DOCTORAL THESIS
PhD Programme in Public Health and the Methodology of Biomedical Research. Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine. Faculty of Medicine, Universitat Autònoma de Barcelona, 2009

TRENDS IN ACUTE MYOCARDIAL INFARCTION INCIDENCE AND CARDIOVASCULAR RISK FACTORS PREVALENCE IN 6 COUNTIES OF GIRONA, SPAIN (1990-2005)

PhD Candidate: Maria Grau

Supervisor: Dr. Jaume Marrugat,
Chair of the Program of Research in Inflammatory and Cardiovascular Disorders,
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To my mother's mother, a dear grandmother, a font of intelligence, positive energy and sense of humour, a paradigm of days gone by whose hands were the very permanence of love during happy childhood days spent dreaming in her lap.

A la madre de mi madre, abuela entrañable, manantial de inteligencia, sentido del humor y energía positiva, paradigma de un tiempo que llevó en sus manos la permanencia del amor en lejanos días radiantes soñados en su regazo.

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This thesis is the culmination of a painstaking personal and professional journey in which I gave up security for uncertainty to follow a dream that has now become a reality.

Many people have, in one way or another, contributed their skills, wisdom, common sense and cordiality to bring this exciting project to a good conclusion; I have always thought that quality is not a goal but rather a shared journey.

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For those closest to me, this thesis is a small compensation for the constant affection and reassurance that are so necessary for personal development and a life in harmony:

My parents, Marina, my first teacher, and Josep, who taught me equally and with one accord as they transmitted their values: freedom, freedom of thought, morality, independence, generosity, the right to be respected and the duty to respect others, the search for knowledge, and to not be afraid ...

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My partner Cristóbal, love, tenderness, understanding, participation and support for my scientific concerns, accomplice in possible pasts and futures.

Elena, a paradigm of friendship, companion in a thousand adventures, emotional support.

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It would not be fair to end this chapter without showing my appreciation for the co-authors of the publications that form part of this doctoral thesis, including the team led by Jean Ferrières in Toulouse, where I felt welcomed and completely integrated into their group as I worked toward the European Doctorate mention (Doctor Europeus).

And finally, I am thankful to Elaine Lilly, expert editor, who helped me to present this thesis in English with confidence.

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Mis padres: Marina, mi primera maestra y Josep, que me educaron en igualdad, con coherencia en la transmisión de los Valores: libertad, libre pensamiento, moralidad, independencia, generosidad, derecho a ser respetada y deber de respetar, búsqueda del conocimiento, a no tener miedo...

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Y finalmente a Elaine Lilly, editora experta por darme la confianza necesaria para la presentación de este trabajo en inglés.

0.2 Abbreviations

AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study
AMI: Acute Myocardial Infarction
ARIC: Atherosclerosis Risk in Communities
CARDIA: Coronary Artery Risk Development in Young Adults
CVD: Cardiovascular Diseases
ERICA: Prediction of coronary heart disease in Europe
EUROASPIRE II: European Action on Secondary Prevention by Intervention to Reduce Events II
HDL: High-density Lipoprotein
HERMES: Harmonización de las Ecuaciones de Riesgo en el Mediterráneo Sur de Europa [Adapting risk equations to Mediterranean Southern Europe]
IBERICA: Investigación, Búsqueda Específica y Registro de Isquemia Cardiaca Aguda [Research, Specific Search, and Acute Cardiac Ischemia Registry]
IHD: Ischemic Heart Disease
LDL: Low-density lipoprotein
MEGA: Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
MONICA: Monitoring Trends and Determinants of Cardiovascular Diseases
NCEP-ATPIII: National Cholesterol Education Program – Adult Treatment Panel III
PAF: Population Attributable Fraction
PRIME: Étude Prospective de l'Infarctus du Myocarde [Prospective Epidemiological Study of Myocardial Infarction]
REACH: Reduction of Atherothrombosis for Continued Health
REGICOR: Registre Gironí del Cor [Girona Heart Registry]
USA: United States of America
WHO: World Health Organization

1. INTRODUCTION

Planning and prioritizing resource allocation in prevention and patient care depends on availability of information on the evolution of incidence and mortality rates, case-fatality, and other related factors regarding the diseases with the greatest population impact on public health[1, 2].

Management of diseases with high prevalence and morbidity/mortality consumes a large amount of resources in developed societies. For instance, health costs in Spain constituted 15.4% of the central government's total 2005 expenditure[3]. Together with gathering population data for decision making, scientific research must be directed to studying the mechanisms of the disease and the impact of interventions, combining multidisciplinary clinical, basic, genetic and epidemiological perspectivess. One example of the importance of having access to quality information is our need to understand cardiovascular diseases (CVD) and the associated risk factors. Indeed, circulatory system diseases constitute the main cause of death in Catalonia and in Spain[4] and accounted for the largest percentage of the Catalan and Spanish health budgets (17.6% and 17.3%, respectively)[5].

Prevention and control of CVD, particularly ischemic heart disease (IHD), its most common expression, is of major public

health importance. In fact, IHD events are precluded by a long induction period that often begins at very early ages[6]. Important insights in the field of CVD and other major non-communicable diseases stem from an understanding of the epidemiology and trends of IHD[7]. A population approach to the study of IHD burden, incidence and mortality trends and related risk factors is described in the ensemble of scientific publications that are incorporated into this doctoral thesis.

1.1 Historical Approach to the Study of Atherosclerotic Diseases

The lipid theory of atherosclerosis has only been known since the middle 19th century and was well established much later[8-11]. The strong association between cholesterol and cardiovascular risk was first observed in ecological studies, then tested in animal models, and confirmed in large epidemiological and intervention studies[12].

The dramatic reduction in mortality from infectious diseases at the beginning of the 20th century in Western Europe and North America resulted in the population considerably longer life expectancy than in the past[13] (Figure 1). As a consequence, the huge impact of atherosclerosis on the general population emerged as a public health issue[14].

The author of the "Epidemiologic Transition" theory explained this change as the effect of eco-biological determinants, such as the balance between disease agents, the level of hostility in the environment and the resistance of the host, and socioeconomic political and cultural determinants, including income, healthy lifestyles, hygiene and nutrition[17]. However, different stages of the epidemiologic transition can be observed all over the world at any given time owing to the fact that these determinants vary widely across countries or even over regions within a country[18]. In the 1930s and 1940s, IHD death rate increased at an alarming rate in the United States of America (USA)[14]. As a consequence, some prospective cohort studies were designed after World War II to better understand the epidemiology of IHD[19, 20]. The Framingham Heart Study has been particularly recognized as the first large-scale, comprehensive study to determine the causes of atherosclerotic disease. In fact, that was the context where, in 1961, the term coronary risk factor was first defined[21-23].

The identification of major risk factors, besides age and sex, for IHD has been one of the most important advances in medicine. Essentially, it was confirmed by means of epidemiologic

Figure 1.
Relationship between life expectancy and cause of death in England and Wales during the 20th century[15, 16].

research that found IHD was preceded by measurable and reversible predisposing conditions[24]. This approach provided a new, research-based framework for managing the increasing uncertainty associated with the occurrence of IHD at that point in time[25]. At present, the term "risk factor" is defined as a measurable element or characteristic causally associated with an increased rate of a disease and as an independent and significant predictor of the risk of presenting that disease[12]. The "risk factor approach" involves an explanatory framework giving some sense of who is at greatest risk and what one might do to decrease that risk[25].

Beginning in the mid 1960s, the IHD mortality rate fell considerably each year for 30 years in the USA, Canada, Australia, and New Zealand. The same pattern became apparent in western Europe after a 10-year lag, including the Mediterranean countries of southern Europe, where IHD incidence and mortality rates had been three- or four-fold those observed in USA or northern Europe[7, 27, 28]. In contrast, the countries in eastern Europe showed remarkably uphill trends in the '80s, similar to those recorded in the USA and Australia in the early '60s[7, 27, 28] (Figure 2).

The Bethesda Consensus Conference in 1979 was the beginning of two epidemiological studies that aimed to answer the questions about this outstanding decline observed in western developed countries[29]: the international WHO MONICA Project (*World Health Organization - Monitoring Trends and Determinants of Cardiovascular Diseases*)[30] and the American ARIC (*Atherosclerosis Risk in Communities*) Study[31]. The follow-up of the recruited cohorts in the two studies produced different answers to the same questions.

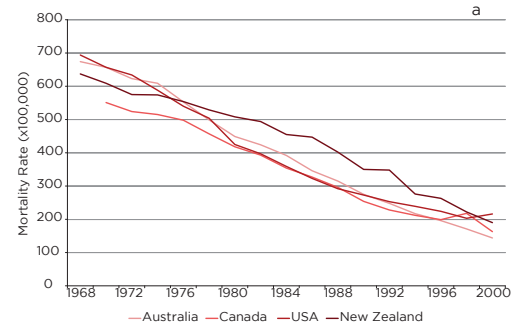
The MONICA Project involved 38 populations in 21 different countries. Using consistent, validated methods for case finding, the MONICA investigators studied nearly 80,000 definite acute myocardial infarction (AMI) or possible coronary deaths among more than 5 million people aged 35 to 64 years[30]. The authors concluded that the observed changes in rates were real: the fall in IHD mortality rates was the result of decreasing event rates rather than reductions in the fatality of these events[32, 33]. On the other hand, the ARIC Study concluded that in the USA the factors predicting better survival after an event, followed by those associated with declines in recurrent hospitalized AMI, were likely the prominent components in the decline in IHD mortality in the past decade[34].

The Seven Countries Study has represented another cornerstone for the comprehension of IHD. The 25-year follow-up of seven cohorts from seven countries in different regions of the world revealed important contributions to identifying population-level risks[35]. In summary, long-term exposure to similarly high levels of total cholesterol and systolic blood pressure, two major risk factors, may not have the same absolute influence in the development of IHD events in southern Europe or Japan as in other regions, particularly Anglo-Saxon countries[36, 37]. Interestingly, all regions showed a similar relative risk for a given level of exposure as compared to a reference level. Data from this study also revealed that the maximum effects of these two risk factors on IHD mortality may be observed 10 or more years after exposure onset or measurement[6].

CVD is advancing in the developing countries. For instance, some 80% of all CVD deaths worldwide in 2000 occurred in low- and middle-income developing countries, while these countries also accounted for 86% of the global CVD disease burden[3].

Globally, CVD deaths have been projected to increase from 16.7 million in 2002 to 23.3 million in 2030, with IHD and stroke among the four leading causes of death worldwide regardless of national economic status[38, 39]. This projected increase is explained by demographics. On one hand, population growth will have the highest impact in low- and middle-income countries. On the other hand, the aging of the population in western countries will result in a significant increase in the absolute number of chronic diseases like IHD, despite the declining trend of age-specific death rates[38-41].

Figure 2.
Ischemic heart disease mortality (per 100,000) in men and women aged 35-74 in (a) Australia, Canada, the USA and New Zealand; (b) Northern European countries; (c) Eastern European countries; (d) South Mediterranean European countries and Japan[26]. Above: Men. Below: Women.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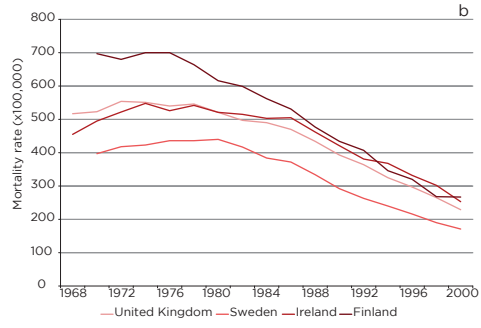
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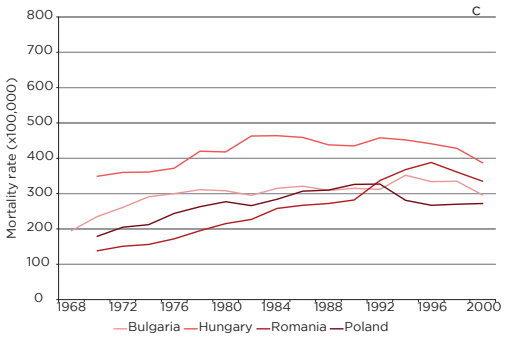
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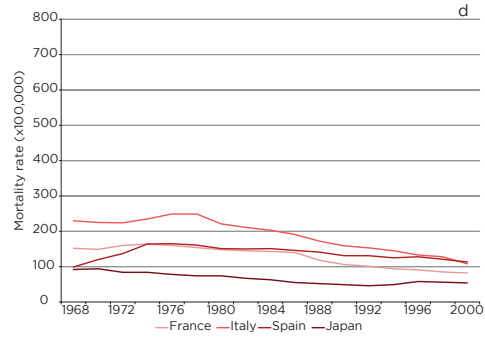
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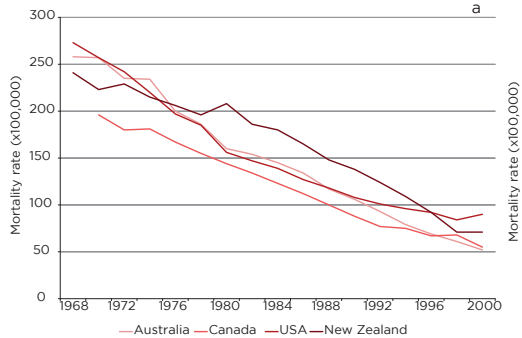
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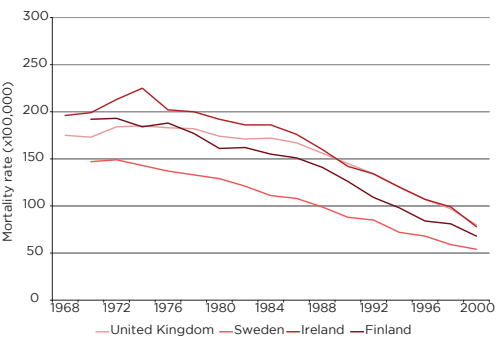
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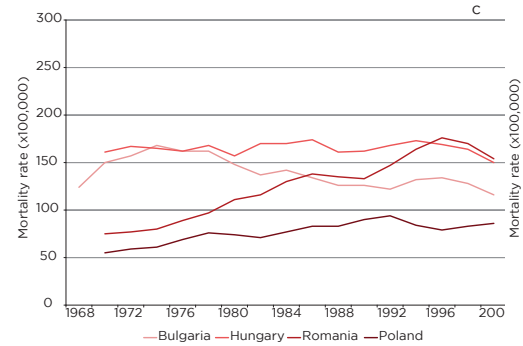
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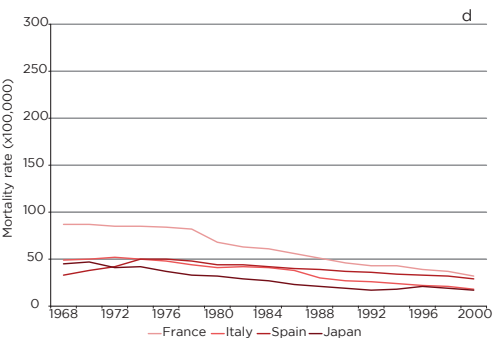
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Mortality rate (x100,000)
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“Population aging gradually increases average cardiovascular risk in the population.

