needed to assess the effect of salt reduction legislation on ACS events.

Moreover, our study has some strengths as the availability of information on gender, age and region which allowed us to assess the robustness of our findings among different subgroups. Also the time series method is preferred over the simpler pre and post proportion comparison method that does not take the pre-intervention trend into account and also allows to correct for autocorrelation (130). The fact that we used two well validated and standardized databases is also a major strength as this allows for an easy comparison with other international studies mainly those developed in other European countries.

Conclusions

Our study extended the existing literature on public health interventions and suggests that smoking legislation is related to a decline in ACS admissions supporting the importance of smoke legislation for public health. Considering that coronary heart disease is one of the leading causes of death in Portugal, even a small reduction in the number of ACS events has important health and economic gains.

The increasing number of ACS events verified from 2002 to 2008, before the law was implemented, may suggest that the decline of 5.8% in ACS events shown in our study is associated with the introduction of smoke legislation. It also suggests that the decline in the number of ACS events is not related to long term trends.

Our results provide encouragement for legislators and public health authorities to keep the efforts to ensure law compliance and to create new normative instruments, clinical and policy strategies to reduce the burden of ACS.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Figures and Tables

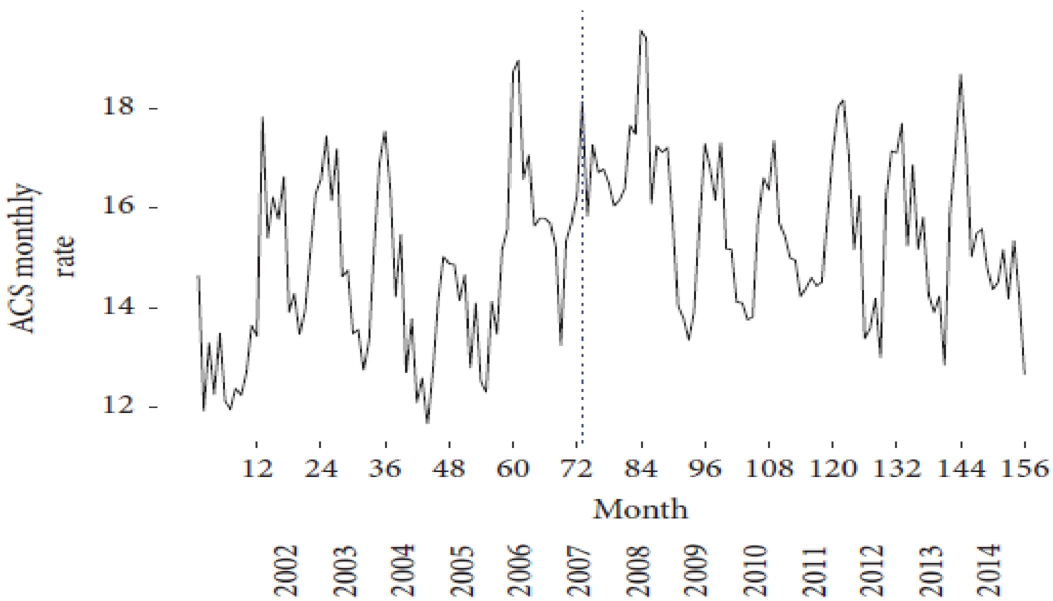

Figure 1: Longitudinal trends for overall monthly crude rates (per 100000 adult population) of ACS admissions from January 2002 to December 2014. Pre-legislation and post-legislation periods.

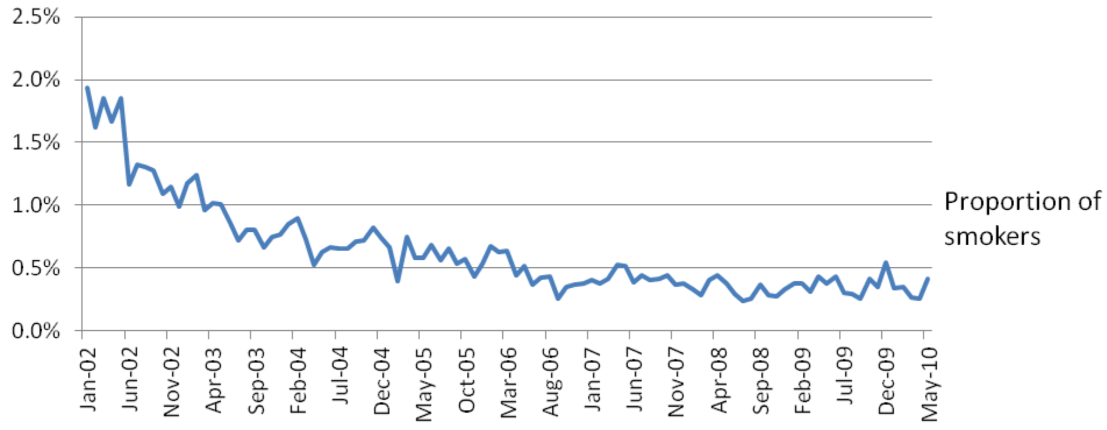

Figure 2: Proportion of ACS patients that are current smokers.

Table 1: Results of multivariate linear regression analyses to detect association between smoke-free legislation and monthly crude rates of ACS admissions per 100000

	Pre-legislation trend (change per month)	Change in trend in post-legislation period compared to pre-legislation	Post-legislation trend (change per month)
Overall			
β *	0.004	-0.006	-0.0018
IC for β	0.0029;0.0055	p-value<0.001	-0.0033;-0.0004
yearly change %	3.84	-5.76	-1.73
Males			
B*	0.0034	-0.0046	-0.0012
IC for β*	0.0021;0.0047	p-value=0.0002	-0.0028;0.0004
yearly change %	3.26	-4.80	-1.15
Females			
B*	0.0017	-0.0033	-0.0016
IC for β	0.0008;0.0023	p-value=0.0002	-0.0027;-0.0004
yearly change %	1.63	-3.17	-1.54
Age ≥65			
B*	0.0016	-0.01352	-0.0119
IC for β	-0.0018;0.0051	p-value<0.001	-0.01625;-0.0075
yearly change %	1.54	-12.98	-11.42
Age<65			
B*	0.0011	-0.0052	-0.0483
IC for β	0.0008;0.0014	p-value=0.2692	-0.1573;0.0607
yearly change %	1.06	-4.99	-4.64

CARDIOVASCULAR DISEASE AND HIGH BLOOD PRESSURE TREND ANALYSES FROM 2002 TO 2016: AFTER THE IMPLEMENTATION OF A SALT REDUCTION STRATEGY

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Abstract

Background

Cardiovascular disease (CVD) is the leading cause of death around the world; however, many CVD events could be prevented if we focused on modification of the main risk factors. Increased salt consumption is estimated to have caused millions of deaths, mostly related to CVD, particularly stroke, which is the leading cause of death in Portugal.

In our study, we aim to assess trends in the proportion of high blood pressure (HBP) in Acute Coronary Syndrome (ACS) patients as well as the trends in stroke and ACS in Portugal, especially after a set of public health initiatives were implemented to reduce salt intake.

Methods

The monthly proportion of ACS patients presenting with previously diagnosed HBP and the monthly rate of CVD admissions into public hospitals in Portugal were calculated. CVD rates were stratified into ACS rate and stroke rates. Data were stratified by demographics variables. An interrupted time-series model was used to assess changes over time.

Results

Breakpoint analysis revealed an estimated breakpoint around the year 2013 for the proportion of HBP patients, the following year there was a decreasing trend, however it was not significant. Analyses showed the trend before 2013 was increasing and started to decrease after this year. This decreased in proportion of HBP patients can be translated into a reduction of 555 people per year presenting with HBP in the ACS population. We analysed trends for ACS and stroke and tested the significance for a breakpoint in the year 2013. Although none of the remaining trends were significant for ACS crude rates and stroke crude rate, a decreasing trend was observed.

Conclusions

This research provides an indication about the impact a population-wide approach to CVD risk factors has on CVD trends themselves. Our results suggest that population-wide approaches can have an impact on the prevention and improvement of CVD control, reducing the number of CVD events, and eventually reducing premature death by CVD. As more restrictions on salt intake are being planned in Portugal in the next years, it is highly relevant to assess what is the current panorama and what further reductions we can expect.

Background

Cardiovascular disease (CVD) is the leading cause of death around the world (1). An estimated 4 million people in Europe die by CVD annually(26). However, many of the CVD events could be prevented if we focused on modification of the main risk factors (6).

In 2010, high blood pressure (HBP) was the leading risk factor contributing to global disease burden, accounting for more than 15% of all health loss in adults (169), and responsible for 62% of all strokes and 49% of ACS events (170). Although sodium is an essential nutrient necessary for maintenance of plasma volume, acid-base balance, transmission of nerve impulses, and normal cell function (171), current salt consumption is much greater than needed for survival, creating an overload on the metabolic system (80). This overload can increase blood pressure (BP) (62). Increased salt consumption is estimated to have caused millions of deaths, mostly related to CVD, particularly stroke, which is the leading cause of death in Portugal (2), being one of the countries with the highest mortality rates by stroke among the Western countries (21). The high prevalence of HBP is pointed to as one of the main reasons.

Implementing both population-wide and high-risk approaches to reduce blood pressure seems almost inevitable due to the large burden of HBP (13, 27). Even small reductions of HBP prevalence in the population could lead to great health gains. Knowing the importance of these approaches, the World Health Organization (WHO) created a set of recommendations to reduce dietary salt to five g/day, in order to prevent chronic disease and improve health (18). In the European Union, 26 out of the 53 Member States, including Portugal, implemented operational salt reduction policies including laws aiming to reduce salt intake. Recent reports have shown that salt consumption in Portugal has been declining in recent decades to a minimum of 7.3 g/day in 2016 (79). Prospective studies have shown that reducing salt intake can lead to reductions in blood pressure and, eventually, to a reduction in CVD events (172).

By 2010 a set of public health initiatives were implemented in Portugal, namely a reduction in salt added to bread and mandatory salt labelling in pre-packed food. As these initiatives are meant to reduce salt intake we hypothesized that it could lead to a reduction in the proportion of HBP and CVD, namely ACS and stroke. Therefore in our study, we aim to assess the trends in the proportion of HBP in ACS patients, as well as the trends in stroke and ACS in the country, before and after these initiatives were applied. For the sake of clarity in our study we refer as salt for all sodium data.

Methods

Study Population

Two population sets were used in this study. Approval to access data was obtained previously. For both sets of data, participants included in the study were over 20 years old.

First population dataset

The National Registry of Acute Coronary Syndrome (NRACS)(167). All data from 2002 to 2015 were extracted for our study. This dataset was used to obtain the proportion of ACS patients previously diagnosed with HBP. This register collects information for ACS only, not just for risk factors but also demographics.

This dataset has the advantage of being integrated into the Euro Heart Survey platform and, consequently, uses the Cardiology Audit and Registration Data Standards (CARDS) system. This system ensures that credible and comparable information is collected in several European countries over time as they use standardised information, both in terms of the definition and coding of variables, and in the form of measurement and collection of data. As this data is validated and standardised, it can be applied to and used to validate analyses in other larger populations, thus being able to obtain more robust results (93). HBP in this dataset was defined as previously diagnosed by a physician, or known blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic on two or more occasions.

Second population dataset

The National database that collects data from all admissions into Portuguese public hospitals (Mainland Portugal). Data from 2002 to 2016 were extracted for our study. This database uses the Diagnosis Related Group (DRG) system holding data on primary diagnosis and some demographic variables, such as sex and age, as well as the geographic region of admission (90). DRG codes for ischemic and haemorrhagic stroke were included in the analysis (ICD 9^{th} codes for stroke: 43301, 43321, 43311, 43331, 43391, 43401, 43411, 43491, 431, 432, 4320, 4321, 4329, and 43381) as well as codes for ACS (ICD 9^{th} codes: 410.00–410.xx to identify admissions diagnosed as Acute Myocardial Infarction and code 4130 to identify unstable angina).

The two datasets were analysed separately as there is no possible method to identify the participants in the dataset, thus the same participant can in fact be registered in both datasets, however as the outcomes studied are independent from each other we do not expect this fact to influence on the validity of the analysis. Similarly the fact that the two datasets used in our study are carefully monitored by the Portuguese Society

of Cardiology, in the case of the NRACS, and the Directorate of General Health, in the case of the DRG data, ensures the validity of these data.