1.2 Magnitude of the Problem in Spain

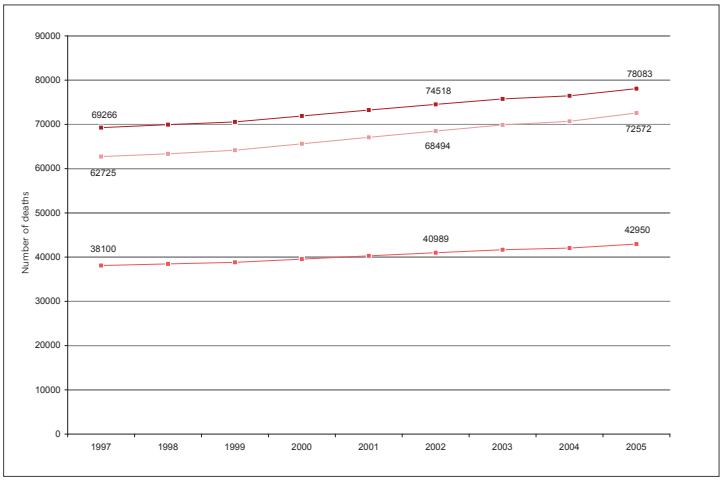
In Spain, approximately 120,000 CVD deaths occurred in 2007: 54,062 in men and 64,792 in women. More specifically, standardized IHD mortality rates were 59 and 41/100,000 men and women, respectively, being the leading cause of death in men and second highest cause of death in women, responsible for 11% and 9% of deaths, respectively[42]. In addition, it was responsible for a large number of premature deaths and the loss of many potential years of life (267.11 and 47.16 age-adjusted years in men and women, respectively)[42]. The annual cost of IHD is estimated to be 326,140,000€: 116,920,000€ direct costs, and 209,220,000€ indirect costs (worker productivity lost to premature disability, 79,740,000€; to temporary disability, 34,950,000€; and to permanent disability, 94,530,000€)[43].

Despite the decrease in age-standardized IHD mortality rates observed since 1980, population aging gradually increases average cardiovascular risk in the population, as the disease predominantly affects people aged more than 55 years[41]. Therefore, the crude death rate from this cause continues to increase[7,41,42,44] (Figure 3). In fact, IHD generated increasing demand for care in recent years, producing around 145,000 hospital admissions in Spain in 2007[45].

Comprehensive and accurate disease surveillance systems are critical to assess the long-term effect of preventive efforts undertaken to reduce the burden of IHD[1]. These public health systems consist of continued, systematic collection, analysis, interpretation, and dissemination of data regarding IHD incidence and mortality[46].

Measuring the occurrence of IHD in different populations and settings requires several conditions to be met: first, a well-delimited population to generate population-based data on trends in location-specific incidence and mortality rates[2]; second, a definition of IHD amenable to standardization, enabling reliable data collection and ensuring comparability with other studies[47]; third, components of this definition that are relatively immune to temporal changes so that time trends can be established; finally, long-term monitoring of incidence and case-fatality, taking advantage of death certificates' validation of mortality, as well as the collection of information on the quality of hospital and secondary prevention IHD care. Population risk factor trends are also required to set up valid pre activities proposals.[7]

Figure 3.
Increased number of IHD due to the aging of the Spanish population[41].



In Spain, incidence data available to date come from three sources, two population studies in Catalonia and one involving Catalonia and six other Autonomous Communities. The international WHO-MONICA study included a region of Barcelona province with ~800,000 inhabitants[48], the REGICOR Study (*Registre Gironí del Cor* [Girona Heart Registry]), was conducted in Girona province, with ~600,000 inhabitants[49], and the IBERICA Study (*Investigación, Búsqueda Específica y Registro de Isquemia Cardiaca Aguda* [Research, Specific Search, and Acute Cardiac Ischemia Registry]) involved populations from seven regions with ~8,000,000 inhabitants[50].

In the MONICA Project, North Karelia (Finland) had the highest 10-year mean IHD rate in men, and Beijing (China) and Catalonia (Spain) the lowest. In women, the highest rate was in Glasgow (UK) and the lowest was again in Catalonia (Spain)[32]. The remarkable differences observed in IHD mortality rates were not related to healthcare systems, nor to ethnic composition, nor to lifestyle characteristics of the countries studied. In addition, length of survival, death in or out of hospital and the distribution between men and women were similar internationally[32,33,48,51] (Figure 4).

REGICOR is a clinical and epidemiology project, both hospital and population-based, with the primary objective of studying the magnitude of IHD in Catalonia and Spain, and the associated risk factors at population scale. REGICOR also monitored utilisation of health care resources, long-term prognosis of patients presenting this disease and the evolution of the population prevalence of IHD risk factors[52]. The catchment area comprises six counties in the province of Girona that are served by a hospital network of the University Hospital Dr. Josep Trueta

(referral hospital), five local public hospitals with the capacity to admit non-complicated AMI patients, and two private clinics[52]. The REGICOR investigators reported that AMI incidence in Girona was from one-half to one-fourth that found in north, east, and west European countries and the USA, despite the fact that the prevalence of risk factors was similar in all these populations[49, 53, 54].

The IBERICA Study monitored AMI incidence and mortality rates in 7 regions in Spain between 1997 and 1998. AMI cumulative incidence rates for men and women aged 25 to 74 years were 207 (95% confidence interval: 175-252) and 45 (36-65) per 100,000, respectively. Age-standardized mortality rates were 73 (62-94) and 20 (13-29) per 100,000. The authors concluded that cumulative AMI incidence and mortality were low in comparison with other industrialized countries, although considerable interregional variation was observed[50].

In summary, the combination of accurate indicators of IHD (e.g., incidence, prevalence, mortality, and case-fatality) over time provides a description of the disease burden in a particular community. It also offers a chance to analyze the relative contribution of treatment versus primary prevention in achieving the observed trends[2, 55]. It has been generally admitted that changes in the incidence of new IHD events reflect the effects of primary prevention measures working through improvements in population risk factor levels[55, 56]. Reducing the recurrence rate depends on the success of secondary prevention efforts, which work in patients who have already presented an IHD event[47]. This includes optimizing the risk factor profile, along with treatments and therapeutic interventions that can modify the normal progression of the disease[57-60]. Finally, changes in case-fatality are assumed to be caused by improvements in IHD care, such as increased use of drugs with proven efficacy[61, 62].

1.3 Major Cardiovascular Risk Factors and the Southern Europe Paradox

Precursors of IHD have been extensively studied in recent decades, and many causal cardiovascular risk factors have been identified[63]. Major cardiovascular risk factors have been defined, given their relatively high prevalence in IHD-prone populations, their causal relationship with an increased incidence rate of disease, their dominance in risk prediction over other putative cardiovascular risk factors, and their well-established amenability to prevention and control[12]. Many epidemiological studies have underlined that AMI rarely occurs in the absence of the major

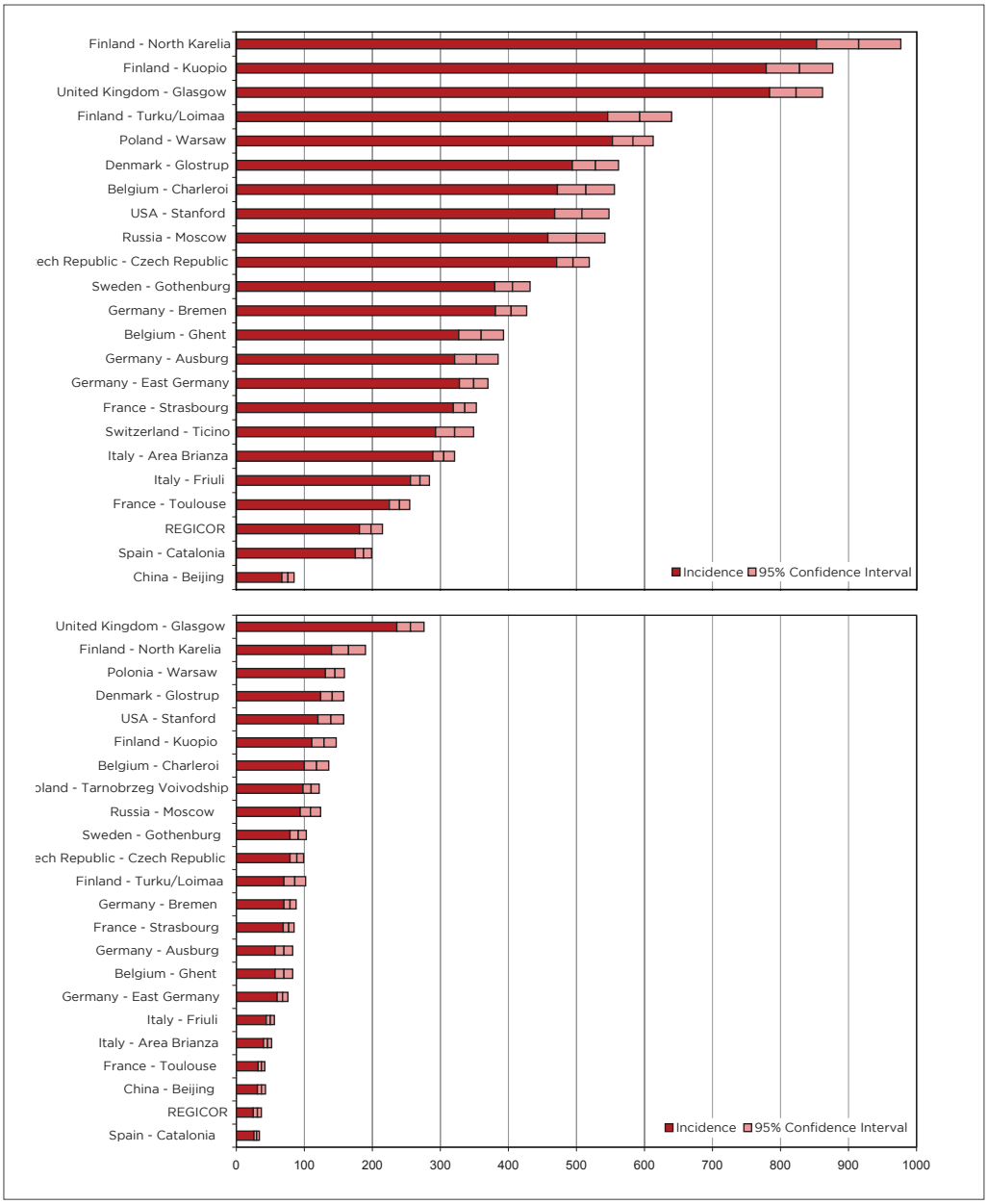


Figure 4.
Incidence rates in men (above) and women (below) aged 35-64 in the MONICA Study and in the REGICOR Study[32, 49].

risk factors: inappropriate diet and physical activity –primarily expressed as unfavourable lipid concentrations, high body mass index, and elevated blood pressure– together with smoking[63-71].