Statistical analysis

Two main outcomes were analysed in our study, the monthly proportion of ACS patients presenting with previously diagnosed HBP and the monthly rate of CVD admission into public hospitals in the country. CVD rates were stratified into ACS rate and stroke rates.

The proportion of ACS patients with HBP was obtained by dividing the number of monthly HBP diagnoses by the total ACS patients registered for month.

We applied an interrupted time series design, implementing a segmented multiple linear regression model, in which the response variable was the monthly the proportion of ACS patients with HBP. These models are useful when the relationship between the response and the independent variables are piecewise linear, namely represented by two or more straight lines connected at unknown values, which are usually referred to as breakpoints. In our case, the breakpoint would be expected for any given year where there was a change in the trend of the proportion of patients with HBP.

R “segmented” package was used to determine the presence of any breakpoints in the trends found.

Crude event rates for ACS and stroke (per 100,000 adults) were computed for each month, using the population of the country, restricted to the population resident in mainland Portugal, with ages over 20 years as the denominator. Crude rates were calculated as the number of events, for each outcome separately, divided by the Portuguese population for that month.

As the effect of this type of population wide approaches might not be immediate(173-174), taking some time to show effects in the population, we used the estimated breakpoint from the monthly proportion of ACS patients with HBP as a proxy for the effect of the estimated breakpoint in CVD trends.

The impact of the breakpoint estimated on the CVD trends, was assessed through a multiple linear regression model using standard methods for interrupted time series.

We included one dichotomous variable that accounted for the main effect on hospital admissions of the estimated breakpoint for the proportion of HBP patients and an interaction between the breakpoint estimated and time, to evaluate changes over time following the breakpoint.

This model was implemented in order to test whether there was a significant change in the number of events, and if there was any change in the proportion of HBP patients was observed.

A month indicator covariable was introduced to adjust for seasonality in the outcomes admissions.
All analyses were stratified by sex and age. Age was grouped into two categories < 65 and ≥ 65 years old. Autocorrelation between month estimates was incorporated adequately into the model, with the presence of short term autocorrelation applying a first order autoregressive - AR (1) - structure to the residuals. Models were fitted in R version 2.3.2 software.
Statistical significance was assessed through p-values, assuming < 5% as significant and 95% confidence intervals (CI) were calculated for each of the regression coefficients.

Results

A total of 43,271 ACS events were registered in the NRACS over the last 14 years. The proportion of males presenting with ACS has been consistently higher than women, with around 69% of ACS events occurring in males. Mean age through the years of study has also been fairly steady, ranging from 65 to 66 years old (Table 1). Male/female ratio for HBP patients (Figure 1) has also remained fairly steady through the years in the ACS population.
The proportions of patients with HBP ranged from a minimum proportion of 50.0% to a maximum of 79.2%.
Breakpoint analysis revealed an estimated breakpoint around the year 2013 for the proportion of HBP patients (Figure 2), the year after there is a decreasing trend, however it was not significant (p-value = 0.832). Analyses showed the trend before 2013 was, in fact, increasing and started to decrease after this year (β_{before} = 0.009, CI: 0.007, 0.011; β_{after} = -0.003, CI: -0.037, 0.0302). Although zero is present in the CI for the slope after 2013, the change between both slopes (before and after 2013) is negative with a decrease of -0.012 in the monthly proportion. Thus, the decrease estimated after 2013 is higher than the increase estimated before 2013. This decrease in proportion can be translated into a reduction of 555 people per year presenting with HBP in the ACS population (Table 2).
Figure 3 displays the frequency of ACS and stroke admissions from 2002 to 2016. A total of 115 public hospitals from mainland Portugal registered ACS admissions from 2002 to 2016 and 122 registered stroke admissions. A maximum age of 99 years old was found in the database and the majority of admissions were for both ACS and stroke.
We analysed trends for ACS and stroke and tested the significance for a breakpoint in the year 2013.

Although none of the remaining trends were significant (Table 2) for ACS crude rates (β = -0.057, CI: - 0.154, 0.039) and stroke crude rate (β = -0.049, CI: -0.128, 0.029), a decreasing trend can be observed.

When further stratified data by sex and age, although no significant trends were observed, a decreasing trend for ACS was found in women but not in men. The largest decrease was found for people over 65 years old for both outcomes. Nevertheless, all these results should be interpreted with caution as none of the coefficients were significant (p-values > 5%), and zero was always included in the confidence interval.

The seasonal pattern observed for ACS and stroke was consistent with that reported elsewhere (100), with higher rates of admission over winter, and lower rates during the summer (Figure 3).

Discussion

Our results showed increasing trends in the proportion of HBP comorbidity in the ACS population until 2013, the following years the trends appear to decrease. This year was used as a breakpoint to test for differences in trends for ACS and stroke. Decreasing trends for both outcomes were also found, but were not significant.

Although our results were not statistically significant, and thus must be interpreted with caution, it is encouraging to find decreasing trends, especially in the proportion of HBP patients in the ACS population, with a reduction of nearly 600 people per year, after the implementation of a major public health measure that was meant to reduce salt intake.

Even a small reduction in the proportion of HBP in the ACS population, as the one observed in our study of 555 persons per year achieved through a population-wide approach, can have huge impacts (66, 131). This impacts has effectively slowed down the development of atherosclerosis in young people, thereby reducing the likelihood of future epidemics of CVD (132).

The decreasing trend for ACS was observed for women but not in men, in fact salt intake have been previously link to higher risk of CV events in women but not in men(61), more particularly studies have found that women could benefit more, concerning stroke reduction, from dietary salt reduction than men(133).

As salt sensitivity is known to be greater in the elderly we hypothesized that if the salt reduction law could have some effect it would be greater for the elderly (22, 134). In fact our results suggest a decreasing trend for all outcomes in the older group.

Results from this type of population-wide approach were seen in the UK, where salt reduction campaigns showed significant results, achieving a 15% salt reduction from 2003 to 2011, which translated into about 6000 fewer deaths from CVD, saving about 1.5 billion pounds a year (62).

The decreasing trends for all of our outcomes was not as great as we expected, however the fact that the starting of the decrease takes place after the implementation of these approaches, and the trend of HBP in ACS patients was steadily increasing before that, supports our hypothesis that this approach of reducing salt in bread and making pre-packed salt labelling mandatory can influence HBP prevalence in ACS patients as well as CVD trends.

The fact that, salt intake levels have been decreasing in Portugal to the most recent value of 7.3 g/day in 2016 (79) also supports our hypothesis of the potentially effect of the regulation applied in the country. Although this value was obtained by a 24 hour dietary recall questionnaire, these values were validated against urinary sodium excretion(135) for a sub-sample of 100 subjects and the values were highly correlated

In addition, BP levels have been declining in the Portuguese population, from a mean BP of 134.7/80.5 mmHg in 2003 (136) to a mean BP of 127/74.6 mmHg in 2012 (21).

Furthermore, several studies showed that bread is one important source of salt in Portugal (80), and contributes to about one-sixth of daily salt intake (80). Results from the National Food, Nutrition and Physical Activity Survey suggest most of the salt consumed by the population comes directly from bread and toast, charcuterie products, and soups (79). It was all this evidence that led to the creation of the regulation to reduce salt in bread to a minimum of 1.4 g of salt per 100 g of final product (85) and mandatory labelling for pre-packed products stating clearly the salt content of the product. Portugal was, thus, the first western country to create a law for the clear definition of the quantity of salt contained in bread.

Besides the legislation in 2010, several initiatives have been carried in Portugal to reduce salt intake, such as: electronic tools, such as websites included in the National Program for the Promotion of Healthy Eating, to free distribution of books and brochures, by the creation of an animated series, and the creation of the National Food, Nutrition and Physical Activity Survey, aiming to collect nationwide data on dietary intake and physical activity (79).

There is already evidence that reducing salt intake could reduce BP in the Portuguese population. One community intervention trial conducted in Portugal demonstrated that reducing salt intake in an entire village, including cooking and processed food, led to a significant reduction in the BP of the population (137).

Policy interventions to reduce national sodium consumption have demonstrated to be highly cost effective in nearly every country in the world. These interventions could reduce millions of disability adjusted life years at low cost and be more cost-effective than pharmacological interventions (64, 133).

Policy and system changes are critical to reduce HBP in populations, including legislation and public education to reduce dietary sodium and food pricing policies, to support prevention and management of CVD (138).

Alternative public health approaches, such as reducing salt in processed foods and bread, and labelling of processed food along with the use of multiple fiscal and educational policies, have already been proposed by the WHO as the first-line approach for CVD reduction, when implemented on a wide scale (132, 138).

In spite of several efforts being made in the country to reduce salt intake, there is still room for improvement, namely in food labelling (139), adjusting it to the level of health literacy in the country. Once the level of health literacy in Portugal was slightly lower than the rest of European countries (140), this might have prevented the population from fully benefiting from the labelling, as the interpretation of salt content in each food can be difficult.

Simpler labelling systems already exist in other countries, such as labels that rely on the use of front-of-pack information such as logos with information on the overall healthiness of the food and traffic light and colour coding systems, which might help citizens make healthier choices. Countries such as Finland and the UK have already implemented some of these labelling systems. In Finland, food products with salt contents below the designated levels display a low-salt label to emphasise their lower-than-conventional salt levels (20). In the UK, a traffic light system to distinguish between high, medium, and low salt content in food products was implemented. These strategies proved to be efficient in reducing salt intake in the population (141). The traffic light labelling system has been proposed by the Portuguese Hypertension Society to help the population choose products regardless of their level of literacy.

More restrictions are being planned in Portugal to further reduce salt intake, such as a taxes on products with more than 1g of salt per 100g of finished product such as: pre-packaged crackers and biscuits; pre-packaged cereal flakes and pressed cereals; and pre-packaged, dehydrated potato chips. A rate of 0.80 Euros per kilogram of finished product will be applied to these products.

On the other hand, further reduction of salt content in bread, to a minimum of one g per 100 g of final product, was proposed to be achieved by 2020, with continuous reductions each year after 2018.

Our study presents encouraging indications suggesting there have been reductions in the proportion of hypertensives among ACS patients after 2013, along with an annual decrease in the rates of ACS and stroke.

Limitations

However, we recognise some limitations of the study. Like any ecological study, it is not possible to prove causal relations, i.e. direct association between the initiatives to reduce salt implement in the country the reduction observed in the proportion of hypertensives ACS patients. However, our methodology was applied, using the same data to analyse the effects of the smoking ban legislation on ACS trends, and a significant reduction was found right after the ban (154).

On the other hand, it might be too soon to notice great effects from salt reduction on CVD trends.

The fact that until 2013, the trend for the proportion of hypertensives was continuously increasing, and right after 2013 a decrease in trend can be observed, suggests that the lack of statistical significance could result from the time period being analysed being too short to capture further reductions.

Moreover, our study has some strengths, such as the fact that we used two well validated and standardised databases is a major strength as this allows for an easy comparison with other international studies mainly those developed in other European countries. As well as the availability of information on gender and age, this allowed us to assess the robustness of our findings among different subgroups. Also the time series method is preferred over the simpler pre- and post-proportion comparison method that does not take the pre-intervention trend into account, and also allows correction for autocorrelation (130).

Conclusions

In conclusion, the fact that we found decreasing trends for both HBP in ACS patients and CVD outcomes after major initiatives to reduce salt intake were implemented in the country, suggests that this type of approaches, although hard to measure, can impact the trends of major public health outcomes. Thus, this research is relevant to the public health community because it provides an indication about the impact that a population-wide approaches can have on CVD risk factors, and CVD trends themselves. Our results suggest that population-wide approaches can have an impact on the prevention and improvement of CVD control, reducing the number of CVD events and eventually reducing premature death, morbidity, and disability by CVD. Our study also highlights the importance of measuring the impact of these types of initiatives. These findings stress the need for public health policy in CVD to improve the health of populations addressing, in the first place, the well identified risk factors for CVD.

Undoubtedly, more studies are needed to assess the impact of such measures, not only for other diseases beside CVD, but also adding more years to the study would

allow analysis of long terms effects of the public health initiatives. On the other hand, as more restrictions on salt intake are being planned in Portugal, in the next years it is very relevant to assess what is the current panorama and what further reductions we can expect.

Declarations

Ethics approval and consent to participate

Approval to access data was obtained previously from the Minister of Health Office and the Portuguese Society of Cardiology. Ethics approval and consent to participate are not applicable to this study.

Availability of data and materials

The data that support the findings of this study are available from the Minister of Health Office, (email: geral@acss.min-saude.pt) for the DRG data. Data from the National Registry of ACS can be requested from the Portuguese Society of Cardiology (sandra.corker@spc.pt). However restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission from both the Minister of Health Office and the Portuguese Society of Cardiology.

Acknowledgements

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Figures and Tables

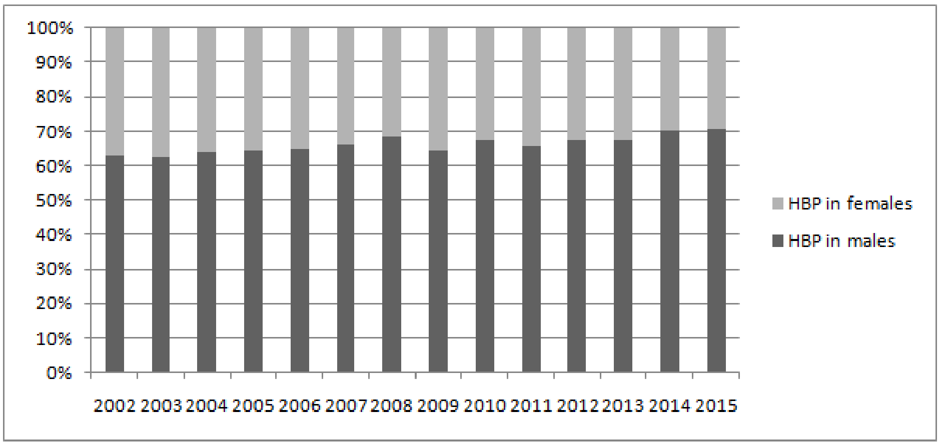

Figure 1: Proportion of patients with HBP in the ACS population. Female/male ratio from years 2002 to 2015.

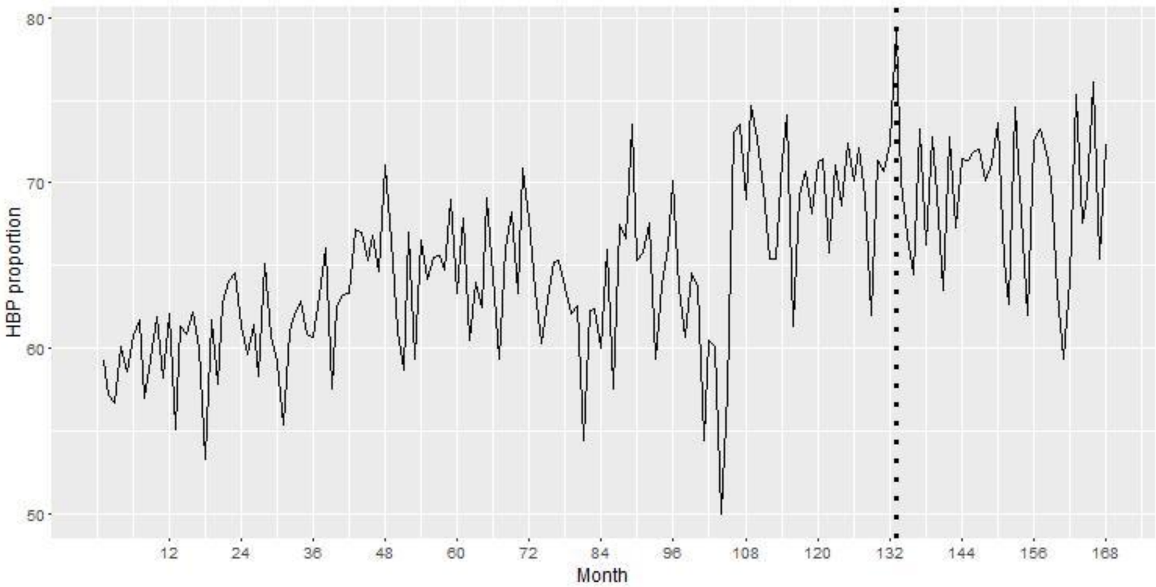

Figure 2: Trends in overall monthly proportion of HBP in ACS patients from January 2002 to December 2015. The dashed line marks year 2013.

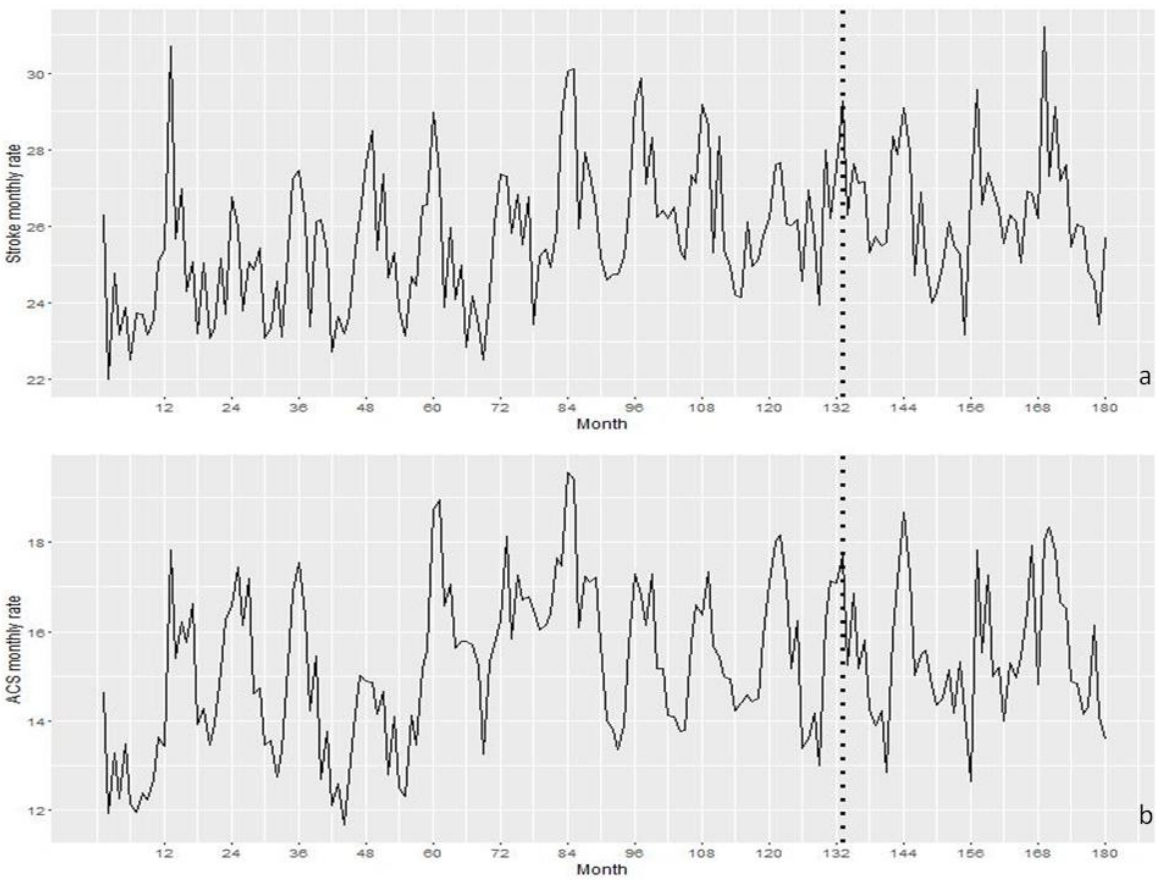

Figure 3: Trends in overall monthly crude rates of CV admissions from January 2002 to December 2016 per 100000 adults. For both panels the dashed line marks year 2013. a) Trends for stroke crude rates admissions. b) Trends for ACS crude rates admissions.

Table 1: Results from segmented multiple linear regression for the proportion of HBP patients and standard multiple linear regression analyses for CVD outcomes

	β (CI)	t-value	p-value
HBP proportion			
Overall*			
Pre-breakpoint trend (change per month)	0.004(0.003;0.006)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.006	-	<0.001
Post-breakpoint trend (change per month)	-0.002(-0.003;-0.001)	-	-
Male*			
Pre-breakpoint trend (change per month)	-0.003(-0.022;0.022)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.016	-	0.215
Post-breakpoint trend (change per month)	-0.019(-0.061;0.023)	-	-
Female*			
Pre-breakpoint trend (change per month)	-0.003(-0.028;0.022)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.016	-	0.215
Post-breakpoint trend (change per month)	-0.018(-0.052;0.014)	-	-
Age<65*			
Pre-breakpoint trend (change per month)	-0.022(-0.798;0.754)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	0.011	-	>0.05
Post-breakpoint trend (change per month)	-0.011(-0.039;0.017)	-	-
Age≥65*			
Pre-breakpoint trend (change per month)	0.029(-0.017;0.075)	-	-
Change in trend (post-breakpoint vs pre-breakpoint)	-0.018	-	>0.05
Post-breakpoint trend (change per month)	0.011(-0.017;0.039)	-	-
ACS crude rates (per 100000 adults)			
Overall*			
Time of the breakpoint	-0.112(-2.041;1.817)	-0.114	0.909
Time of the breakpoint* time interaction	-0.031(-0.09;0.036)	-0.903	0.368
Male*			
Time of the breakpoint	0.289(-2.269;2.848)	0.222	0.825
Time of the breakpoint* time interaction	-0.018(-0.108;0.072)	-0.393	0.695
Female*			
Time of the breakpoint	-0.497(-1.927;0.932)	-0.682	0.496
Time of the breakpoint* time interaction	0.013(-0.034;0.060)	0.560	0.576
Age<65*			
Time of the breakpoint	0.151(-0.723;1.024)	0.338	0.736
Time of the breakpoint* time interaction	-0.015(-0.044;0.015)	-0.986	0.325
Age≥65*			
Time of the breakpoint	0.151(-5.159;6.721)	0.258	0.7970
Time of the breakpoint* time interaction	-0.015(-0.358;0.066)	-1.349	0.1792
Stroke crude rates (per 100000 adults)			
Overall*			
Time of the breakpoint	0.265(-1.399;1.929)	0.312	0.755
Time of the breakpoint* time interaction	-0.037(-0.091;0.016)	-1.370	0.172
Male*			

Time of the breakpoint	0.900(-0.743;2.543)	1.074	0.284
Time of the breakpoint* time interaction	-0.022(-0.074;0.030)	-0.822	0.412
Female*			
Time of the breakpoint	0.999(-1.204;3.202)	0.888	0.376
Time of the breakpoint* time interaction	-0.047(-0.121;0.027)	-1.244	0.215
Age<65*			
Time of the breakpoint	0.448(-0.261;1.157)	1.238	0.217
Time of the breakpoint* time interaction	-0.014(-0.037;0.009)	-1.207	0.229
Age≥65*			
Time of the breakpoint	2.548(-5.351;10.446)	0.632	0.528
Time of the breakpoint* time interaction	-0.238(-0.502;0.026)	-1.764	0.079

*All models were adjusted for seasonality.
Values not presented in the table (-) are not available for the type of regression
β represents the coefficients in the regression

TRENDS OF CASE-FATALITY RATE BY ACS IN PORTUGAL: IMPACT OF A FAST-TRACK TO THE CORONARY UNIT

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Abstract

Introduction

Efforts were made to improve management of coronary disease as the fast-track system (FTS) to the Coronary Unit. We aim to analyse case-fatality rates by Acute Coronary Syndrome (ACS) in Portugal from 2000-2016, mainly the impact of the FTS and the proportion of patients that activate the FTS.

Methods

We analysed monthly ACS case-fatality before and after the implementation of the FTS in 2007. Impact of the system was assessed through regression models for interrupted time-series. We calculated annual proportion of FTS admissions.

Results

After 2007 case-fatality by ACS decreased($\beta=-1.27$,p-value<0.01). Comparison of rates between hospitals with vs without FTS indicated lower rate for hospitals with FTS. The highest percentage of patients admitted through the FTS was 35%.

Conclusions

FTS contributed to a decline in ACS case-fatality. However, more than half of patients were not admitted through the system. This should encourage health authorities to make efforts to ensure compliance.

Introduction

Cardiovascular Disease (CVD) is the leading cause of death in Europe and the most common cause of death in Portugal(2). It is estimated that by 2030, ischemic heart disease will be the third leading cause of death worldwide(3). Despite recent decreases in mortality rates in many countries, CVD is still responsible of almost half of all deaths in Europe(4), constituting a major public health challenge in Western Europe(5).