Epidemiologic studies have consistently demonstrated a dose-response relationship between serum total cholesterol level and IHD risk[72, 73]. The atherogenic feature of the total cholesterol level has been recognized as its low-density lipoprotein (LDL) component[73-75]. Findings from the Bogalusa Study showed that the

extent of fatty streaks, the first visible lesion in the development of atherosclerosis, occurring even in childhood, was associated with LDL cholesterol prior to death[76]. Moreover, LDL cholesterol level in young adulthood predicted coronary and cardiovascular event occurrence later in life[6, 65, 77]. These findings support the idea that the relationship between LDL cholesterol and development of IHD should be viewed as a continuous process beginning early in life[12].

High-density lipoprotein (HDL) cholesterol, on the other hand, has been inversely related to atherogenesis[78-80]. An analysis of 4 prospective studies conducted in the USA showed a consistent protective effect of HDL cholesterol, suggesting that each 1mg/dl increment was associated with 2-3% decrease in coronary risk[81]. In the AFCAPS/TexCAPS (*Air Force/Texas Coronary Atherosclerosis Prevention Study*) primary prevention trial, baseline levels of total cholesterol, LDL cholesterol, triglycerides, and non-HDL cholesterol –computed as total cholesterol minus HDL cholesterol– were not predictive of IHD events, whereas HDL cholesterol level was significantly predictive at baseline, along with ratios of LDL cholesterol to HDL cholesterol, total cholesterol to HDL cholesterol, and non-HDL cholesterol to HDL cholesterol[82, 83]. Subsequent publications on this topic have shown how efficiently total to HDL cholesterol ratio predicts coronary risk at all ages[84, 85].

Both systolic and diastolic blood pressure have a continuous, independent, positive association with cardiovascular outcomes[37,86, 87]. For individuals aged 40 to 70 years, each increment of 20mmHg in systolic blood pressure or 10mmHg in diastolic blood pressure doubles vascular mortality risk across the entire range of blood pressure from 115/75 to 185/115 mmHg[88]. This continuous relationship is illustrated by the fact that high-normal blood pressure values have been associated with an increased risk of CVD[89, 90]. Nonetheless, the assessment of hypertension has placed greater emphasis on the systolic component[91]. Hypertension has been strongly associated to the atherosclerosis of brain vessels as the major risk factor[92], although its association with IHD seems weaker[93].

Some studies have shown a dose-dependent relationship between smoking and the risk of IHD[94, 95]. In fact, smoking cessation resulted in a rapid decline in risk for incident and recurrent IHD events[96-99] and for sudden cardiac death[100] in those of any age with and without overt IHD[96, 101]. As a consequence, IHD risk for former smokers becomes similar in 5 years to that of never-

smokers[102, 103]. In addition, it has become clear that not only is active smoking associated with increased risk of IHD, but passive smoking also increases the risk by 30%[104].

Diabetes is associated with a 2- to 4-fold increase in the likelihood of developing IHD[105], this increase being higher in women than in men[106, 107]. Impaired fasting glucose in women also has been associated with an increase in the risk of developing IHD[108]. However, determination of cardiovascular risk in type 2 diabetes continues to be a topic for debate and a moving target. Some studies suggest that the cardiovascular risk of diabetes patients is similar to that of IHD secondary prevention patients[109-111]. Other publications, however, did not confirm these observations[112].

Finally, obesity is an independent risk factor for all-cause mortality[113, 114] and also for chronic metabolic disorder associated with numerous comorbidities such as IHD[115], CVD[116], type 2 diabetes[117], and hypertension[116]. Moreover, higher body mass index during childhood has been associated with an increased risk of IHD in adulthood[118] and the Coronary Artery Risk Development in Young Adults (CARDIA) Study found that elevated risk factors in young adulthood appeared to be a major consequence of weight gain[119].

Results from a meta-analysis of 130,945 subjects from 48 studies showed that 23% of the Spanish population had total cholesterol levels above 250mg/dl, 33% were smokers, 34% suffered hypertension, 20% were obese, and diabetes affected 8% and 12% of women and men, respectively[120]. More recently, a pooled analysis of data from different studies has shown similar prevalence with little variability among communities in Spain[121]. These results agreed with those already observed in the cross-sectional REGICOR study conducted in the same six counties in Girona in 1995 as the AMI registry study[53]. At that time, investigators observed that in spite of the relatively low AMI incidence and mortality in this region, the prevalence of major cardiovascular risk factors was even higher than in countries with incidence rates two or three times higher than in Spain[53]. This surprising situation, which has been confirmed in subsequent studies[122], has led to the discussion of a paradox in southern Europe, similar to that previously described in France, of high fat consumption and low IHD mortality[123-125].

Some evidence from the Prediction of Coronary Heart Disease in Europe (ERICA) study and, more conclusively, from the Seven Countries and the Prospective Epidemiological Study of Myo-

“Cardiovascular risk factors may not have the same influence in IHD incidence in Southern Europe as in other countries.

cardial Infarction (PRIME: *Étude Prospective de l'Infarctus du Myocarde*) studies indicated that cardiovascular risk factors may not have the same influence in the development of IHD events in southern Europe as in other countries[36, 37, 126-128]. Within Europe, similar relative risks for IHD in relation to cholesterol or systolic blood pressure were observed, but with notably different absolute risks[36, 37].

All these findings provide further evidence that classic cardiovascular risk factors only permit partial assessment of IHD risk and do not take into account protective factors that may be acting in areas of low IHD incidence[125]. The role of these protective factors, such as the interaction between environmental factors –particularly, diet and physical activity– and genetic characteristics remain to be elucidated[125, 129]. The importance of modifying dietary habits is supported by data from randomized clinical trials[130, 131] as is the recommendation of physical exercise[132], which has become an important element of preventive policies in adults[133], the elderly[134], and children[135]. However, the Spanish population still shows an increasing prevalence of obesity[136], type 2 diabetes[137] and cigarette smoking, particularly in young women[138].

In summary, knowledge of the trends in the prevalence and control of cardiovascular risk factors, and the impact of their modification on IHD incidence, mortality and disease progression, is essential to perfect the preventive public health interventions suitable for each country.

1.4 Strategies for Ischemic Heart Disease Prevention

In the organization of IHD prevention programmes, it is common practice to distinguish between primary and secondary prevention. Primary prevention includes pre-event preventive activities, while secondary prevention concentrates on recurrence prevention. There are three reasons for the crucial role of primary IHD prevention in clinical practice. First, IHD is the leading cause of mortality in the world, and continues to increase in developing countries[3]. Second, the long induction period –generally asymptomatic– of atherosclerosis means that its first manifestation is frequently an event such as AMI, which is fatal in more than 35% of cases[6, 139]. Finally, the control of risk factors leads to a reduction in IHD incidence[12]. A major inconvenience is that current screening procedures offer no means to identify those in the population who are developing atherosclerosis and at what pace atherosclerotic lesions are growing[140]. As a consequence, primary prevention activities must be addressed to the whole

population, prioritizing certain sectors of the population with some admittedly blunt screening instruments such as coronary risk functions[141].

In recent years, some claims have been put forward to consider only one type of prevention, disregarding whether or not a subject has experienced a first IHD event[142]. However, in the Reduction of Atherothrombosis for Continued Health (REACH) study, people with risk factors but no overt IHD were at lower 2-year IHD risk (less than one third) than patients with at least one previous IHD event, even when preclinical signs of atherosclerosis (e.g., abnormal ankle-brachial index and intima-media thickness) were considered "risk factors"[71]. These findings support the efficiency of dividing prevention into primary and secondary strategies.

The estimation of coronary risk initially conceived and developed by the Framingham investigators makes it possible to structure the primary prevention of IHD toward the best candidates for response; therefore, this process should entail the highest possible level of reliability and accuracy[141]. The objective of the coronary risk functions was to synthesize the impact of a number of major cardiovascular risk factors into a single statement of IHD risk[143]. A simple prediction algorithm was then developed using categorical variables, allowing physicians to predict multivariate IHD risk in middle-aged patients without overt IHD[24, 141, 144].

As the main consequence of the different risk levels observed between populations[36, 37, 126, 128], the Framingham risk functions overestimated coronary risk when applied to populations that differed from the American profile[145-150]. However, the Framingham investigators developed a methodology to allow the adaptation of these tools to other populations[151] and the Framingham risk function has been adapted and validated for its use in the Spanish population[148, 152].

Although many epidemiological studies have underlined the rare occurrence of AMI in the absence of the major risk factors, their sensitivity regarding IHD risk prediction is very low[153-155]. It should be taken into account that the IHD burden is determined more by a large fraction of the population exposed to a low risk than by the few who are at high risk[13, 56]. In fact, people classified at medium IHD risk have been consistently shown to have the highest proportion of IHD events that cannot be completely prevented[140, 152, 156]. The potential mechanisms that trigger an IHD event in some but not all people with similar cardiovascular

“IHD burden is determined more by a large fraction of the population exposed to a low risk than by the few who are at high risk.

risk factor prevalence remains unknown. Some years ago, this observation led various authors to encourage the “50% myth” which implied that, even if we could fully control the established cardiovascular risk factors, IHD incidence or death would be reduced only by half[157-160]. Despite this myth being refuted in several publications[63, 71], the experts have persevered in their search for new population screening strategies for atherosclerosis at the population scale[161-164].

Three general strategies for the primary prevention of IHD are generally used (Figure 5). First is the single risk factor “high-risk” approach promoted by LaLonde[165], which focusses the attention on that segment of the population with the highest exposure levels to a particular risk factor[166]. This approach requires a prior screening and, most likely, medical interventions expected to reduce the impact of IHD morbidity and mortality in the short to medium term[167-169]. However, using unrealistic cut-points to define risk factor prevalence (e.g., total cholesterol <190mg/dl) could result in inefficient population drug use, such as excessive use of lipid-lowering medications[170].

The second strategy includes risk estimation, which has been described as the best tool for establishing priorities for primary prevention[141]. For instance, risk estimation is a key factor when deciding to begin pharmacological treatment for dyslipemia[57,60]. The convention by which individuals at a high level of risk according to the Framingham function (greater than 20% at 10 years) receive this type of treatment has been established by consensus. According to the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATPIII) guidelines, it is not cost-effective to treat individuals with a risk lower than 10%[57]. The problem is apparent when we assess the management of individuals in the intermediate risk band (10%-20%) to decide at which point they should receive treatment. According to several clinical trials in primary prevention[83, 171-175], treating populations with a coronary risk ≥16% is effective, whereas in individuals with a coronary risk <13% there is no proof that the benefits of statins counterbalance their potential adverse effects on mortality at 10 years[169, 176].

Screening for cardiovascular risk factors is often opportunistic (case-finding), since this is the most feasible method to detect high-risk people. Rather than recruiting patients to attend for the purpose of being screened, the strategy is to test all those who present for care (non-selective) or, alternatively, to test those who meet predefined elegibility criteria (selective)[177].

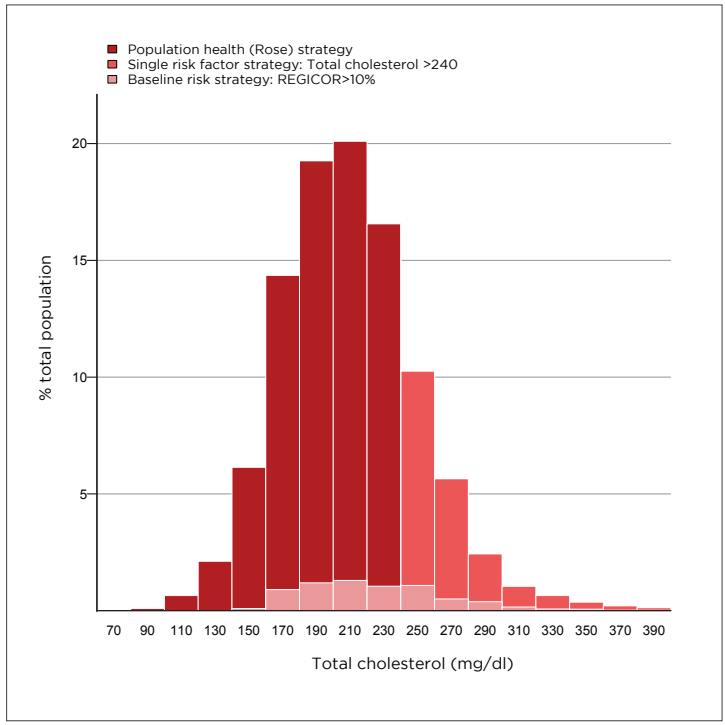


Figure 5.
Total cholesterol concentration in the population targeted by three preventive strategies. Based on data from the Adapting risk equations to Mediterranean Southern Europe (*Harmonización de las Ecuaciones de Riesgo en el Mediterráneo Sur de Europa* [HERMES]) Study conducted in Girona in people aged 35-79 in 2005[179].

Among the factors that limit the effectiveness of opportunistic screening are nonattendance at the practice by healthy patients and the preference for immediate care related to health problems that take precedence over preventive issues[178].

Rose proposed a third preventive strategy based on modification of the conditions that lead to a particular risk factor distribution in a given population. This strategy is known as the "population" approach: although the excess risk is low for individuals at average risk factor levels, so many are exposed to it that in absolute terms the effect is large[13, 56]. This approach relies basically on population lifestyle modification that leads to the desired beneficial shift in the population risk factor distribution.