Although Coronary Herat Disease (CHD) mortality rates have been declining since the 1980s in Portugal, more steeply after the mid-1990s, particularly among women(142) and across the EU, there is evidence of a consistent pattern of recent plateaus in CHD mortality rates(7).

The observed reduction in CDV mortality in the last decades, albeit at a low rate, is the result of a set of changes from efforts made by most European countries in disease prevention, tackling mainly risk factors, and of the improvements in disease management and treatment.

Particularly in Portugal, several improvements in CHD management have been made, with improvements in the availability of drug treatments and, more importantly, in the easiest and fastest access to reperfusion and revascularisation interventions(7).

The evidence-based effectiveness of the health policies is increasing, and we have realised that a variety of policy- and practice-related measures will be necessary to effectively reduce CVD prevalence and mortality as well as to promote changes in the healthcare system.

Thus, it is important to assess the relative contribution of these underlying factors to the observed decline in CHD mortality in different settings to develop future health policies.

In Portugal, several policies have been implemented that could impact mortality rates by ACS, from polices more focusing on disease prevention to policies more directly targeting mortality, such as the recent implementation of a fast-track system with direct admission to the CCU. There is, therefore, a growing consensus about the unmet need for health policy impact analysis(8).

As time is crucial in ACS, time is muscle, it is essential to create measures that can help reducing the time to treatment, thus reducing mortality and morbidity associated with ACS.

Although the fast-track system was implemented in Portugal to reduce the time to CCU, recent studies have shown a small proportion of patients activating the system. Therefore, we analysed the impact of a fast-track system to CCU (via verde coronária in Portuguese) in case fatality rates by ACS in Portugal from 2000 to 2016, even when a small proportion of patients activated the system.

Material and Methods

Data

Data were obtained from the Diagnosis Related Group (DRG) National Database, which collects data from all admissions into Portuguese public hospitals (Mainland Portugal), storing data on primary diagnosis and some demographic variables such as sex and age, as well as the geographic region of the admission(90).

Approval to access data was obtained previously from the Minister of Health Office and the Portuguese Society of Cardiology.

All admission cases from 2002 to 2016 were extracted, and only participants aged 20 and over, with primary diagnosis of ACS coded in ICD 9 (international classification of disease, 9th revision) as 410.00-410.xx to identify admission diagnosis of Acute Myocardial Infarction (AMI) and 4130 codes, to identify unstable angina, were analysed.

A second population dataset was used from the National Registry of Acute Coronary Syndrome (NRACS)(167), and for our study, we extracted all data from 2002 to 2015. This dataset was used to obtain the proportion of ACS patients that were admitted into the hospital through the fast-track system. We used number of STEMI patients to compute the proportions of patients activating the fast track system, once the system was mainly directed to STEMI. STEMI are frequently more symptomatic and the fast track is a patient initiated process, thus patients with NSTEMI are less likely to activate the fast track system.

This dataset has the advantage of being integrated into the Euro Heart Survey platform and, consequently, uses the Cardiology Audit and Registration Data Standards (CARDS) system, which ensures that credible and comparable information is collected in several European countries over time as they use standardised information, both in terms of the definition and coding of variables and in the form of data measurement and collection. As the data is validated and standardised, this allows for the possibility of applying and validating analyses in other larger populations, thus obtaining more robust results(93).

The fast-track system was implemented in all regions of Portugal in 2007, providing seven years of data before the implementation of the regulation (January 2000 through December 2007) and nine years of data after the regulation was implemented (January 2008 through December 2016).

The unit of analysis was monthly deaths by ACS.

Fast track to CCU

The fast-track system was implemented in Portugal with the goal of creating a priority system and facilitated access to clinical, therapeutic and complementary diagnostic resources. Direct admission into the CCU is essential not only to improve accessibility, but also to allow a more effective treatment, since the time between the onset of symptoms and treatment is, in the case of AMI, vital for the reduction of morbidity and mortality. The system is initiated by the patients when calling the emergency number (112). The National Institute of Medical Emergency (INEM) initiates the diagnosis and treatment earlier while referring the person to a hospital unit specialising in ACS treatment(46).

The INEM has the capacity to intervene prematurely, and after the clinical diagnosis and the electrocardiogram, if the diagnosis is established, decides jointly with the Urgent Care Counselling Center (CODU) on the pre-hospital treatment as well as on the referral to hospitals, increasing the likelihood of therapeutic success. The CODU contacts the hospital unit in order to take the necessary steps for the admission and treatment of the patient(47). The system was first implemented as a pilot project in the Algarve region of the country in 2002, but only by 2007, it was implemented as a policy throughout Mainland Portugal(48).

Statistical analysis

The main outcome in our study was monthly case fatality rate, later stratified by age and sex, which were obtained using data from ACS patients admitted into public hospitals in the country. All missing data was removed from all the analysis.

The ACS case fatality rate was computed for each month, using the total of patients admitted into public hospital as the denominator and the number of ACS deaths as the numerator.

The impact of the breakpoint estimated for the impact of the fast-track implementation on ACS case fatality rate was assessed through multiple linear regression models, using standard methods for interrupted time-series. We included one dichotomous variable that accounted for the main effect on ACS case fatality rate of the estimated breakpoint and an interaction between the breakpoint estimated and the time, to evaluate changes over time following the breakpoint.

The model was implemented to test whether there was a significant change in the number of ACS case fatality rates and if the fast track had any impact.

A month indicator covariable was introduced to adjust for seasonality in the outcome admissions.

All analyses were stratified by sex and age. Age was grouped into two categories, < 65 and ≥ 65 years old. Autocorrelation between month estimates was incorporated adequately into the model, with the presence of short-term autocorrelation, applying a first-order autoregressive - AR (1) - structure to the residuals.

As not all hospitals in mainland Portugal have the capacity to adopt the fast-track system because of a lack of human and technical resources, we also compared case fatality trends for hospitals with the fast-track system in place vs. hospitals with no such system. Generalised least squares regression was applied, with a dichotomous variable distinguishing hospitals with the fast-track system from those without such a system and a month indicator to account for seasonal variations.

We also calculated the total time from symptom onset to first medical contact (FMC). The time was then analysed through a generalised linear model, assuming a linear behaviour of time, using as covariates a dichotomous variable before and after the fast-track implementation, demographic variables (sex and age) and risk factors (smoking, hypertension, diabetes, dyslipidemia, obesity). The variable representing the use of the fast-track system was a "yes" or "no" categorical variable, which included fast-track admission vs. self-transportation and non-medical ambulance.

Although we are aware that there might be differences in case fatality rates according to the day of the week, weekend vs. week day, we did not adjust for that in our models since there are studies pointing to a steady reduction in CVD for both weekends and weekdays(175). There are also studies showing that after accounting for mode of arrival at hospital, there are no differences in case fatality rates between weekdays or weekends(176).

Using data from the NRACS, we computed the monthly proportion of patients with ACS, namely STEMI diagnosis, that were admitted into the hospital through the fast-track system, divided by the total number of patients admitted into the hospitals.

Statistical significance was assessed through p-values, assuming < 5% as significant, and 95% confidence intervals (CI) were calculated for each of the regression coefficients.

Models were fitted in R version 2.3.2 software.

Results

A total of 20,849 in-hospital deaths by ACS were registered in the country (Mainland Portugal) from 2000 to 2016, out of a total of 203,040 ACS admissions.

We assessed monthly case fatality rates by ACS for the period of 2000 to 2016, and our results show a decline in the number of registered deaths for the period studied. After the year of the implementation of the fast-track system in 2007, the year used as

a breakpoint in the model created (Fig. 1), there was a steep decrease in case-fatality rate, although there was no significant differences from the rate observed in the period before thus the rate of the decline has remain steady throughout the last 15 years.

There was a significant change in level, i.e. a significant drop in ACS case-fatality rate (β = -1.268 p-value: <0.01) after the fast-track system implementation, representing an abrupt intervention effect(98).

Although the change in trend was not significant, i.e. there was not a significant decrease in the slope after the fast-track implementation, the fact that there was a significant change in level denotes a clear change in ACS case-fatality rate after 2007, on the other hand it also points out to the fact that the rates after have remain fairly similar to the rates of decline observed before the fast-track system.

We stratified the ACS case-fatality rate by sex, and the trends observed for the pre-system implementation and the post-system implementation were similar for both men and women (Fig. 2, Table 1).

For both men and women, there was a steep decrease after the system was implemented; however, as for the overall rate, the decreasing trends remained fairly steady. Although the immediate decrease was similar for men and women, the reduction in ACS case-fatality rate was more marked in women (β = -1.45, p-value = 0.01) than in men (β = 1.06, p-value = 0.01) (Fig. 2, Table 1).

Interestingly, the results for age stratification showed that for people under 65, there was an increasing trend in case fatality (β = 0.01, p-value = 0.01), although the value of the change trend was significant, it was in fact a minor increase, with less than 0.05%.

However, for patients aged 65 and over, the case fatality trend was also significant (β = 0.02, p-value = 0.02). For younger participants, although the increase trend was significant, it was a minor increase of less than 0.05%.

The seasonal pattern observed was consistent with that reported elsewhere(100), with higher rates of admission over winter and lower rates during the summer.

Analysis of the NRACS data allowed us to assess the actual proportion of patients that activated the fast-track system over time. Although the proportion of fast-track admission has been increasing over time it has only reached a maximum value of 38% in 2016, it has been a slow increase (Fig 3).

Furthermore, we compared the ACS case-fatality rate between hospitals with a fast-track system implemented and hospitals with no such system, as a proxy to compare case fatality rates, although we acknowledge the fact that hospitals with the fast-track system can still admit patients that reach the hospital by any other way of transportation. Our results indicate a significantly lower case-fatality rate for hospitals with the fast track system implemented (β = -0.67, p-value < 0.01; Fig. 4).

Mean time from symptom onset to FMC was also analysed. For patients admitted through the fast-track system, the mean time from symptom onset to FMC was 224.20 minutes, approximately 3 hours, while for patients that were not admitted through this system, mean time from symptom onset to FMC was 354 minutes, approximately 6 hours (Fig.5). When assessing the results from the multivariate regression (Table 1), time from symptom onset to FMC was significantly lower for participants admitted through the fast-track system, up to around 50 minutes less. Analysis of the demographics and risk factor covariates used in the model denoted that older people and women, as well as patients with diabetes and obesity, had longer delays. Surprisingly, smokers had lower times from symptom onset to FMC.

Discussion

Trends in mortality in mortality by AMI have been decreasing steadily in Europe. In Portugal mortality by ACS has been studied up to 2008 and showed around 3,760 fewer deaths in 2008 compared to the expected number if the rates observed in 1995 had persisted(142). More recently, a set of health policies tackling not only disease prevention, but also decrease in mortality, were implemented in the country, namely the fast-track system in 2007, the smoking ban in 2008 and a salt reduction regulation in mid-2010. Although in our study, we focused on the impact of the fast-track system on case-fatality rates, all these policies can affect CVD mortality.

Although CHD mortality rates in Portugal decreased by more than 25% between 1995 and 2008, we found a significant decrease immediately after the implementation of the fast-track system up to 2016. Although we cannot attribute this directly to the fast-track system, the reductions found up to 2008 were attributable to better care and treatments, explaining half of the overall decline in CHD deaths. Furthermore, by 2008, the fast track-system was already implemented, and also there was an increased in the number of centres with a catheterisation laboratory. Also, by 2008, approximately 42% of the decrease could be attributed to an improvement in major risk factors(142); therefore, regulations such as the smoking ban and mandatory salt reduction probably had a greater influence on mortality rates.

Our study also shows there was a steep decrease in case fatality rate the year of the implementation of the fast track however the rate of decline observed after that was similar to the years previous to the policy. This is most likely to low proportion of patients activating the system. By 2016 only a total of 38% of the STEMI patients have activated the system thus more than half of the patients are not beneficiating from the fast-track policy.