Some advantatges arise from focussing efforts on the entire population, and not just on high-risk individuals. First, many of the underlying causes are behavioural; therefore they depend on social factors and individual preferences. Second, changes in the IHD incidence may reflect population-wide beneficial shifts in the associated risk factor distribution: even a small shift in the distributions may have a large effect on the number of individuals falling into the highly vulnerable tail. Third, frequently most of the risk factor-attributable cases occur in the low/moderate risk population with average risk factor levels[13, 56]. Since the popula-

tion approach includes the whole population as the target, these interventions require national policies with local approaches[180].

In summary, individual and population strategies are fundamentally different but provide complementary benefits and therefore should be introduced in parallel.

One way to predict the impact of medical and public health interventions on the health status of a population is to estimate the population attributable fraction (PAF)[181, 182]. This indicator is most commonly defined as the proportional reduction in average disease risk over a specified time interval that would be achieved by eliminating the exposure(s) of interest from the population while the distribution of other risk factors in the population remains unchanged[183]. Actually, the PAF is not a replacement for relative measures of effect; rather, they provide a public health dimension to the appraisal of risks[182, 183].

The assumptions underlying valid PAF estimation include a causal relationship between the risk factors and the disease; the immediate risk reduction of the exposed population when the risk factor is eliminated, to that of the non-exposed; and independence of the considered risk factors from other factors that influence the disease occurrence[181, 183].

The magnitude of PAF varies with age and region[68, 184-189], which are known to modify the risk factor prevalences[121, 190]. Moreover, the secular changes in the prevalence of risk factors should also have an effect on the value[190]. Another important determinant of the magnitude of PAF related to the relative risk or hazard ratio of the risk factor is the time of follow-up of the cohorts included in estimating these effect measurements[191, 192].

The clinical guidelines on IHD prevention promote an overall approach that would be similar worldwide, but adapted to different subgroups (e.g., geographic region) on the basis of the risk factor prevalence, event rates, and economic and cultural factors[59, 60]. In fact, the measures to prevent CVD will have an impact not only on the individuals at risk, but also on the population as a whole, as many individual attitudes are shaped by the community's attitude toward health problems[13, 56]. In addition, it is worth mentioning the current and future impact on the National Health System's sustainability of the treatment needed to prevent a given number of cardiovascular events[141]. All in all, the final measure of the effectiveness of public health programs or treatment interventions is population-based trends in disease incidence rates[2, 47].

2. HYPOTHESES

2.1 IHD incidence and mortality rates as well as case-fatality will have decreased in all or in subgroups of the population aged 25 to 74 years of six counties in Girona since 1990: improvements in therapeutics during the acute phase of the event may have played a determinant role in some of these changes, particularly case-fatality.

2.2 The goal for CVD prevention at population level is to lower the mean level of cardiovascular risk factors and shift the whole distribution of exposure in a favourable direction, as expressed by Geoffrey Rose in 1985[56]. The efforts directed to better risk factor control in the studied region in recent decades should result in population changes in prevalence and control of cardiovascular risk factors. The impact on IHD population incidence and mortality should, however, be observed in a distant future to take into account the induction time required for risk factors to operate or to decrease their influence on IHD population incidence.

2.3 South European populations, where incidence and mortality from IHD is low, have shown a cardiovascular risk factor prevalence close to that observed in countries characterized by much higher IHD incidence and mortality. Clinical management guidelines have contributed to homogenize medical practice in

Europe. Cardiovascular risk factor prevalence, control and management in stable IHD individuals should be consistent in France and Spain.

2.4 Attributable risk measures the proportion of disease cases over a specified time that would be prevented following elimination of the exposures, assuming the exposures are causal. Since this measure depends on the prevalence of the considered risk factor, it could differ by the epoch in which a survey is completed.

3. OBJECTIVES

3.1 To analyze trends in AMI mortality, incidence, attack rates, and 28-day case-fatality between 1990 and 1999 in the population aged 35-74 years in Girona, and to analyze trends in the use of therapies with proven efficacy in the acute phase of the patients hospitalized for AMI in the same period.

3.2 To analyze the trends of cardiovascular risk factor prevalence and distribution in 1995, 2000, and 2005 in the same Spanish population.

3.3 To compare cardiovascular risk factor prevalence, distribution, management and control in two independent surveys conducted in men with stable IHD from two countries in South Europe: France and Spain.

3.4 To estimate the PAF of classical and some emerging cardiovascular risk factors in the general population of Girona in 1995, 2000, and 2005.

4. METHODS & RESULTS

4.1. Chapter I

Gil M, Martí H, Elosúa R, Grau M, Sala J, Masiá R, Pérez G, Roset P, Bielsa O, Vila J, Marrugat J.
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Analysis of Trends in Myocardial Infarction Case-Fatality, Incidence, and Mortality Rates in Girona, Spain, 1990-1999

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Introduction and objectives. The incidence of myocardial infarction in Spain is low, and mortality has been decreasing over the last few decades. The objective of this study was to analyze trends in myocardial infarction mortality, incidence, attack rates, and 28-day case-fatality attack rates between 1990 and 1999 in the general population aged 35-74 years in Girona, Spain.

Methods. The study included all myocardial infarction cases in Girona classified according to the MONICA algorithm. Attack, incidence, mortality rates and case-fatality were calculated. In addition, the annual percentage change in each of these indicators during the study period was also calculated.

Results. The mean attack rate per 100,000 inhabitants was 258 (95% CI, 249-267) in men and 55 (95% CI, 51-59) in women. The mean mortality rate per 100,000 was 99 (95% CI, 93-104) in men and 25 (95% CI, 22-28) in women. Significant reductions in attack, incidence and recurrence rates were observed in men aged 35-64 years during the period 1990-1999, but not in men aged 65-74 years, nor in women.

Conclusions. Myocardial infarction incidence and mortality rates were low in the general population aged 35-64 years. Rates improved in men aged 35-64 years during the period 1990-1999, but not in those aged 65-74 years, which indicates that a combination of primary and secondary prevention has increased the age at which a myocardial infarction or its recurrence is observed. Rates in woman were lower and did not change during the study period.

Key words: *Myocardial infarction. Epidemiology. Mortality. Incidence. Trends.*

SEE EDITORIAL ON PAGES 342-5

A complete list of the REGICOR researchers can be found at: www.regicor.org/regicor_inv

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Análisis de la tendencia en la letalidad, incidencia y mortalidad por infgarto de miocardio en Girona entre 1990 y 1999

Introducción y objetivos. La incidencia por infarto de miocardio en España es baja y la mortalidad está disminuyendo en las últimas décadas. Hemos analizado las tendencias en las tasas de mortalidad, incidencia y ataque, y en la letalidad a 28 días por infarto de miocardio entre 1990 y 1999 en la población de 35 a 74 años de Girona.

Métodos. Se incluyeron todos los casos de infarto de miocardio de Girona clasificados según el algoritmo MONICA. Se calcularon las tasas de ataque, incidencia y mortalidad, y la letalidad, así como el porcentaje de cambio anual en cada uno de los indicadores durante el período analizado.

Resultados. La tasa anual media de ataque fue de 258 (intervalo de confianza [IC] del 95%, 249-267) y 55 (IC del 95%, 51-59) por 100.000 habitantes para varones y mujeres, respectivamente, y la de mortalidad de 99 (IC del 95%, 93-104) por 100.000 en varones y de 25 (IC del 95%, 22-28) por 100.000 en mujeres. Las tasas de ataque, incidencia y recurrencia disminuyeron significativamente en varones de 35 a 64 años durante el período 1990-1999, pero no en los de 65 a 74 años ni en las mujeres.

Conclusiones. La incidencia y la mortalidad por IAM fueron bajas en la población de 35 a 64 años, y mejoraron en los varones de 35 a 64 años durante el período 1990-1999, pero no en los de 65 a 74 años, lo que indica que la combinación de prevención primaria y secundaria ha retrasado la edad de aparición del infarto de miocardio o de las recurrencias. Las tasas en mujeres fueron inferiores y no cambiaron durante el período estudiado.

Palabras clave: *Infarto de miocardio. Epidemiología. Mortalidad. Incidencia. Tendencias.*

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of mortality in most industrialized countries.[1] In Spain, it was the cause of 11.2% of deaths in males and 9.6% in females in 2004,[2] although these rates vary considerably

ABBREVIATIONS

ARIC: atherosclerosis risk in communities
CHD: coronary heart disease
AMI: acute myocardial infarction
IBERICA: Research, Specific Search, and Registry of Acute Coronary Heart Disease
MONICA: Monitoring Trends and Determinants of Cardiovascular Diseases
REGICOR: Girona Heart Registry

between countries.[3,4] In southern European countries, mortality due to CHD and its incidence is between three to five times less than in northern countries, Spain having the second-lowest rates in Europe.[3-6]

In Spain, as in most western countries, mortality due to CHD has been decreasing since 1976,[2,7,8] probably due to the effect of primary prevention regarding improvements in controlling cardiovascular risk factors. This decrease can also be attributed to secondary prevention in the patients who have already presented a coronary event, which includes optimizing the risk factor profile and treatments and therapeutic interventions that can modify the natural history of the disease. Improvements in the treatment of the patients in the acute phase of a coronary event, such as the increase in the use of drugs with proven efficacy, have also helped to maintain this trend.[9-12] Primary prevention reduces the incidence of new coronary events, and secondary prevention, the number of recurrent events. In addition, improvements in treatment in the acute phase after a coronary event, such as acute myocardial infarction (AMI), would be associated with a decrease in the percentage of deaths among such patients. In order to study the influence of primary and secondary prevention on the evolution of case-fatality over time, and AMI incidence and mortality rates, the number of cases (fatal or not) of this disease in the population has to be calculated on an annual basis.[13]

The REGICOR project (Girona Heart Registry) has recorded all the patients with fatal and non-fatal AMI in the population of six regions in Girona since 1990.

The aim of this study was to analyze trends in AMI mortality, incidence, attack, and 28-day case-fatality rates between 1990 and 1999 in the population aged 35-74 years in Girona, and trends in the use of therapies with proven efficacy in the acute phase of the patients hospitalized for myocardial infarction in the same period.

METHODS

The methodology used to identify and classify the cases has already been published.[3,6] In short, a population of 227 598 inhabitants aged 35-74 years was studied in six regions in Girona (1996 census). All AMI episodes in residents from the area were included in the registry: this was done prospectively, regarding those admitted to the only referral hospital in the area, and retrospectively regarding the nine regional hospitals. Furthermore, patients transferred to hospital centers from outside the area were identified. Patients who died without managing to contact the hospital system were identified by reviewing the mortality record, and all suspected cases of death due to CHD were investigated by interviewing the certifying physician and, if necessary, the family.[14]

Diagnostic and Selection Criteria

In order to be eligible, the subjects had to be clinically diagnosed with AMI or angina. Once identified, the patients were classified according to the MONICA (MONItoring of trends and determinants in CArdiovascular diseases) project algorithm,[14] which takes into account the type of symptoms, electrocardiographic findings, enzymes and, for fatal cases only detected through the registry of deaths, a background of CHD and the autopsy results, if carried out. According to this information, each case investigated was classified as: ischemic cardiac arrest successfully resuscitated, noncoronary death, definite AMI (fatal or non-fatal), possible AMI (fatal), and fatal case with insufficient data to classify it in one of the previous categories. The last four constitute definition 1 in the MONICA study, and are used to present the data in our study.[14]

Statistical Analysis

The following annual rates have been calculated: *a)* attack (or cumulative incidence): number of cases of AMI (first or recurrent) per 100 000 population; *b)* incidence: number of first AMI per 100 000 population; *c)* recurrence: number of cases of recurrent AMI per 100 000 population; *d)* hospitalization: number of AMI patients admitted to hospital alive per 100 000 population; *e)* mortality: fatal cases per 100 000 population; this mortality rate was also calculated depending on whether death occurred in or outside the hospital; *f)* case-fatality in the population: percentage of fatal cases in the first 28 days among all the patients with AMI in the region studied; and *g)* in-hospital case-fatality: percentage of fatal cases among the patients with AMI arriving at the hospitals alive. All the indicators were calculated separately for every year for the period studied.

The annual inter-census estimations — calculated on the basis of the electoral censuses of 1991 and 1996 — were used as denominators to calculate the annual rates.

The rates, which were standardized using the direct method, are presented using the world population as the reference: 12, 11, 8, and 5 for the age groups 35-44, 45-54, 55-64, and 65-74 years, respectively.[15] Case-fatality was standardized by calculating weights based on the standard distribution by patient age-group: 7, 16, 26, and 50 for the age groups 35-44, 45-54, 55-64, and 65-74, respectively.[6,14]

To analyze trends, log-linear models were used assuming a Poisson distribution.[16,17] Aggregate data were analyzed and adjusted using the following general linear model:

$$\ln(E[M_{e,t}])=\alpha_0+\alpha_e e+\beta_1 t+\beta_2 t^2+\gamma_e te+\eta_e t^2+\ln(P_{e,t})_{e,t}$$

where t is the period, $M_{e,t}$ is the number of cases in age group *e* and period *t*, $E[M_{e,t}]$ is the number of cases expected in age group *e* and period *t*, α_0 is the model constant, α_e are coefficients of the age groups (e)m, β_1 is the coefficient of the period (t), β_2 is the coefficient of the quadratic term for the period, γ_e is the interaction between the age groups and the period, η_e is the interaction between the age groups and the quadratic term of the period, and $\ln(P_{e,t})_{e,t}$ is the natural logarithm of the risk population in age group *e* and period *t*. This term is equivalent to standardization by age.