We found similar decreasing case-fatality rates for men and women, which has previously been observed in other studies where the rate of decrease in CHD mortality appeared to be stable across both sexes(7).
Surprisingly, our results for age stratification were not consistent with the overall case-fatality rate. Either for the youngest or older patients, we observed no immediate change in case-fatality rate after the fast-track system was implemented. For both groups, there were significant changes in trend; however, the trends observed were increasing. The prevalence of obesity and therefore diabetes(143) is in fact increasing in the country, which can be attenuating the reductions for the younger groups. This fact has also been observed in other studies(7, 144) where the increase of obesity led to lower decrements of mortality for the younger groups. A similar pattern was observed for the older group, which has already been found in other datasets and indicates that older persons benefit the least from the decline in CVD mortality(144). Other studies have also reported a persistently high case-fatality rate among the elderly(145).
Furthermore, when we compared ACS case-fatality rates between hospitals with a fast-track system implemented and hospitals without such a system, the rates were significantly different, and lower case-fatality rates were observed for hospitals that had the fast-track system. Although the trends were decreasing for both groups, hospitals with vs. hospitals without the system, the decrease was more accentuated in the group with the fast-track system. This kind of system allows earlier diagnosis and direct communication between the ambulance team and the CCU, bypassing the ER, thus minimising time to treatment, which leads to better prognosis and, consequently, less case fatality rates.
Previous studies have shown that minimising time to treatment using the fast-track system can directly lead to diminished case-fatality rates(146-147).
The observed mean time (3 hours), even for patients admitted through the fast-track system, was longer than the recommended time(44), which is 1.5 to 2 hours after symptom onset.
These type of results have already been reported in other studies where the average delay time from symptom onset to FMC remained at around 2 hours and did not decrease despite multiple public education campaigns(148).
A decrease of 50 minutes was observed for patients admitted through the fast-track system when compared to patients not admitted through this system, and similar reductions in time have been observed in other studies(149).
The variables affecting symptom onset to FMC were not surprising, as most were found in other studies and associated with longer delays

Although there is clear evidence, in our study as well as in previous studies, of the effectiveness of a fast-track system, more than half of the patients are not using this system. As this is a patient-initiated process, even when proven to be the best way of admission if patients and the community at risk do not have either sufficient health literacy to acknowledge their symptoms or the process is not widespread enough, the impacts of these health policies will not reach full capacity.

Moreover, Portugal was one of the countries to participate in a global initiative that aims to improve the delivery of facilities by increasing timely access to primary percutaneous coronary intervention, thus reducing mortality and morbidity in STEMI patients. The project was responsible for the launch of a national public campaign to raise public awareness of the symptoms of MI, among other objectives.

The OCDE recently revealed that the use of primary PCI increased dramatically in countries that had been participating in the “Stent for Life” initiative. In fact, 1 year after implementation of the initiative in Portugal, a positive impact was observed, with greater use of the 112 emergency call service and a smaller number of patients arriving by their own means at local hospitals without PCI facilities(150). This suggests that health campaigns, such as the “stent for life” campaign, can have an impact on the health community and the general community.

Limitations

Nonetheless, we recognise some limitations of the study. Like in any ecological study, it is not possible to directly prove the association between the implementation of the fast-track system and the reduction in case-fatality rate by ACS. In Portugal, considerable efforts have been made to improve patient care, thereby increasing patient awareness to symptoms and improving patient health. The implementation of a national smoking ban(154) and of a salt reduction regulation(85) might have affected the findings in our study, making this decrease in case-fatality rate a multifactor effect rather than a “one approach effect”. The fact that the decrease in case-fatality rate was observed after 2007 support our theory that fast-track system played a major role in this decrease, once the smoke ban and salt regulation were implemented after this year.

In addition, we compared case-fatality rates between hospitals with a fast-track system and hospitals without such as system. Although we could not distinguish the patients admitted through this system, we found significant differences in case-fatality rates between hospitals with vs. hospitals without this system.

One of the strengths of our study is the use of two well validated and standardised databases, allowing for an easy comparison with other international studies, mainly

those developed in other European countries. As well as the availability of information on gender and age, this allowed us to assess the robustness of our findings among different subgroups. Also, the time-series method is preferred over the simpler pre- and post-proportion comparison method, because it does not take the pre-intervention trend into account and also allows to correct for autocorrelation(130).

Conclusions

Our study extends the existing literature on the patterns of ACS mortality over time and allows assessing whether the current strategies to reduce mortality by ACS, namely policy interventions, are successful. Furthermore, our study suggests that policies such as the fast-track system are related to a decline in ACS case fatality, supporting the importance of this policy type in achieving health gains.

Considering that coronary heart disease is the number one cause of death in the Western world and as such constitutes an immense public health problem(6), even a small improvement in treatment and an increase in patient awareness can have important clinical, economic and social gains. On the other hand, our study showed that although the proportion of patients activating the fast-track system is increasing, more than half of the patients are not using the system. This highlights the importance of continuous education to the general community in terms of guideline adherence, regarding the importance of rapid reperfusion therapy, which can directly affect case-fatality rates. Although it is a learning curve, since the fast-track system is a patient-initiated process and thus, although the system is available, not all patients resort to it, as more evidence arises for the effectiveness of this type of policy, more investment should be applied into the education of the population.

Our results encourage legislators and public health authorities to make efforts to ensure compliance with the fast-track system, leading to a patient´s timely access to treatment and allowing better prognosis, thus reducing mortality and morbidity by ACS.

Figures and Tables

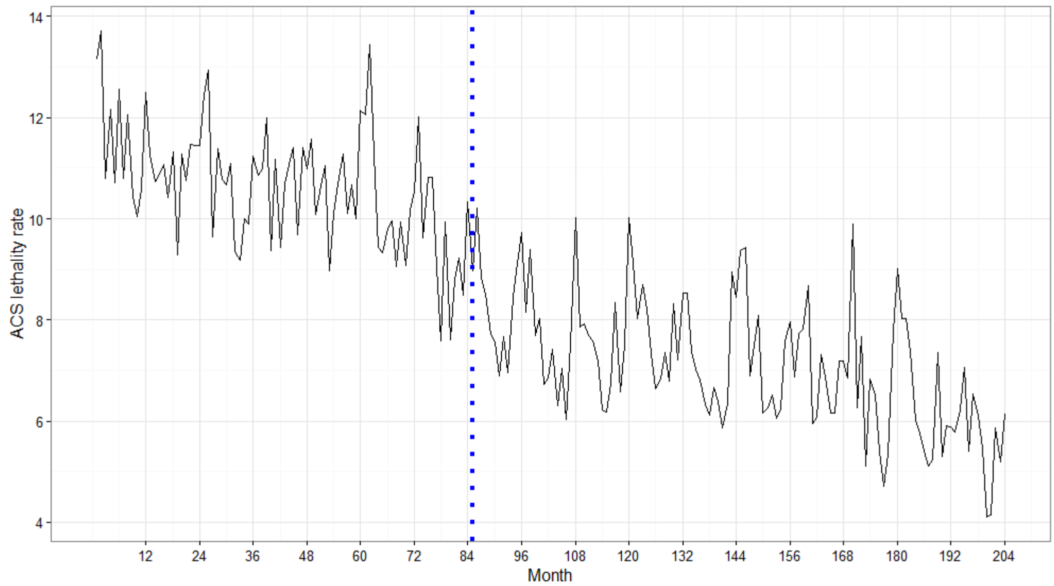

Figure 1: Longitudinal trends for case-fatality rate by ACS (percentage) from January 2000 to December 2016. The vertical line marks the year 2007 for the full implementation of the fast-track system in the entire country.

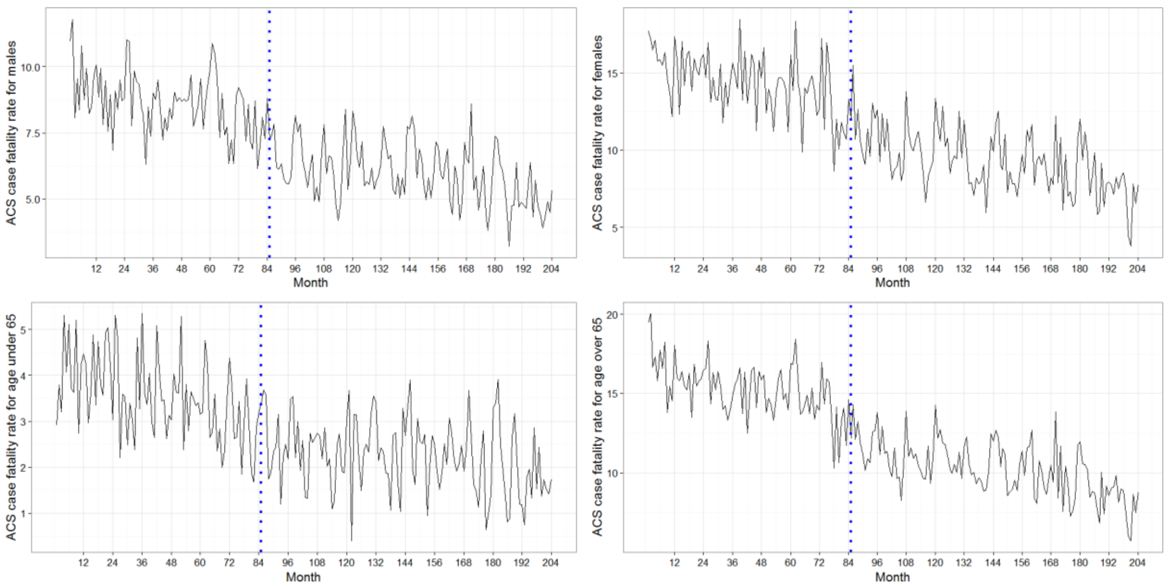

Figure 2: Stratified longitudinal trends for case-fatality rate by ACS (percentage) from January 2000 to December 2016. The vertical line marks the year 2007 for the full implementation of the fast-track system in the entire country. a) Longitudinal trends for males. b) Longitudinal trends for females. c) Longitudinal trends for patients under 65. d) Longitudinal trends for patients over 65.

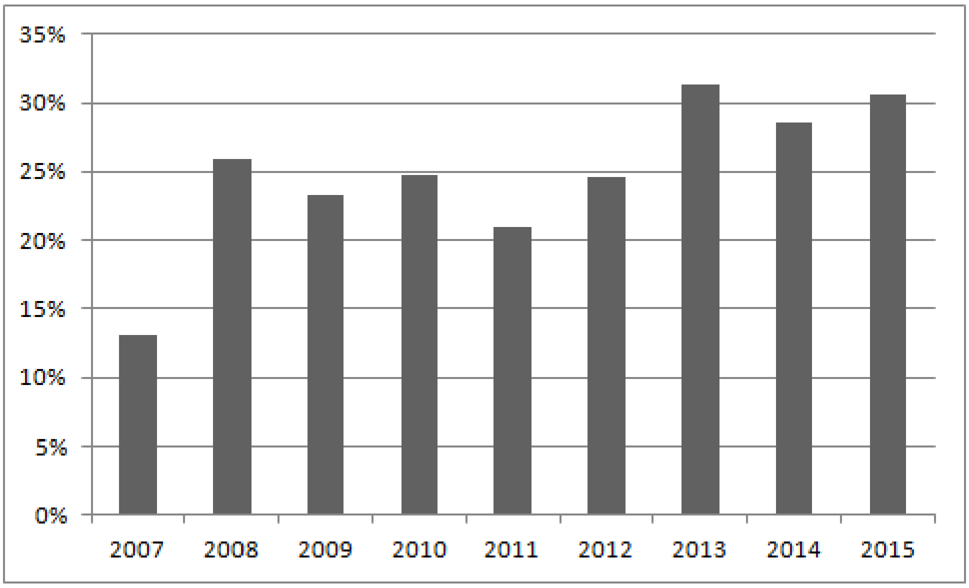

Figure 3: Percentage of annually STEMI patients admitted through the fast-track system.