The annual percentage change (APC) was estimated using the expression $APC=(e^{\beta 1+\gamma e}-1)\times 100$. For the indicators where there is significant interaction between age groups and period, PCA was estimated using the expression $APC=(e^{\beta 1+\gamma e}-1)\times 100$.

RESULTS

Between 1990 and 1999, 3951 eligible cases were recorded: 75.8% were classified as definite AMI and the remainder as possible AMI (fatal), or unclassifiable due to insufficient data (Table 1).

Table 2 presents the mean annual attack rate (first and recurrent) in the population aged 35-74 years between 1990 and 1999. The standardized mean annual incidence rate (first AMI only) was: 178 (95% confidence interval [CI], 170-185) per 100 000 males between 35-74 years and 39 (95% CI, 35-42) per 100 000 females. It could not be determined if there was a background of AMI in 14.1% of the cases. If the cases without information on a background of AMI were all incident cases, the standardized mean annual incidence rate would be 212 (95% CI, 203-220) per 100 000 males and 48 (95% CI, 44-51) per 100 000 females. Both approaches showed that the conclusions regarding the trends were similar.

On the other hand, the mean annual age-specific and age-standardized mortality rates are presented in Table 2. The standardized mean annual out-of-hospital mortality rate for the population between 35-74 years was 68 (95% CI, 63-72) and 16 (95% CI, 14-18) per 100 000 males and females, respectively. The standardized mean annual hospital mortality rates were 31 (95% CI, 28-34) and 9 (95% CI, 7-10) per 100 000 males and females, respectively.

Table 3 shows the distribution of mean case-fatality by age and by sex. The standardized population mean 28-day case-fatality rate in the age group between 35-74 years in the study period was 42.1% (95% CI, 41.5%-42.8%). The age-standardized hospital case-fatality rate in the period 1990-1999 was 20.0% (95% CI, 19.6%-20.5%). Both were significantly higher in females than in males (Table 3). Some 66.8% of the fatal episodes occurred without patients accessing specialized hospital care: 67.8% in males and 63.2% in females.

TABLE 1. **Distribution of Fatal and Nonfatal Acute Myocardial Infarction in Patients Aged 35-74 Years in the Different Diagnostic Categories and by Sex. Aggregate Data 1990-1999***

AMI Case Classification	Males	Females	Total
Definite non-fatal	1885 (59.7%)	421 (53.1%)	2306 (58.4%)
Definite fatal	554 (17.5%)	134 (16.9%)	688 (17.4%)
Possible fatal	397 (12.6%)	105 (13.2%)	502 (12.7%)
Fatal with insufficient data	322 (10.2%)	133 (16.8%)	455 (11.5%)
Total	3158	793	3951

*AMI indicates acute myocardial infarction.

TABLA 2. **TAttack Rates and Mean Annual Mortality (Per 100 000 Population and Year) Due to AMI. Period 1990-1999. Distribution by Sex and Age Groups. Definite Fatal or Non-Fatal Cases, Possibly Fatal or Those With Insufficient Data**

	Attack Rate (Cumulative Incidence)		Mortality Rate	
	Males	Females	Males	Females
35-44 years	65	6	15	3
45-54 years	188	21	50	8
55-64 years	361	79	136	30
65-74 years	709	211	349	109
35-64 years*	185 (176-194)	30 (27-34)	59 (54-64)	12 (9-14)
35-74 years*	258 (249-267)	55 (51-59)	99 (93-104)	25 (22-28)

*Mean annual standardized rates using world population weights. Rate (95% confidence interval).

Trend Analysis

Models were adjusted to analyze the effect of the year of registry on the different rates, including age groups

TABLE 3. **Population and in-Hospital Standardized 28-Day Case-Fatality. Definite Fatal or Non-Fatal Cases, Possible Fatal Cases or Those With Insufficient Data. Aggregate Data 1990-1999**

	Population Case-Fatality		In-Hospital Case-Fatality	
	Males n/N, %	Females n/N, %	Males n/N, %	Females n/N, %
35-44 years	52/229 (22.7%)	10/21 (47.6%)	19/195 (9.7%)	6/17 (35.3%)
45-54 years	138/522 (26.4%)	21/55 (38.2%)	27/410 (6.6%)	3/37 (8.1%)
55-64 years	336/890 (37.8%)	76/203 (37.4%)	109/657 (16.6%)	21/148 (14.2%)
65-74 years	747/1517 (49.2%)	265/514 (51.6%)	255/1022 (24.9%)	107/355 (30.1%)
35-64 years*	33.3% (32.6-34.0)	39.1% (35.8-42.4)	13.2% (12.8-13.7)	15.2% (13.3-17.2)
35-74 years*	41.6% (40.9-42.3)	45.3% (44.0-46.7)	19.3% (18.8-19.9)	22.6% (21.7-23.6)

*Standardized rates by patient age distribution in the MONICA study.

35-44, 45-54, 55-64, and 65-74 years. A different trend was found in the age group 65-74 years compared to age groups 35-44, 45-54, and 55-64 years, which behaved similarly. This interaction between age group and year of registry was statistically significant in males for attack rates (P=.01) and recurrence (P=.04) and was marginally significant for mortality (P=.09) (Figure 1A). The interaction did not reach statistical significance in any of the indicators for females (Figure 1B). Table 4 presents the mean annual changes in the linear trend for different indicators for age groups 35-64 and 65-74 years in males. There was a statistically significant decrease in attack, incidence, recurrence, and hospitalization rates in males aged 35-64 years. There were no statistically significant annual changes in any of these in males aged 65-74 years. On the other hand, mortality rates remained stable in males in both age groups during period studied. In-hospital case-fatality significantly decreased in males aged 65-74 years, whereas population case-fatality remained stable in both groups.

No statistically significant changes were found in any of the frequency or case-fatality indicators analyzed in females (Table 4).

Figure 2 shows the evolution of the percentage of patients hospitalized and treated in the acute phase of AMI with those drugs and procedures demonstrating their efficacy in clinical trials. Thus, between 1990 and 1999, a significant increase was seen in the percentage of patients who received the different treatments. On the other hand, patient severity as measured by maximum Killip class did not change significantly (from 17.2% Killip class III-IV to 19.3%, respectively) during the period studied.

DISCUSSION

Our results show that Girona, as in other areas of Spain and southern Europe, has lower AMI attack and mortality rates in the population aged 35-64 years than those of other industrialized countries.[3-6] The incidence in the population aged 65-74 years is much higher than that in younger people of both sexes and, alarmingly, the population 28-day case-fatality due to AMI continues to be above 40%.[18] The evolution of the indicators is different according to age group in males: the decrease in the number of cases in the population aged 35-64 years was not found in those aged 65-74 years. This indicates that the combination of primary and secondary prevention in the area has contributed to a delay in the incidence or recurrence of AMI in those aged 35-64 years to more advanced ages.

In males, the decrease in in-hospital case-fatality indicates that health care in the acute phase in AMI patients has significantly helped to reduce the number

TABLE 4. **Annual Percentage Change in Girona 1990-1999 for the Different Epidemiological Indicators of Myocardial Infarction by Sex and Age Group in Males**

	Males			Females
	35-64 Years	65-74 Years	Total	35-74 Years
Attack rate	–1.9 (–3.6~–0.3)	1.1(–0.6~2.9)	–0.005 (–1.2~1.2)	–0.7 (–3.1~1.7)
Incidence rate	–2.1 (–4.0~–0.1)	–0.5 (–2.7~1.7)	–0.97 (–2.4~0.5)	0.5 (–2.4~3.4)
Recurrence rate	–5.6 (–9.6~–1.5)	2.2 (–1,6~6,1)	–0.8 (–3.6~2.0)	–4.2 (–10.3~2.2)
Hospitalization rate	–2.7 (–4.5~–0.8)	–1.4 (–3.5~0.7)	–1.7 (–3.1~–0.25)	–0.3 (–3.1~2.7)
Mortality rate	–2.0 (–4.8~1.0)	1.4 (–1.1~4.0)	0.5 (–1.4~2.5)	–1.7 (–5.1~1.8)
Population case-fatality	–0.05 (–3.0~3.0)	0.3 (–2.2~2.9)	0.2 (–1.7~2.2)	–1.1 (–4.6~2.5)
In-hospital case-fatality	–4.4 (–9.5~1.0)	–6.4 (–10.4~–2.1)	–5.4 (–8.6~–2.1)	–2.7 (–8.1~3.3)

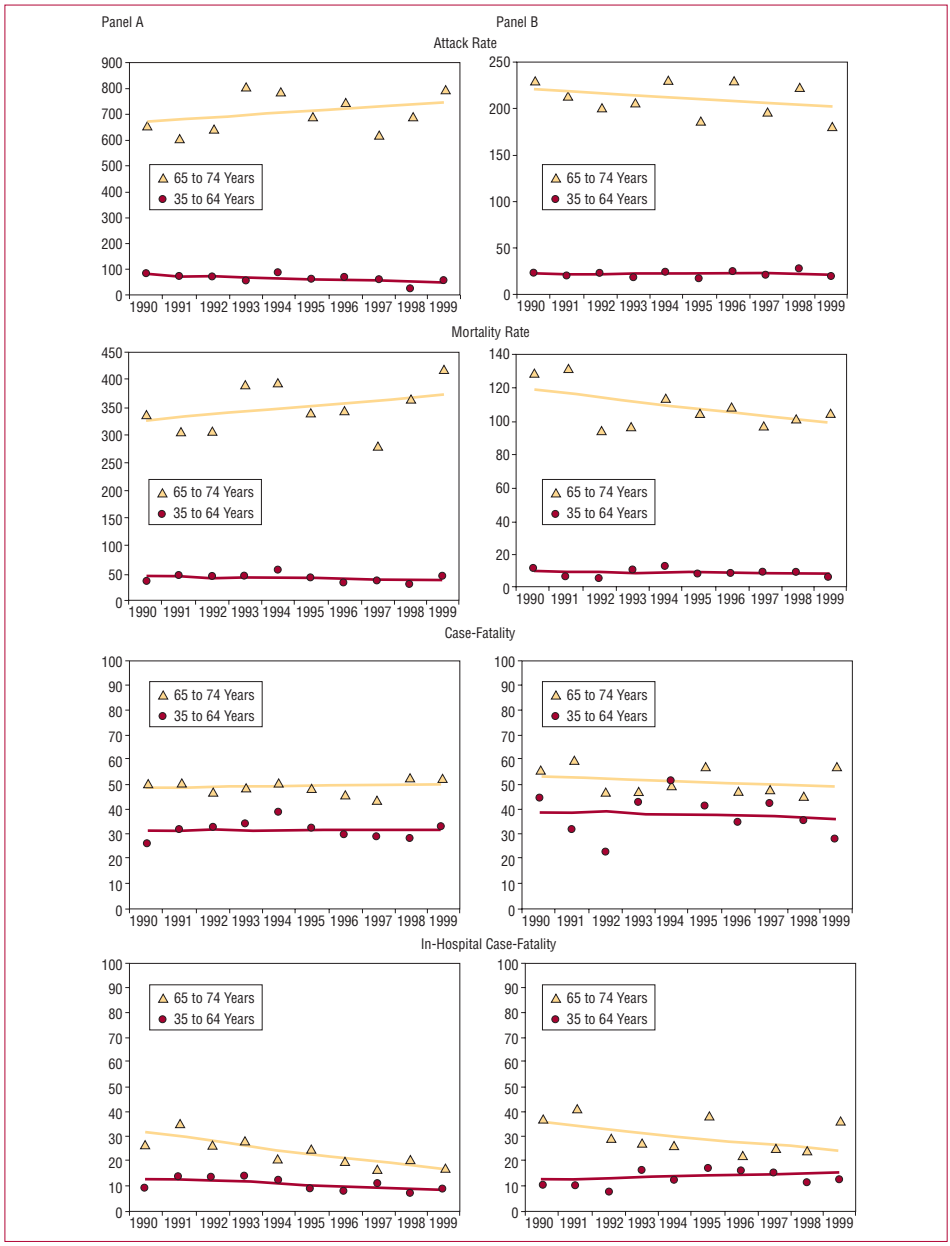

Figure 1. Evolution of attack and mortality rates per 100 000 population, and total and in-hospital case-fatality rates due to myocardial infarction for two age groups in males (A) and females (B) with their linear trends. Definite infarction, fatal or non-fatal, possible fatal or those with insufficient data are included. Period 1990-1999.

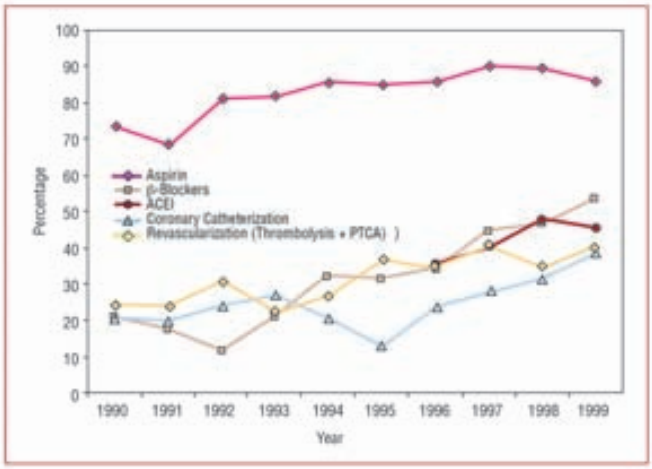

Figure 2. Percentage of patients hospitalized due to myocardial infarction receiving therapies with proven efficacy in the acute phase. Period 1990-1999.

of fatal cases in the patients who reach hospital, although those over 64 years seem to have benefited more. There is no significant change in any indicator in females. This is probably due to the limited statistical power of the study, due to the very small number of cases of AMI in the female population and, perhaps, to the structural impossibility of modifying the indicators which are among the lowest in the world.

The population 28-day case-fatality after AMI in the present registry was lower (33.3% in males and 39.1% in females) than the mean in the MONICA project (49.0% and 53.8%, respectively) for the age group 35-64 years.[4,19] This indicates that patient prognosis is better in Girona due to hospital treatment improving in the period between the two registries, the patients presenting less severe AMI or better access to hospitals. Case-fatality is 19% higher in females than in males. The countries with the lowest incidence of AMI have greater case-fatality in females than in males.[4] It has been hypothesized that in the countries with low incidence non-fatal cases are diagnosed less frequently in females.[4,7,20] The reasons for this variability should be investigated via specific in-depth studies.[21,22]

Some 66.8% of the patients who die do so before arriving at hospital. This percentage is higher in males than females, indicating that death is basically due to heart failure rather than acute complications such as ventricular arrhythmias.[22]

Trend Analysis

Changes in incidence, attack, and out-of-hospital mortality rates tend to reflect the effects of primary prevention due to the changes in risk factors at the population level. On the other hand, the changes in case-fatality, especially in-hospital, are related to changes in the treatment of AMI patients or to severity in patients admitted to hospital. The changes in the recurrence rate would depend on the success of secondary prevention, both regarding controlling risk factors and the pharmacological treatment of the CHD patients.[4,23-25] The situation is probably more complex in practice since the effects of treatment in the acute phase and primary and secondary prevention overlap.[4,10,24]

The decrease in the incidence, attack and recurrence rates in the population under 65 years, which is not found in the population aged 65-74 years, may reflect an improvement in the prevalence of risk factors thanks to primary and secondary prevention, thereby delaying the appearance of incident and recurrent AMI to more advanced ages. Other studies have supported the likelihood of this hypothesis in other contexts.[13,26,27]

In-hospital case-fatality has improved in males. This indicates that the treatment of the patients who arrive at hospital alive has been optimized, since its severity has not changed during the period studied. In fact, the percentage of patients who receive therapies with proven efficacy has increased during the study period. The effectiveness of this process of improvement in the use of platelet aggregation inhibitors and thrombolysis in the region has been shown in previous studies.[9,28,29]

Although the case-fatality of patients arriving at hospital alive (in-hospital case-fatality) has decreased considerably, the population case-fatality remains stable, both for males and females.[18] In fact, some two-thirds of the deaths occur before the patient contacts the health system. This high percentage of out-of-hospital deaths highlights the key role of primary prevention in reducing AMI mortality.

The two main multicenter collaborative studies, MONICA, and Atherosclerosis Risk In Communities (ARIC), which were designed to analyze the trends in mortality and its determinants, differ in their conclusions regarding assessing the relative importance of changes in treatment or modification of risk factors in the reduction in observed mortality.[4,8] Whereas the MONICA project researchers concluded that the reduction in mortality observed between 1985 and 1994 was basically due to a decrease in the number of cases, the ARIC study researchers (done in several communities in the United States) pointed out the key role in increased patient survival of improvements in treatment. Part of this discrepancy could be explained by the differences in the age groups analyzed (35-74 in the ARIC study and 35-64 years in MONICA), case definition, and study periods, in addition to the high percentage of Afro-American patients in the ARIC study and inequalities in access to the health services in the United States.

The results from the different centers in the MONICA study[4] varied considerably regarding the age group 35-64 years. Both the attack and case-fatality rate decreased or remained stable in most western European centers. In the MONICA-Catalonia center the attack rate increased in males (1.0% per year) and case-fatality decreased in all the age groups (35-74 years).[4,19] Part of these differences could be explained by the overlap of only 5 years between our registry and the MONICA-Catalonia registry, and the presence of an interaction between our age group and year of selection data, which is not addressed in the MONICA-Catalonia study.

Characteristics and Limitations of the Study

One of the problems common to AMI population registries is that it is not possible to obtain all the information necessary for definitively classifying the etiology of death, usually sudden, in some fatal out-of-hospital cases. Cases with "insufficient data" form a percentage of deaths similar to the MONICA study mean.[4]

The linear trend is the simplest of those trends that can be compared and the one more frequently used by authors who have addressed this type of analysis.[4,8,19,25-27,30] Analyzing the trends via other nonlinear functions (quadratic or cubic) may present difficulties given the number of years available. A steady increase in the indicators of incidence and mortality in males was observed up to 1994 which subsequently decreased; thus, the evolution of these two indicators seems to be quadratic in form.

The trend analysis in woman and its interpretation is limited by the low number of events and the consequent instability of the estimations.

The results of the IBERICA[6] (Research, Specific Search, and Registry of Acute Coronary Ischemia) study indicate that Girona has the lowest rate in the regions studied and, thus, cannot be extrapolated regarding magnitude to the rest of Spain. However, there is no reason why the temporal changes should be different from those observed in other regions.

CONCLUSIONS

Incidence and mortality rates due to AMI are low in Girona. Almost half of the patients with AMI die within 28 days following symptom onset and two-thirds of these without accessing hospital care. The improvements found in the attack, incidence and recurrence rates of cases of AMI in males aged 35-64 years between 1990 and 1999 were not seen in those aged 65-74 years, indicating a delay in age regarding AMI onset or recurrence. Attention in the acute phase of AMI has probably helped to reduce the number of fatal cases in hospitalized males, especially in those over 64 years. There are no changes in any indicator in females, who present extraordinarily low rates.

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4. METHODS & RESULTS

4.2 Chapter II

Grau M, Subirana I, Elosua R, Solanas P, Ramos R, Masiá R, Cordón F, Sala J, Juvinyà D, Cerezo C, Fitó M, Vila J, Covas MI, Marrugat J.

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Original Scientific Paper

Trends in cardiovascular risk factor prevalence (1995–2000–2005) in northeastern Spain

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Background **High prevalence of cardiovascular risk factors has been observed in Spain along with low incidence of acute myocardial infarction. Our objective was to determine the trends of cardiovascular risk factor prevalence between 1995 and 2005 in the 35–74-year-old population of Gerona, Spain.**

Design **Comparison of cross-sectional studies were conducted in random population samples in 1995, 2000, and 2005 at Gerona, Spain.**

Methods **An electrocardiogram was obtained, along with standardized measurements of body mass index, lipid profile, systolic and diastolic blood pressure, glycaemia, energy expenditure in physical activity, smoking, use of lipid-lowering and antihypertensive medications, and cardiovascular risk. Prevalence of diabetes, hypertension, and obesity was calculated and standardized for age.**

Results **A total of 7571 individuals (52.0% women) were included (response rate 72%). Low-density lipoprotein cholesterol >3.4 mmol/l (130 mg/dl) (49.7%) and hypertension (39.1%) were the most prevalent cardiovascular risk factors. In 1995, 2000 and 2005, low-density lipoprotein cholesterol decreased in both men and women: 4.05–3.91–3.55 mmol/l (156–151–137 mg/dl) and 3.84–3.81–3.40 mmol/l (148–147–131 mg/dl), respectively. Increases were observed in lipid-lowering drug use (5.7–6.3–9.6% in men and 4.0–5.8–8.0% in women), controlled hypertension (14.8–35.4–37.7% in men and 21.3–36.9–45.0% in women); (all *P*-trends <0.01), and obesity (greatest for men: 17.5–26.0–22.7%, *P*-trends=0.020). Prevalence of myocardial infarction or possibly abnormal Q waves in electrocardiogram also increased significantly (3.9–4.7–6.4%, *P*-trends=0.018).**

Conclusions **The cardiovascular risk factor prevalence change in Gerona was marked in this decade by a shift of total cholesterol and low-density lipoprotein cholesterol distributions to the left, independent of the increase in lipid-lowering drug use, and better hypertension control with increased use of antihypertensive drugs.** ***Eur J Cardiovasc Prev Rehabil*** **14:653–659 © 2007 The European Society of Cardiology**

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Keywords: blood pressure, cardiovascular disease, cholesterol, coronary disease, epidemiology, lipids, risk factors

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Introduction

Coronary heart disease (CHD) is the primary cause of population mortality and morbidity in industrialized countries [1,2], but geographical variability is substantial;

France and Spain show particularly low rates. Several coronary risk factors (CRF) have been identified in recent decades [3,4] and most of them are causally associated with CHD. Therefore, the goal for CHD prevention at the population level is to lower the mean level of CRFs and shift the whole distribution of exposure in a favorable direction [5]. In this context, it is important to collect valid information about the prevalence of CRFs and their time trends in the population.

Estimations of the prevalence of classic CRF in Spain have been made in population samples from various communities and groups of workers [6–8]. Analyses of trends in CRF prevalence, however, are seldom done [9]. Knowledge of the trends in prevalence and control of CRF, and of the impact on CHD population incidence and mortality, when changes occur is essential to design and implement preventive public health interventions.

The aim of this study was to analyze the trends of CRF prevalence and distribution in 1995, 2000, and 2005 in the same Spanish population.

Methods

Population

Population-based cross-sectional studies were conducted in the province of Gerona, in north-eastern Spain, in 1995, 2000, and 2005. The reference population was approximately 600 000 inhabitants [10].

We selected participants aged 35–74 years stratified by 10-year age and sex groups for the present analysis. A two-stage sampling method was used in 1995 and 2000: 33 and 17 towns, respectively, were randomly selected in the first stage. Half of the towns were urban (> 10 000 inhabitants) and half were rural (500–10 000 inhabitants). In both studies, the second sampling stage consisted of randomly recruiting the same number of women and men participants, stratifying by 10-year age groups from the closest census. The survey of 2005 was conducted on a random sample of participants from the city of Gerona (approximately 70 000 inhabitants) and three surrounding rural towns. In all three surveys, selected participants were contacted by a letter informing them of the aims of the study and the tests to be performed. Participants were requested to fast for at least 10 h before their appointment at the health examination site; a telephone number for inquiries was also supplied. Participants who provided a phone number were contacted 1 week before the examination to confirm attendance.

The sample size in each survey was designed to allow (i) at least an 80% chance to detect as statistically significant ($P < 0.05$) differences of at least 15, 11 and 10% units in a categorical variable, with a point estimate of 50% between any two strata in the surveys of 1995, 2000 and 2005, respectively, and (ii) a statistical power > 85% to detect differences greater than 6% units among the three surveys in each sex at a P value of 0.05.

All participants were duly informed and signed their consent to participate in the studies. The studies were approved by the local ethics committee and the results of the examination were sent to participants.

Measurements

Examinations were performed by a team of trained nurses and interviewers who used the same standard questionnaires and measurement methods in all three surveys [11].

A precision scale of easy calibration was used for weight measurement with participants in underwear. Height was also measured. Body mass index (BMI) was determined as weight divided by squared height (kg/m^2).

Blood pressure was measured with a periodically calibrated mercury sphygmomanometer. A cuff adapted to upper arm perimeter (young, adult, obese) was selected for each participant. Measurements were performed after a 5-min rest. Two measurements were taken, at least 20 min apart, and the lower value was recorded for the study. The cut-off points for blood pressure followed the criteria in the Seventh Report of the Joint National Committee [12].

The following rates were calculated regarding hypertension and its treatment and control (i) history of hypertension: when participants reported a previous diagnosis or treatment for hypertension; (ii) real hypertension: systolic blood pressure (SBP) $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg in previously nondiagnosed and nontreated participants; (iii) treated hypertension: patients with history of hypertension under drug treatment but not satisfactorily controlled; and (iv) controlled hypertension: SBP < 140 and DBP < 90 mmHg in participants with treated hypertension. SBP and DBP reference values were 130/85 mmHg for population with diabetes.

A standard 12-lead electrocardiogram (ECG) recording was obtained for each participant and interpreted by the same senior cardiologist in all three surveys. We present the proportion of participants with possibly abnormal Q waves, left ventricular hypertrophy by ECG Minnesota code [13], complete right or left branch block, and rhythm disorders, which includes ventricular extrasystolia, and atrial fibrillation or flutter. Participants were asked to disclose previous diagnosis of acute myocardial infarction (AMI); we present the combined information of history of AMI or possibly abnormal Q waves in ECG.