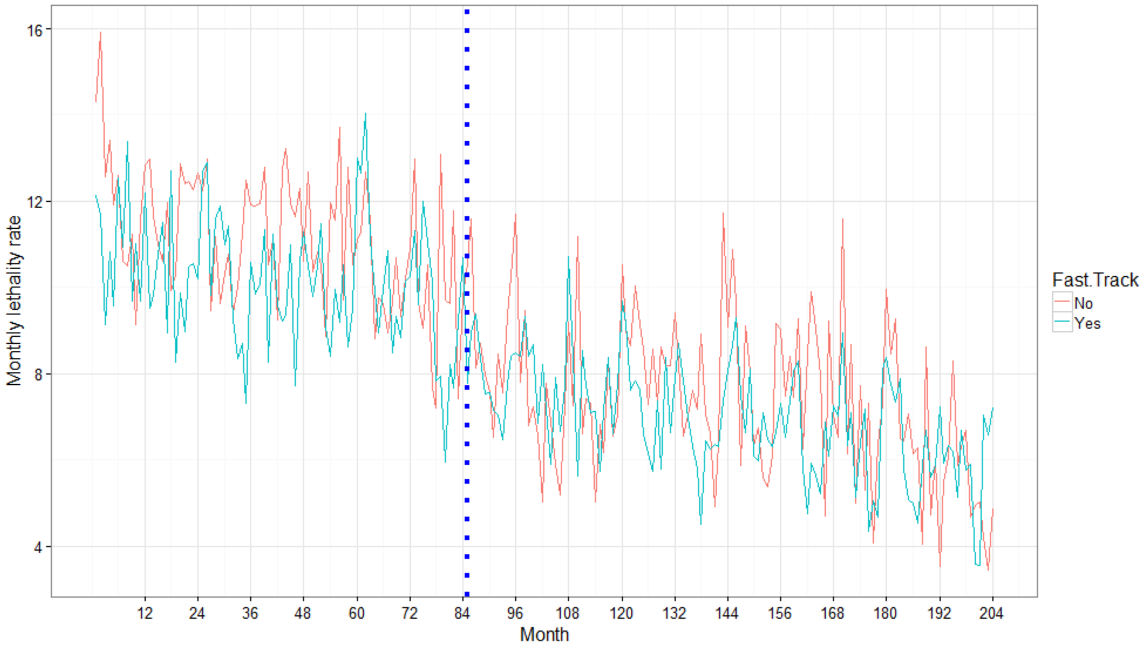

Figure 4: Comparison of longitudinal case fatality trends between hospitals with fast-track system vs. hospitals without the fast-track system.

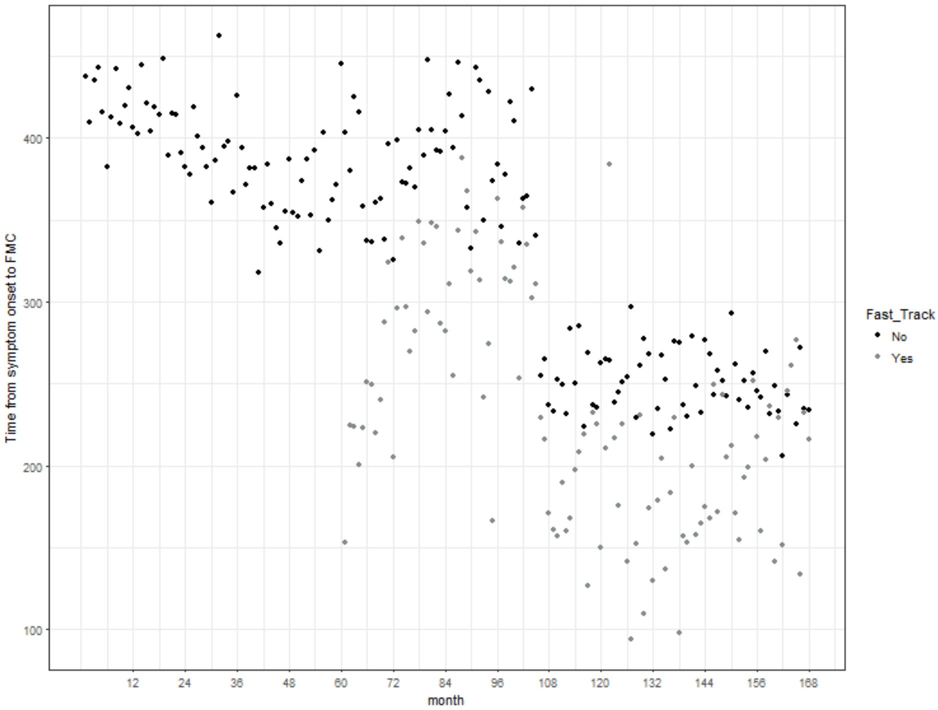

Figure 5: Time from symptom to FMC between patients that activated the fast-track system and patients who did not activate it.

Table 1: Results of segmented linear regression analyses to detect association between fast-track system and monthly case-fatality rate ACS and multivariate regression analysis between time from symptom onset and several predictors.

	β (CI)	**t-value**	**p-value**
Impact of the fast-track system on case-fatality rate by ACS			
Overall*			
Fast track implemented	-1.27 (-2.10; -0.436)	-2.99	< 0.01
Fast track implemented* time interaction	0.005 (-0.011; 0.020)	0.58	0.565
Male*			
Fast track implemented	-1.064 (-1.869; -0.258)	-2.59	0.01
Fast track implemented* time interaction	0.006 (-0.009;0.021)	0.74	0.46
Female*			
Fast track implemented	-1.453 (-2.555; -0.352)	-2.59	0.01
Fast track implemented* time interaction	0.009 (-0.011;0.029)	0.89	0.37
Age < 65*			
Fast track implemented	0.184 (-0.302; 0.669)	0.74	0.46
Fast track implemented* time interaction	0.011 (0.003; 0.019)	2.60	0.01
Age ≥ 65*			
Fast track implemented	-0.348 (-1.413; 0.716)	-0.64	0.52
Fast track implemented* time interaction	0.023 (0.004; 0.041)	2.44	0.02
Time from symptom onset to first medical contact			
Fast Track (Yes)	-47.14 (-60.48; -33.79)	-6.92	< 0.01
Age	1.60 (1.28; 1.92)	9.73	< 0.01
Sex (Male)	15.28 (6.91; 23.66)	3.58	< 0.01
Smoker (yes)	-17.58 (-26.92; -8.23)	-3.69	< 0.01
Hypertension (yes)	3.88 (-4.12; 11.88)	0.95	0.34
Diabetes (yes)	15.72 (7.45; 23.98)	3.73	< 0.01
Dyslipidemia (yes)	-2.84 (-10.22; 4.54)	-0.76	0.45
Obesity (yes)	9.02 (0.12; 17.92)	1.99	0.05

*All regression models were adjusted for seasonal effects

β represents the coefficients of the regression

CI: confidence interval

IMPACT OF PUBLIC HEALTH INITIATIVES IN ACS CASE-FATALITY RATE IN PORTUGAL

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Background

Each year cardiovascular disease (CVD) causes 3.9 million deaths in Europe. Portugal has implemented a set of public health policies that tackled CVD mortality, a smoking ban regulation in 2008, a salt reduction regulation in 2010 and fast-tracking (FTS) of cases to coronary care unit in 2007.

Our goal in this study was to analyse the impact of these 3 public health policies in reducing case-fatality rates by ACS from 2000 to 2016.

Material and Methods

The impact of these policies in ACS monthly case fatality was assessed by creating individual models for each of the initiatives and implementing multiple linear regression models, using standard methods for interrupted time-series. We also implemented a segmented regression to test which year showed a significant difference in the case fatality slopes.

Results

Separate modelling showed that the smoking ban (β=-0.861, p-value=0.050) and the FTS (β=-1.27,p-value:=0.003) had immediate impact after its implementation however, it did not have a significant impact on ACS trends. The salt reduction strategy did not have a significant impact. For the segmented model, we found significant differences between case fatality trends before and after end 2008, with rates before 2009 showing a steeper decrease.

Conclusions

The smoking ban and the FTS led to an immediate decrease in case fatality rates; however, after 2009 no major decrease in case fatality trends was found. Coronary heart disease constitutes an immense public health problem, it remains critical that decision makers, public health authorities and the cardiology community keep working to reduce ACS mortality-rates.

Introduction

Each year cardiovascular disease (CVD) causes 3.9 million deaths in Europe and over 1.8 million deaths in the European Union (EU), accounting for 37% of all deaths in the EU(11). In Portugal and Europe as a whole, CVD is the most common cause of death(4).

Despite recent decreases in mortality rates in many countries, CVD is still responsible for almost half of all deaths in Europe(4), constituting a major public health challenge in Western Europe(5).

Of all behavioural components, dietary factors pose the greatest risk for CVD mortality and reduced CVD disability-adjusted life years (DALYs) in the European population. High systolic blood pressure and smoking represent the major risk factors.

Several European countries have implemented a set of measures to tackle CVD mortality, from disease prevention, tackling major risk factors, to improvements in disease management and treatment.

Likewise, in recent years Portugal has instigated a set of health policies that directly or indirectly tackled CVD mortality, such as a smoking ban regulation in 2008, a salt reduction regulation in 2010 and fast-tracking cases to coronary care units (CCU) in 2007, a policy more directed linked to reducing mortality.

Data on evidence-based effectiveness of these health policies and public health initiatives is increasing worldwide; however, reports on the effectiveness of similar policies in Portugal is scarce. More importantly, there has been no analysis of the cumulative effect of the 3 major polices recently implemented in Portugal. In the setting of increasingly limited resources for health-care, investment in population-wide policy strategies needs to show an appropriate return, in this case a decline in CVD mortality. Therefore, it is important to assess the contribution of these policies on observed coronary heart disease (CHD) mortality.

Therefore our goal was to analyse the impact of the 3 health policies implemented in Portugal to reduce acute coronary syndrome (ACS) case-fatality rates, namely the fast-track system (FTS) to the CCU, the smoking ban and the salt reduction regulation, using case-fatality rates from 2000 to 2016.

Material and Methods

Data

Data were obtained from the Diagnosis Related Group (DRG) National Database, which collects information from all admissions into mainland Portuguese public hospitals, including primary diagnosis, demographic variables such as sex and age,

and the geographic region of the admission(90). Approval to access data was previously obtained from the office of the Minister of Health.

All admissions from 2002 to 2016 of individuals ≥ 20 years of age with a primary diagnosis of ACS, as coded by the International Classification of Disease, 9th revision (ICD 9), were extracted. Designations 410.00 - 410.xx were used to identify admission diagnoses of Acute Myocardial Infarction (AMI) and 4130 codes were used to identify unstable angina. All participants with missing data were removed from all the analyses.

Health policies and public health initiatives

The fast-track system (FTS)

FTS was implemented in all regions of Portugal in 2007. As a result we analysed 7 years of data before the implementation of the regulation (January 2000 - December 2007) and 9 years of data after the regulation was implemented (January 2008 - December 2016).

FTS was implemented in Portugal with the goal of creating a priority system and facilitating access to clinical, therapeutic and diagnostic resources. Direct admission into the CCU was essential since the time between the onset of symptoms and treatment is, in the case of AMI, vital for the reduction of morbidity and mortality. The system is initiated by patients calling the emergency number (112). As a result, the National Institute of Medical Emergency (INEM) initiates diagnosis and treatment earlier, while referring the person to a hospital unit specialising in ACS treatment(46).

The INEM has the capacity to intervene prematurely, and after the clinical diagnosis and the electrocardiogram, decide jointly with the Urgent Care Counselling Centre (CODU) on the pre-hospital treatment and hospital referral, increasing the likelihood of therapeutic success. The CODU contacts the hospital unit to organize the admission and treatment of the patient(47).

The smoking ban

The smoking ban was implemented in January 2008. As a result, we analysed 6 years of data before implementation of the legislation (January 2002 - December 2007) and 9 years of data after the legislation was implemented (January 2008 - December 2016).

Portugal was one of the countries that signed the World Health Organization (WHO) Framework Convention on Tobacco Control(76), leading to implementation in January 2008 of the most recent anti-smoking measure, the 37/2007 legislation(74). This legislation contained a new framework to protect individuals from passive secondhand smoking and for cutting down and stopping consumption(74, 77). This law banned smoking in all enclosed public places, such as hospitals, public transport, and workplaces. In addition, it established further regulation regarding information provided

on tobacco products, their packaging and labeling, as well as further restricting advertising(78).

Salt reduction policy

The salt reduction policy was implemented in September 2010. As a result, we analysed 8 years of data before implementation of the legislation (January 2002 - September 2010) and 6 years of data after the legislation was implemented (October 2010 - December 2016).

Even small reductions of high blood pressure (HBP) prevalence in the population could lead to major health gains. Knowing the importance of these approaches, the WHO created a set of recommendations to reduce dietary salt to 5 g/day, in order to prevent chronic disease and improve health(18). In the European Union, 26 out of the 53 member states, including Portugal, implemented operational salt reduction policies, including those aimed at reducing salt intake.

Notably, bread contributed about one-sixth of daily salt intake(80-81), with Portugal, Poland and Japan having the highest levels of salt in bread(82-83). The policy introduced in Portugal aimed to reduce salt to 1.4 g per 100 grams bread. It also mandated clear salt content labelling of packaged products.