Blood was withdrawn after 10–14 h fasting, with less than 60-s duration. Serum sample aliquots were stored at

–80°C. Total cholesterol and triglyceride concentrations were determined enzymatically (Roche Diagnostics, Basel, Switzerland). High-density lipoprotein cholesterol (HDL-c) was measured as cholesterol after precipitation of apoprotein B-containing lipoproteins with phosphotungstic-Mg^{2+} (Boehringer, Mannheim, Germany). Analyses were performed in a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Basel, Switzerland). Quality control was performed with External Quality Assessment – WHO Lipid Program (WHO, Prague, Czech Republic) and Monitrol-Quality Control Program (Baxter Diagnostics, Dudingen, Switzerland). Interassay coefficients of variation were 2.5, 4.5, and 3.2% for total cholesterol, HDL-c, and triglycerides, respectively. Low-density lipoprotein cholesterol (LDL-c) was calculated by the Friedewald equation whenever triglycerides were < 3.4 mmol/l (300 mg/dl).

Glucose metabolism alterations were classified as follows (i) history of diabetes: participants already diagnosed by a physician; (ii) impaired fasting glycaemia: fasting glycaemia 6.1–6.9 mmol/l (110–125 mg/dl) in participants not diagnosed previously with diabetes; and (iii) real diabetes: participants with history of diabetes or with a fasting glycaemia > 6.9 mmol/l (125 mg/dl). Insulin and oral antidiabetic treatments were also recorded.

Cardiovascular risk in participants free of CHD symptoms was calculated by the REGICOR (*Registre Gironí del Cor*) function adapted from the original Framingham function and validated for Spain [14,15].

The Minnesota leisure-time physical activity questionnaire validated for the Spanish population was used to assess the amount of leisure time physical activity performed during the previous year [11,16,17]. This questionnaire allows us to estimate the average daily energy expenditure in physical activity in the last year.

Statistical analysis

Prevalence is presented by sex and is standardized for the world age distribution. Continuous variables are presented as mean and standard deviation or median and interquartile range when their distribution departs from normal (e.g. glycaemia, triglycerides, and energy expenditure in physical activity), and categorical variables as proportions.

Analysis of variance and Kruskall–Wallis tests were used as appropriate to compare means and medians of continuous variables, respectively. Chi-squared test was used to compare proportions. To assess the linear trend of variables, analysis of variance and chi-squared tests were used. Standardization for age was done using the world standard population [18].

Statistical analysis was done with *R* Statistical Package (*R* Foundation for Statistical Computing, Vienna, Austria; Version 2.0).

Results

We included 7571 individuals aged 35–74 years: 1480 individuals (52.1% women) from 1995, 2540 (51.1% women) from 2000, and 3551 (52.7% women) from 2005. The response rates in these three surveys were 72.4, 70.0, and 73.8%, respectively.

Table 1 shows the lipid profile by sex, observed in the three surveys. Total cholesterol and LDL-c decreased steeply and significantly for both sexes, resulting in a shift of the entire population distribution curve of 2005 to the left as compared with those of 2000 and 1995 (Fig. 1a). On the contrary, the HDL-c mean showed no significant change (Fig. 1a). A significant increase in the percentage of participants under lipid-lowering treatment was observed. A sensitivity analysis, however, showed that the LDL-c trends held after excluding participants with lipid-lowering drugs: values were 4.02 (1.00), 3.91 (0.97), and 3.57 (1.01) mmol/l [155 (39), 151 (37), and 138 (39) mg/dl], *P*-trends < 0.001, for men; and 3.83 (1.06), 3.81 (1.00), and 3.41 (1.07) [148 (41), 147 (39), and 132 (42) mg/dl], *P* trends < 0.001, for women.

SBP significantly decreased in both sexes (Tables 2 and 3). Awareness of hypertension tended to increase together with the percentage of participants with hypertension and with participants with controlled hypertension in both sexes.

Glycaemia and the proportion of participants with impaired fasting glycaemia values decreased in both sexes (Tables 2 and 3). History of diabetes increased in men, but not in women; BMI tended to increase among men, although reported physical activity also increased over the studied period in both sexes.

The percentage of smokers significantly decreased, although this continued to be over 30% in men and actually increased in women to 21% in 2005. The percentage of ex-smokers increased for both sexes. The mean of 10-year cardiovascular risk remained unchanged over these 10 years for men, and decreased a little, but significantly, for women (Tables 2 and 3).

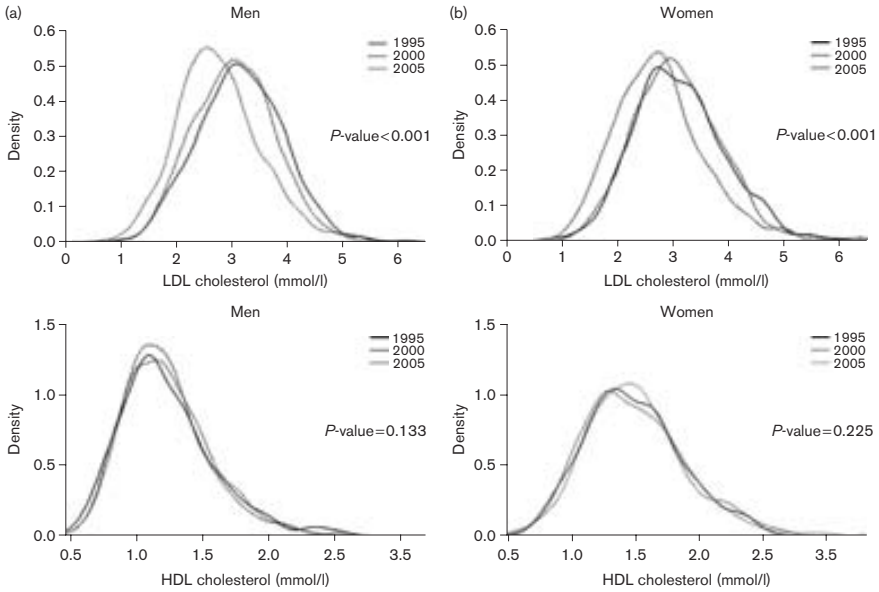
The prevalence of several ECG disorders is shown by sex in Table 4. Intraventricular conduction disorders were by far the more prevalent ECG finding in both sexes. The percentage of men with ECG signs of left ventricular hypertrophy and definite or possible AMI increased a little, but significantly.

Table 1 **Lipid profile and lipid-lowering treatment in population of Gerona aged 35–74 years from 1995 to 2005**

	1995	2000	2005	*P* value	*P* for trends
Men	*N*=709	*N*=1243	*N*=1681		
Total cholesterol (mmol/l)[a]	5.91 (1.12)	5.76 (1.09)	5.47 (1.09)	<0.001	<0.001
Total cholesterol >6.5 mmol/l (250 mg/dl)[b]	196 (30.0)	262 (23.5)	279 (17.1)	<0.001	<0.001
HDL-c (mmol/l)[a]	1.24 (0.38)	1.21 (0.32)	1.23 (0.33)	0.133	–
HDL-c <1.0 mmol/l (40 mg/dl)[b]	207 (30.8)	350 (31.3)	478 (28.4)	0.162	–
LDL-c (mmol/l)[a]	4.05 (1.02)	3.91 (0.98)	3.55 (1.00)	<0.001	<0.001
LDL-c >3.4 mmol/l (130 mg/dl)[b]	473 (74.6)	751 (70.3)	852 (53.1)	<0.001	<0.001
Triglycerides (mmol/l)[c]	1.20 (0.85–1.70)	1.22 (0.89–1.67)	1.23 (0.89–1.74)	0.291	–
Triglycerides >2.3 mmol/l (200 mg/dl)[b]	79 (12.6)	99 (9.28)	212 (13.6)	0.012	0.148
Lipid-lowering treatment[b]	51 (5.70)	94 (6.28)	211 (9.58)	<0.001	<0.001
Women	*N*=771	*N*=1297	*N*=1870		
Total cholesterol (mmol/l)[a]	5.79 (1.17)	5.79 (1.15)	5.43 (1.21)	<0.001	<0.001
Total cholesterol >6.5 mmol/l (250 mg/dl)[b]	210 (25.0)	329 (25.4)	360 (16.7)	<0.001	<0.001
HDL-c (mmol/l)[a]	1.49 (0.37)	1.48 (0.40)	1.51 (0.38)	0.225	–
HDL-c <1.2 mmol/l (46 mg/dl)[b]	238 (32.5)	413 (36.5)	552 (28.5)	<0.001	0.010
LDL-c (mmol/l)[a]	3.84 (1.06)	3.81 (1.01)	3.40 (1.06)	<0.001	<0.001
LDL-c >3.4 mmol/l (130 mg/dl)[b]	474 (64.2)	767 (65.1)	951 (47.2)	<0.001	<0.001
Triglycerides (mmol/l)[c]	0.92 (0.69–1.26)	0.92 (0.70–1.25)	0.94 (0.69–1.32)	0.248	–
Triglycerides >2.3 mmol/l (200 mg/dl)[b]	30 (3.48)	40 (3.07)	101 (4.56)	0.036	0.053
Lipid-lowering treatment[b]	43 (3.95)	98 (5.78)	202 (7.98)	<0.001	<0.001

'*P* for trends' have not been computed for those variables whose differences were not significant among the 3 years. To convert total, HDL and LDL cholesterol to mg/dl, multiply by 38.61. To convert triglycerides to mg/dl, multiply by 88.50. HDL-c, High density lipoprotein cholesterol; LDL-c, Low density lipoprotein cholesterol. [a]Mean (standard deviation). [b]*N* (%). [c]Median (25th percentile. 75th percentile).

Fig. 1



(a) Distribution of LDL-c (above) and HDL-c levels (below) in male population aged 35–74 years. (b) Distribution of LDL-c (above) and HDL-c levels (below) in female population aged 35–74. Three measurements over the past decade are presented. HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

Discussion

The most prevalent CRFs in Gerona in the past 10 years were consistently LDL-c >3.4 mmol/l (130 mg/dl) (50.8%) and hypertension (44.8%). A substantial decrease, however, occurred in total and LDL-c mean values, but not in HDL-c, with a shift to the

Table 2 Coronary risk factors in male population of Gerona aged 35–74 from 1995 to 2005

	1995 (*N*=709)	2000 (*N*=1243)	2005 (*N*=1681)	*P* value	*P* for trends
Systolic blood pressure (mmHg)[a]	131 (19)	134 (18)	128 (17)	<0.001	<0.001
Diastolic blood pressure (mmHg)[a]	81 (11)	82 (9)	80 (10)	<0.001	0.166
History of hypertension *N* (%)	168 (19.8)	331 (23.8)	603 (29.6)	<0.001	<0.001
Real hypertension *N* (%)	350 (44.5)	680 (50.6)	854 (43.6)	0.074	–
Treated hypertension *N* (%)[b]	99 (36.8)	152 (32.5)	362 (44.8)	<0.001	0.018
Controlled hypertension *N* (%)[c]	16 (14.8)	20 (35.4)	84 (37.7)	0.008	0.011
History of diabetes *N* (%)	97 (11.5)	140 (9.7)	259 (11.7)	0.004	0.052
Glycaemia (mmol/l); (mg/dl)[d]	5.58 (5.12–6.10)	5.71 (5.25–6.30)	5.27 (4.84–5.89)	<0.001	0.022
Impaired fasting glycaemia *N* (%)[e]	90 (12.6)	154 (15.8)	145 (7.9)	<0.001	<0.001
Real diabetes *N* (%)	125 (15.9)	203 (18.8)	321 (15.3)	0.285	–
Insulin treatment *N* (%)[f]	10 (9.4)	9 (6.7)	35 (19.1)	0.078	–
Oral diabetes treatment *N* (%)[f]	39 (27.1)	60 (28.2)	125 (48.4)	0.155	–
BMI (kg/m^2)[a]	26.6 (3.8)	27.8 (3.9)	27.6 (4.0)	<0.001	<0.001
Obesity (BMI ≥ 30) %	129 (17.5)	347 (26.0)	413 (22.7)	<0.001	0.020
EEPA (kcal/day)[d]	286 (149–557)	283 (138–534)	320 (163–596)	<0.001	0.003
Current smoker *N* (%)	224 (36.2)	386 (35.5)	517 (34.5)	<0.001	<0.001
Former smoker *N* (%)	235 (30.6)	412 (30.5)	697 (38.0)		
Ten-year cardiovascular risk[a]	8.0 (7.8)	8.2 (8.7)	7.3 (7.3)	0.190	–

'*P* for trends' have not been computed for those variables whose differences were not significant among the 3 years. To convert glycaemia to mg/dl, multiply by 18.02. BMI, body mass index; EEPA, energy expenditure in physical activity. [a]Mean (standard deviation). [b]Among participants with history of hypertension. [c]Among participants with treated hypertension. [d]Median (25th percentile. 75th percentile). [e]Glycaemia 6.1–6.9 mmol/l (110–125 mg/dl). [f]Among participants with history of diabetes.