Statistical analysis

The main outcome in our study was monthly case fatality rates, later stratified by age and sex.

ACS case fatality rates were calculated for each month, using the total number of patients admitted into public hospital as the denominator and the number of ACS deaths as the numerator.

The impact of the 3 policies was studied individually, using a binary covariable indicating the start of the policy (also called the breakpoint), as well as a continuous covariable to account for the effect of the policy after its implementation. To evaluate changes over time, we implemented a segmented multiple linear regression model. These models were useful when the relationship between the response and the independent variables were piecewise linear, namely represented by ≥ 2 straight lines connected at unknown values (breakpoints)(99). In this study, the segmented model was implemented to test for significant changes in case fatality rates after the introduction of the 3 policies. The Davies test was used to assess if the differences between slopes, before and after the breakpoint, were significant. This model was fitted in R version 2.5.1 software using the segmented library(168).

For all models created, case fatality rate was the response variable. Four models were created in total, one for each of the policies, and one used later to test which year showed a significant difference in case fatality rate.

All analyses were stratified by sex and age. Two age categories were used, < 65 and ≥ 65 years old. Short-term autocorrelation between monthly estimates was adequately incorporated into the model, by applying a first-order autoregressive, AR (1) process to the residuals.

Although we were aware that there might be short-term temporal differences in case fatality rates, such as relating to the day of the week, and weekends vs. week days, we did not adjust for this in our models. In fact, other studies have shown a steady reduction in CVD for both weekends and weekdays(175). There were also studies showing that after accounting for mode of arrival at the hospital, there was no difference in case fatality rates between weekdays and weekends(176).

Statistical significance was assessed through p-values, assuming < 5% as significant, and 95% confidence intervals (CI) were calculated for each of the regression coefficients. Models were fitted in R version 2.5.1 software.

Results

A total of 20,849 in-hospital deaths from ACS were registered in mainland Portugal from 2000 to 2016, out of a total of 203,040 admissions for ACS.

For the models created individually, one for each policy, FTS showed an immediate decrease in case fatalities (β= -1.27, p-value= 0.003); however, it did not impact case fatality trends after 2007, as they remained steady. Similarly, the smoking ban resulted in an immediate decrease in case fatalities after its implementation (β= -0.861, p-value= 0.05); however, no significant decrease in trends was observed after 2008 (Table 1).

By contrast, the salt reduction policy did not produce any significant impact on case fatalities (β= 0.012, p-value = 0.189), or any immediate impact after its implementation (β = 0.421, p-value = 0.365; Table 1).

Using a model where segmented regression was applied, end 2008, more accurately September 2008, was identified as the year where a difference in rates of case fatalities existed. Both slopes before (β = -0.004; CI= -0.005; -0.004) and after (β= -0.003; CI=-0.003;-0.002) end 2008 showed a decrease; however, after 2009 it was less pronounced (β = 0.002, p-value = 0.004; Table 2).

All 4 models were stratified for ACS case-fatality rates by gender. For females (β =-1.306, p-value = 0.020) and people older than 65 years old (β = -1.169, p-value = 0.029), there was a significant decrease in case fatality rates after the smoking ban.

For the FTS both genders presented with a significant decrease in case fatality rates; however, there was no difference in trends between age groups.

In the segmented model, the year found to have a differential rate of case fatalities was consistent with the model including all the data, end 2008. Both trends, before and after end 2008, were decreasing, although after end 2008 the decrease was not as pronounced as for the period before end 2008, as observed for the model including all the patients.

The differences in rates of case fatalities before and after end 2008 were higher for women ($\beta = 0.003$, p-value = 0.029) than for men, and for individuals older than 65 years old ($\beta = 0.003$, p-value = 0. 0.008; Table 2).

The seasonal pattern was consistent with that reported elsewhere(100), with higher rates of admission in winter and lower rates during the summer.

Discussion

In the last 11 year, a set of health policies have been implemented in Portugal to help decrease CVD mortality. The first initiative was the FTS in 2007, followed by the smoking ban in 2008 and a salt reduction regulation in mid-2010.

We created a set of statistical models; firstly, models to assess the individual impact of each of the policies. Finally a model was created to assess if there was any year during the study that could indicate a difference between trends, suggesting a possible impact of the policies in the country.

FTS and the smoking ban led to an immediate decrease in case-fatality rate. Previous national and international studies have shown that FTS, substantially shortening the time between symptom onset and treatment, directly impacts survival. It has been demonstrated that time between symptom onset and treatment above 120 min translates into increased in-hospital mortality in an almost linear fashion(147, 151-152).

The relationship between smoking and CVD mortality has been extensively proven, since smoking increases atherosclerotic changes with narrowing of the vascular lumen and induction of a hypercoagulable state. Such changes increase the risk of acute thrombosis leading to death(54). The results of this current study were very encouraging regarding the smoking ban, as an immediate decrease in case fatalities was found once the ban was implemented. Since the ban target both smokers and second-hand smokers, case fatality rates should decrease for both groups. Smoking cessation, or even small reductions in consumption, has been previously linked to a decrease in the number of CVD events and also a fall in the mortality risk(153).

There are not many studies analysing the effect of the smoking regulations on CVD mortality. Of those available, most focused on how regulations affected hospital admissions(154); however, the impact on mortality is equally important. Nevertheless, we are not the first to analyse the impact on mortality. A recent study similarly found a reduction of up to 11% in acute myocardial infarction (AMI) mortality 1 year after a smoking regulation was implemented(155). Another study also found a 13% decrease in all-cause mortality, with up to a 26% decrease in ischaemic heart disease (IHD) mortality.

In this current study, we found end of 2008 (more accurately September 2008) as breakpoint in our observed trends, which supported the results from the individual models. Up to 2009 the trends were significantly impacted by the policies, leading to a significant decrease in case-fatality rates. After this year, although the trend continued to decrease it was less pronounced. The impact of the salt regulation in mid-2010 showed a similar effect, with no change in trends after this year. A similar pattern was observed when analyzing the impact of this policy on ACS admissions(156).

We hypothesised that although the salt regulation was an important initiative, it was very dependent on an individual's adherence. The way the regulation was implemented might not have produced the desired effect on the population, perhaps due to the low level of health literacy observed in Portugal.

When stratified by sex and age, our results showed that the smoking ban led to an immediate decrease in case-fatality rates for women and individuals older than 65 years old. Although the number of women smoking has increased in recent years, the number of men smoking was even larger and their length of time smoking was also greater. As a consequence, men will have increased mortality from CVD, even if they quit smoking or reduce their smoking habit. Older people are more vulnerable to exposure from secondhand smoking, thus reducing it could lead to a decrease in case fatalities in this group. Our findings were also consistent with another study, where post-ban reductions in IHD mortalities were seen in ages ≥ 65 years, but not in younger subjects(157).

Analysing FTS by groups, we found similar decreasing case-fatality rates for men and women, an effect previously observed in other studies where the rate of decrease in CHD mortality was stable across both sexes(7). In addition, no immediate change in case-fatality rate after the FTS was observed for either the youngest or the older patients. For both groups, there were significant changes in trend; however, the trends observed were increasing. The prevalence of obesity and diabetes(143) is increasing in Portugal, which could have attenuated any reduction for the younger group. This effect has been observed in other studies(7, 144) where an increase of obesity leads to lower

reductions in mortality for the younger groups. A similar pattern was observed for the older group, which has previously been found in other datasets(144).

Our results for age stratification when using segmented regression showed significant differences between the trends before and after end 2008, for females and older subjects. As for the non-stratify model, the decrease in trends observed before end 2008 was steeper than the decrease observed after. These results were consistent with those observed when studying the smoking ban with age stratification, where a significant decrease in case fatality was observed for older people, but not for younger. For the sex stratification, although the FTS analysis showed a significant decrease after 2007 for men, this was related to an immediate effect and not a trend.

Limitations

As in any ecological study, it is not possible to directly prove the association between policy implementation and the reduction in case-fatality rates from ACS.

One of the strengths of our study is the use of a well-validated and standardized database, allowing for easy comparison with other international studies, mainly those developed in other European countries. In addition to the availability of information on gender and age, this allowed us to assess the robustness of our findings among different subgroups. The time-series method is preferred over the simpler pre- and post-proportion comparison method, because it does not take the pre-intervention trend into account and also allows corrections to be made for autocorrelation(130).

Conclusions

This study extended the existing literature on the patterns of ACS mortality over time, and assessed whether public health interventions to reduce mortality by ACS were successful. Furthermore, it indicated that to decrease case-fatality rates a multifactorial strategy was needed, rather than a single approach.

Strategies such as the smoking ban and the FTS led to an immediate decrease in case fatality rates; however, after 2009 no major decreases in ACS trends were found.

Considering that CHD constitutes an immense public health problem(6), it remains critical that different stakeholders, such as decision makers, public health authorities, scientific societies and the cardiology community, keep working together to reduce ACS mortality rates.

Figures and Tables

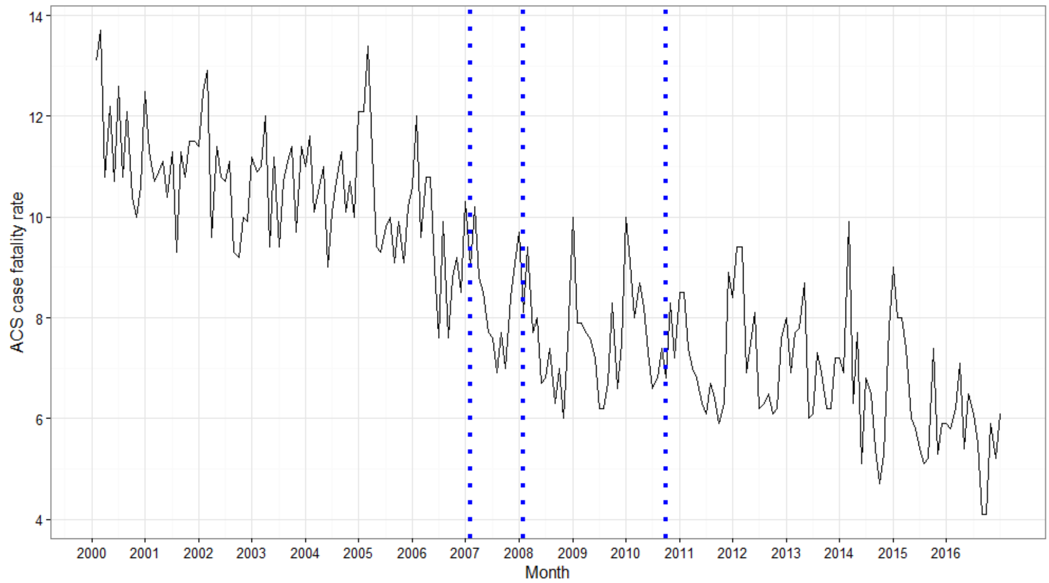

Figure 1: Longitudinal trends for case-fatality rates from ACS (percentage) for January 2000 - December 2016. The vertical lines mark the year 2007, when FTS was fully implemented in the entire country. The line at 2008 denotes the implementation of the smoking ban, and the line mid-way through 2010 denotes the implementation of the salt reduction regulation.

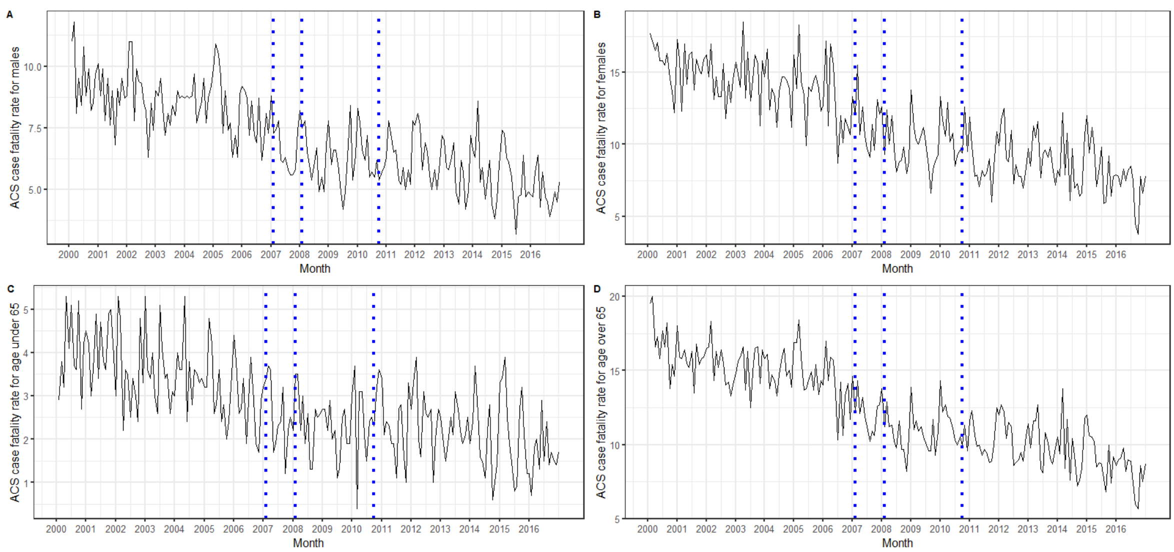

Figure 2: Stratified longitudinal trends for case-fatality rate from ACS (percentage) for January 2000 - December 2016. The vertical lines mark the years the policies were implemented. A) Longitudinal trends for males. B) Longitudinal trends for females. C) Longitudinal trends for patients under 65. D) Longitudinal trends for patients over 65.

Table 1: Results of segmented linear regression analyses for each of the models for the individual policies.

		β (CI)*	p-value
Smoking ban			
Overall	Time of the breakpoint	-0.861(-1.72;-0.003)	0.051
	Time of the breakpoint* time interaction	0.013(-0.002;0.028)	0.087
Male	Time of the breakpoint	-0.457(-1.288;0.374)	0.283
	Time of the breakpoint* time interaction	0.013(-0.002;0.027)	0.089
Female	Time of the breakpoint	-1.306(-2.394;-0.217)	0.020
	Time of the breakpoint* time interaction	0.019(0.001;0.038)	0.051
Age<65	Time of the breakpoint	0.141(-0.362;0.645)	0.583
	Time of the breakpoint* time interaction	0.012(0.003;0.020)	0.009
Age>=65	Time of the breakpoint	-1.169(-2.209;-0.129)	0.029
	Time of the breakpoint* time interaction	0.019(0.001;0.037)	0.045
Salt reduction regulation			
Overall	Time of the breakpoint	0.421(-0.488;1.295)	0.365
	Time of the breakpoint* time interaction	0.012(-0.006;0.031)	0.190
Male	Time of the breakpoint	0.538(-0.319;1.395)	0.220
	Time of the breakpoint* time interaction	0.008(-0.009;0.026)	0.341
Female	Time of the breakpoint	0.243(-0.921;1.408)	0.683
	Time of the breakpoint* time interaction	0.023(0.0001;0.046)	0.052
Age<65	Time of the breakpoint	0.557(0.061;1.053)	0.029
	Time of the breakpoint* time interaction	0.005(-0.005;0.015)	0.320
Age>=65	Time of the breakpoint	0.711(-0.404;1.826)	0.213
	Time of the breakpoint* time interaction	0.016(-0.007;0.039)	0.170

*All regression models were adjusted for seasonal effects.

Table 2: Results of segmented linear regression analyses where end 2008 was found as the breakpoint for differences in slopes. Stratified results, by gender and age group, are also included.

		β (CI)*	**p-value**
All	FTS- breakpoint	-1.236(-2.379;-0.092)	0.035
	FTS breakpoint* time interaction	-0.004(-0.052;0.044)	0.861
	Salt reduction regulation- breakpoint	0.329(-0.757;1.415)	0.554
	Salt reduction regulation breakpoint* time interaction	-0.006(-0.044;0.033)	0.774
Male	FTS- breakpoint	-1.271(-2.314;-0.228)	0.018
	FTS breakpoint* time interaction	0.012(-0.024;0.048)	0.527
	Salt reduction regulation- breakpoint	0.328(-0.717;1.372)	0.539
	Salt reduction regulation breakpoint* time interaction	-0.014(-0.051;0.023)	0.472
Female	FTS- breakpoint	-1.256(-2.726;0.214)	0.096
	FTS breakpoint* time interaction	-0.001(-0.051;0.049)	0.968
	Salt reduction regulation- breakpoint	0.245(-1.228;1.718)	0.745
	Salt reduction regulation breakpoint* time interaction	0.011(-0.041;0.062)	0.687
Age<65	FTS- breakpoint	-0.212(-0.858;0.434)	0.520
	FTS breakpoint* time interaction	0.004(-0.018;0.026)	0.699
	Salt reduction regulation- breakpoint	0.473(-0.175;1.121)	0.154
	Salt reduction regulation breakpoint* time interaction	0.0003(-0.023;0.022)	0.974
Age>=65	FTS- breakpoint	-1.803(-3.128;-0.477)	0.008
	FTS breakpoint* time interaction	0.007(-0.038;0.051)	0.765
	Salt reduction regulation- breakpoint	0.541(-0.792;1.873)	0.427
	Salt reduction regulation breakpoint* time interaction	-0.008(-0.054;0.038)	0.731

*All regression models were adjusted for seasonal effects.

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ANNEX 1: ICD-9 CODES

All ICD 9 codes used in our study for principal diagnosis of ACS and stroke.

Code	Description
41041	ENFARTE AGUDO DO MIOCARDIO, PAREDE INFERIOR NCOP, EPISODIO INICIAL
41042	ENFARTE AGUDO DO MIOCARDIO, PAREDE INFERIOR NCOP, EPISODIO SUBSEQUENTE
4105	ENFARTE AGUDO DO MIOCARDIO DA PAREDE LATERAL NCOP
41050	ENFARTE AGUDO DO MIOCARDIO, PAREDE LATERAL NCOP, EPISODIO NAO ESPECIFICADO
41051	ENFARTE AGUDO DO MIOCARDIO, PAREDE LATERAL NCOP, EPISODIO INICIAL
41052	ENFARTE AGUDO DO MIOCARDIO, PAREDE LATERAL NCOP, EPISODIO SUBSEQUENTE
4106	ENFARTE AGUDO DO MIOCARDIO DA VERDADEIRA PAREDE POSTERIOR
41060	ENFARTE AGUDO DO MIOCARDIO, PAREDE POSTERIOR VERDADEIRA, EPISODIO N/ESPECIFICADO
41061	ENFARTE AGUDO DO MIOCARDIO, PAREDE POSTERIOR VERDADEIRA, EPISODIO INICIAL
41062	ENFARTE AGUDO DO MIOCARDIO, PAREDE POSTERIOR VERDADEIRA, EPISODIO SUBSEQUENTE
4107	ENFARTE AGUDO SUBENDOCARDICO
41070	ENFARTE AGUDO SUBENDOCARDICO, EPISODIO DE CUIDADOS NAO ESPECIFICADO
41071	ENFARTE AGUDO SUBENDOCARDICO, EPISODIO DE CUIDADOS INICIAL
41072	ENFARTE AGUDO SUBENDOCARDICO, EPISODIO DE CUIDADOS SUBSEQUENTE
4108	ENFARTE AGUDO DO MIOCARDIO, LOCAL NCOP
41080	ENFARTE AGUDO DO MIOCARDIO, LOCAL NCOP, EPISODIO DE CUIDADOS NAO ESPECIFICADO
41081	ENFARTE AGUDO DO MIOCARDIO, LOCAL NCOP, EPISODIO DE CUIDADOS INICIAL
41082	ENFARTE AGUDO DO MIOCARDIO, LOCAL NCOP, EPISODIO DE CUIDADOS SUBSEQUENTE
4109	ENFARTE AGUDO DO MIOCARDIO, LOCAL NAO ESPECIFICADO
41090	ENFARTE AGUDO DO MIOCARDIO, LOCAL NAO ESPECIFICADO, EPISODIO NAO ESPECIFICADO
41091	ENFARTE AGUDO DO MIOCARDIO, LOCAL NAO ESPECIFICADO, EPISODIO INICIAL
41092	ENFARTE AGUDO DO MIOCARDIO, LOCAL NAO ESPECIFICADO, EPISODIO SUBSEQUENTE
413	ANGINA DE PEITO
4130	ANGINA DE DECUBITO
4139	ANGINA DE PEITO NAO CLASSIFICADA EM OUTRA PARTE OU NAO ESPECIFICADA
410	ENFARTE AGUDO DO MIOCARDIO
4100	ENFARTE AGUDO DO MIOCARDIO, PAREDE ANTERO-LATERAL, EPISODIO NAO ESPECIFICADO
41000	ENFARTE AGUDO DO MIOCARDIO, PAREDE ANTERO-LATERAL, EPISODIO NAO ESPECIFICADO
41001	ENFARTE AGUDO DO MIOCARDIO, PAREDE ANTERO-LATERAL, EPISODIO INICIAL
41002	ENFARTE AGUDO DO MIOCARDIO, PAREDE ANTERO-LATERAL, EPISODIO SUBSEQUENTE
4101	ENFARTE AGUDO DO MIOCARDIO DA PAREDE ANTERIOR NCOP
41010	ENFARTE AGUDO DO MIOCARDIO, PAREDE ANTERIOR NCOP, EPISODIO NAO ESPECIFICADO
41011	ENFARTE AGUDO DO MIOCARDIO, PAREDE ANTERIOR NCOP, EPISODIO INICIAL
41012	ENFARTE AGUDO DO MIOCARDIO, PAREDE ANTERIOR NCOP, EPISODIO SUBSEQUENTE
4102	ENFARTE AGUDO DO MIOCARDIO DA PAREDE INFERO-LATERAL
41020	ENFARTE AGUDO DO MIOCARDIO, PAREDE INFERO-LATERAL, EPISODIO NAO ESPECIFICADO
41021	ENFARTE AGUDO DO MIOCARDIO, PAREDE INFERO-LATERAL, EPISODIO INICIAL
41022	ENFARTE AGUDO DO MIOCARDIO, PAREDE INFERO-LATERAL, EPISODIO SUBSEQUENTE
4103	ENFARTE AGUDO DO MIOCARDIO DA PAREDE POSTERO-INFERIOR
41030	ENFARTE AGUDO DO MIOCARDIO, PAREDE POSTERO-INFERIOR, EPISODIO NAO ESPECIFICADO
41031	ENFARTE AGUDO DO MIOCARDIO, PAREDE POSTERO-INFERIOR, EPISODIO INICIAL
41032	ENFARTE AGUDO DO MIOCARDIO, PAREDE INFERO-POSTERIOR, EPISODIO SUBSEQUENTE
4104	ENFARTE AGUDO DO DO MIOCARDIO DA PAREDE INFERIOR NCOP
41040	ENFARTE AGUDO DO MIOCARDIO, PAREDE INFERIOR NCOP, EPISODIO NAO ESPECIFICADO
43301	OCLUSAO E ESTENOSE DE ARTERIA BASILAR, COM ENFARTE CEREBRAL
43321	OCLUSAO E ESTENOSE DE ARTERIA VERTEBRAL, COM ENFARTE CEREBRAL
43311	OCLUSAO E ESTENOSE DE ARTERIA CAROTIDA, COM ENFARTE CEREBRAL
43331	OCLUSAO E ESTENOSE ARTER.PRE-CEREBR.MULTIPLAS OU BILATERAIS, COM ENFARTE CEREBR.
43391	OCLUSAO E ESTENOSE DE ARTERIA PRE-CEREBRAL NAO ESPECIFICADA, COM ENFARTE CEREBR.
43401	TROMBOSE CEREBRAL, COM ENFARTE CEREBRAL
43411	EMBOLIA CEREBRAL, COM ENFARTE CEREBRAL
43491	OCLUSAO DE ARTERIA CEREBRAL NAO ESPECIFICADA, COM ENFARTE CEREBRAL
431	HEMORRAGIA INTRACEREBRAL
432	HEMORRAGIA INTRACRANIANA NAO ESPECIFICADA OU NCOP
4320	HEMORRAGIA EXTRADURAL NAO TRAUMATICA
4321	HEMORRAGIA SUBDURAL
4329	HEMORRAGIA INTRACRANIANA NAO ESPECIFICADA
43381	OCLUSAO E ESTENOSE DE ARTERIA PRE-CEREBRAL ESPECIFICADA NCOP, COM ENFARTE CEREBR

APPENDIX 1: MANUSCRIPT PUBLISHED

APPENDIX 2: MANUSCRIPT PUBLISHED