Table 3 Coronary risk factors in female population of Gerona aged 35–74 from 1995 to 2005

	1995 (*N*=771)	2000 (*N*=1297)	2005 (*N*=1870)	*P* value	*P* for trends
Systolic blood pressure (mmHg)[a]	126 (20)	125 (21)	122 (20)	<0.001	<0.001
Diastolic blood pressure (mmHg)[a]	76 (12)	77 (10)	77 (11)	0.098	–
History of hypertension *N* (%)	206 (22.0)	373 (24.6)	600 (26.0)	0.008	0.002
Real hypertension *N* (%)	357 (38.8)	576 (38.5)	769 (35.1)	0.073	–
Treated hypertension *N* (%)[b]	129 (47.8)	217 (41.7)	365 (47.1)	0.337	–
Controlled hypertension *N* (%)[c]	28 (21.3)	48 (36.9)	124 (45.0)	<0.001	<0.001
History of diabetes *N* (%)	84 (8.8)	120 (8.1)	221 (10.8)	0.071	–
Glycaemia (mmol/l); (mg/dl)[d]	5 (5–6)	5 (5–6)	5 (5–5)	<0.001	<0.001
Impaired fasting glycaemia *N* (%)[e]	49 (6.1)	115 (10.8)	86 (3.9)	<0.001	<0.001
Real diabetes *N* (%)	104 (11.2)	157 (13.9)	273 (13.4)	0.550	–
Insulin treatment *N* (%)[f]	12 (6.2)	10 (9.7)	24 (6.1)	0.476	–
Oral diabetes treatment *N* (%)[f]	27 (14.0)	48 (30.1)	65 (19.2)	0.102	–
BMI (kg/m^2)[a]	26.4 (4.4)	27.4 (5.1)	26.3 (5.1)	<0.001	0.213
Obesity (BMI ≥ 30) %	166 (19.0)	381 (26.5)	453 (21.2)	<0.001	0.756
EEPA (kcal/day)[d]	180 (92–313)	194 (101–327)	241 (127–418)	<0.001	<0.001
Current smoker *N* (%)	97 (17.1)	205 (20.1)	308 (21.5)	<0.001	<0.001
Former smoker *N* (%)	25 (4.2)	81 (7.3)	230 (14.1)		
Ten-year cardiovascular risk[a]	2.8 (3.0)	3.0 (3.1)	2.6 (2.6)	<0.001	0.004

'*P* for trends' have not been computed for those variables whose differences were not significant among the 3 years. To convert glycaemia to mg/dl, multiply by 18.02. BMI, body mass index; EEPA. energy expenditure in physical activity. [a]Mean (standard deviation). [b]Among participants with history of hypertension. [c]Among participants with treated hypertension. [d]Median (25th percentile. 75th percentile). [e]Glycaemia 6.1–6.9 mmol/l (110–125 mg/dl). [f]Among participants with history of diabetes.

Table 4 Electrocardiographic findings in the population of Gerona aged 35–74 years from 1995 to 2005

	1995	2000	2005	*P* value	*P* for trends
Men	*N*=709	*N*=1243	*N*=1681		
Acute myocardial infarction *N* (%)[a]	35 (3.93)	64 (4.73)	125 (6.38)	0.038	0.018
Left ventricular hypertrophy *N* (%)	15 (2.06)	27 (2.06)	62 (3.73)	0.022	0.013
Intraventricular conduction disorders *N* (%)	30 (3.41)	103 (8.00)	120 (6.60)	0.003	0.058
Rhythm disorders *N* (%)	8 (0.72)	19 (1.10)	42 (1.63)	0.040	0.014
Women	*N*=771	*N*=1297	*N*=1870		
Acute myocardial infarction *N* (%)[a]	13 (1.35)	18 (1.18)	45 (1.97)	0.158	–
Left ventricular hypertrophy *N* (%)	5 (0.46)	23 (1.44)	23 (1.12)	0.086	–
Intraventricular conduction disorders *N* (%)	22 (2.09)	53 (4.06)	88 (4.50)	0.094	–
Rhythm disorders *N* (%)	13 (1.25)	10 (0.65)	26 (1.24)	0.141	–

'*P* for trends' have not been computed for those variables whose differences were not significant among the 3 years. [a]History of acute myocardial infarction or possibly abnormal Q waves in electrocardiogram.

left in the population distribution curves. BMI and obesity have dramatically increased over this decade in men. Improvements in hypertension awareness, treatment, and control were also remarkable. Diabetes prevalence remained stable over the studied decade.

The decrease in total cholesterol and LDL-c population mean level, which has been observed in other European countries and USA [19–23], and the left shift in their population distribution curve might be related either to the increasing use of lipid-lowering drugs or to changes in lifestyle. Lipid-lowering drugs predominantly affect total cholesterol and LDL-c levels. Although the proportion of treated participants increased, particularly between 2000 and 2005, both measures decreased independently of such treatments. HDL-c mean values, which play a key role in lowering CHD risk, remained unchanged over the 10-year period. The intake of vegetables, fruits, fish, red meat, dairy products, pulses, and cereals remained stable between 2000 and 2005 (data not shown). Weekly physical activity equivalent to brisk walking, however, increased from 1995 to 2005 by approximately 40 min in men and 70 min in women.

BMI increased over this period, particularly in men, bringing the percentage of male obesity close to 23% in 2005. Smoking prevalence increased in women and remained steadily high in men over the period, together with a growth in the percentage of former smokers for both sexes, probably related to anti-smoking policies developed in recent years. Concurring with the Spanish National Health Surveys report, the percentage of smokers among women significantly increased [24]. Prevalence of smoking for Spanish men is among the highest for European countries [1].

Hypertension prevalence remained similar in the three studies. Our data show that almost 50% of men and 40% of women were diagnosed with hypertension or had blood pressure measurements beyond the limits of hypertension. These results concur with those by Wolf-Maier *et al.* [25] who found the hypertension prevalence in Spain to be approximately 45% in the general population (35–74 years). This percentage was higher than that observed in USA or Sweden. More individuals were aware of their hypertension in 2005 in our region, which probably results from better hypertension screening and management.

The cardiovascular risk, which was already very low in initially CHD-free women, decreased. In men, however, it remained similar over the decade, despite the decrease in total and LDL-c levels and improved control of hypertension. The shift to the left observed in the population distribution curves of total cholesterol and LDL-c should have an impact on CHD incidence, according to the 'population strategy' theory by Geoffrey Rose [5], although the efficiency of this approach has been called into question recently [26]. The slight but significant increase in the history of AMI or possibly abnormal Q waves in ECG in men may be due to the overall stabilization of AMI incidence accompanied by a significant (–5.4%) decrease in in-hospital AMI case-fatality observed recently in the region among men, 35–74 years of age [27].

Paradoxically, the prevalence of classical CRF is similar or even higher in Mediterranean than in other industrialized countries [7,28]. Therefore, the role of CRF in the development of CHD may differ among populations [28,29]. The absolute CHD risk for different levels of exposure to total cholesterol and SBP varied across populations in the Seven Countries study [30], although the relative risk for these risk factors was similar in all populations.

CHD mortality rates have decreased consistently in most industrialized countries in the past decade [1]. Despite this generalized trend, AMI mortality rates continue to be four times lower in South Mediterranean areas of Europe [1]. This suggests that primary prevention needs to be adapted to local characteristics of prevalence of CRF, AMI mortality and incidence rates, and economic and cultural factors [31]. The achievements in cholesterol levels and hypertension control in our region are likely to be related to 'high risk' or opportunistic intervention rather than a population preventive approach [5]. Our findings suggest that there is room for preventive activity concerning lifestyle in the studied area to decrease cardiovascular risk in the population, particularly increased efforts to promote physical activity, and smoking cessation or reduction.

Participation in the three independent cross-sectional studies considered was consistently around 72%, which guarantees representativeness. The basal age and sex characteristics of responders and nonresponders were similar in all three surveys. History of hypertension, diabetes and dyslipidaemia were also similar in the 2000 and 2005 surveys: in 1995 this information was not collected in nonresponders (data not shown). Although minimal differences are to be expected among regions [7,32], generalization of our results to the rest of Spain should be made with caution.

In conclusion, the prevalence of classic CRF in Gerona is high despite the low AMI incidence and death rates observed in this region. The CRF prevalence change in Gerona has been marked in the last decade by a shift of total cholesterol and LDL-c distributions to the left, independent of the increase in lipid-lowering drug use, and by better hypertension control, accompanied by increased use of antihypertensive drugs.

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Erratum

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A typographical error was published in the article 'Trends in cardiovascular risk factor prevalence (1995–2000–2005) in northeastern Spain' by Grau *et al.* [1] which appeared on pp. 653–659 of the *European Journal of Cardiovascular Prevention and Rehabilitation*, Volume 14, issue 5.

There was an error in the calculation of the variable 'Ten-year cardiovascular risk' presented in Tables 2 and 3.

The corrected values are presented below:

Table 2 Ten-year cardiovascular risk mean (standard deviation) in male population of Gerona aged 35–74 from 1995 to 2005

Men	1995 (*N*=709)	2000 (*N*=1243)	2005 (*N*=1681)	*P* value	*P* trend
Ten-year cardiovascular risk	5.3 (4.5)	5.4 (4.7)	4.5 (4.0)	0.002	<0.001

Table 3 Ten-year cardiovascular risk mean (standard deviation) in female population of Gerona aged 35–74 from 1995 to 2005

Women	1995 (*N*=771)	2000 (*N*=1297)	2005 (*N*=1870)	*P* value	*P* trend
Ten-year cardiovascular risk	2.8 (3.0)	2.9 (3.0)	2.4 (2.5)	<0.001	<0.001

Reference

1 Grau M, Subirana I, Elosua R, Solanas P, Ramos R, Masiá R, *et al.* Trends in cardiovascular risk factor prevalence 1995–2000–2005 in northeastern Spain. *Eur J Cardiovasc Prev and Rehabil* 2007; **14**:653–659.

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5. ANNEX

5.1 Supplementary Material I

Grau M, Bongard V, Fito M, Ruidavets JB, Sala J, Taraszkiewicz D, Masia R, Galinier M, Subirana I, Vila J, Puel J, Marrugat J, Ferrières J and the REGICOR and GENES Investigators.

Prevalence of cardiovascular risk factors in men with stable coronary heart disease in France and Spain.

PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN MEN WITH STABLE CORONARY HEART DISEASE IN FRANCE AND SPAIN

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Abstract

Background

Unfavourable lipid concentrations, raised blood pressure, diabetes, smoking and overweight are the most prevalent cardiovascular risk factors (CRF) in developed and developing countries. The aim of our study was to compare CRF prevalence, treatment and control in two surveys conducted in French and Spanish men with stable coronary heart disease (CHD).

Methods

Standardized measurements of body mass index, systolic and diastolic blood pressure, lipids, glycaemia, and smoking were collected and drug use was registered. Cross-sectional comparisons were performed between French and Spanish samples.

Results

A group of 982 individuals was analyzed (420 French and 562 Spanish men). More than 97% of participants presented with at least one of the five major CRF (dyslipidaemia, hypertension, diabetes, obesity or smoking). Dyslipidaemia (70.4% vs. 71.9% in France and Spain, respectively, p=0.632) and hypertension (66.7% and 51.3%, respectively, p<0.001) were the most prevalent CRF. Current smoking was higher in Spanish participants (24.3% in France vs 54.8% in Spain, p<0.001) and no significant difference was observed regarding obesity and diabetes. Antiplatelet agents, calcium inhibitors, diuretics and hypoglycaemic drugs were more frequently used in France, whereas ACE-Inhibitors and lipid-lowering treatments were more frequent in Spain.

Conclusion

CRF prevalence is high among French and Spanish patients with stable CHD. French participants show higher blood pressure levels whereas Spanish patients are more frequently current smokers. A great proportion of CHD patients do not reach recommended levels for CRF control.

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Keywords: Cardiovascular risk factors; coronary heart disease; myocardial infarction; secondary prevention; cardiovascular drugs; lipids; blood pressure.

Introduction

Understanding the crucial role of cardiovascular risk factors (CRF) has established a new paradigm in the epidemiological study of coronary heart disease (CHD). In the past decades, many potential new precursors of CHD have been identified, such as thrombotic and genetic factors, infectious agents, early life exposures, oestrogen deficiency and psychosocial factors[i]. However, traditional risk factors partially promoted by inappropriate diet and physical inactivity (unfavourable lipid concentrations, raised blood pressure, diabetes and to a less extent overweight), together with cigarette smoking, are the most prevalent CRF in both developed and developing areas of the world, and have also the highest impact on CHD incidence[ii-v].

It has been previously suggested that major CRF may only explain half of the burden of CHD incidence, based on the observation that many individuals with significant levels of CRF never experience CHD events, and, conversely, that some individuals with CHD lack any of these CRF[vi-viii]. However, this hypothesis is not supported by epidemiological studies showing that only 15% to 20% of stable CHD patients lack any of the major CRF[ix-x]. Epidemiological studies have underlined another important issue: major CRF are largely uncontrolled[xi-xiii].

South-European populations, where incidence and mortality from CHD is low, have shown a CRF prevalence close to the

prevalence observed in countries characterized by much higher CHD incidence and mortality[xiv,xv]. Information has already been published on CRF at discharge after acute myocardial infarction (AMI) in France and Spain[xii,xvi,xvii], but CRF prevalence and long-term management in stable CHD individuals have not been studied in details, especially as regard to lipid disorders.

The aim of our study was to compare CRF prevalence, treatment and control in two independent surveys conducted in men with stable CHD from two countries from Southern Europe: France and Spain.

Materials and methods

Setting

This analysis was designed to compare prevalence of CRF in stable CHD individuals from two regions from Southern Europe (France and Spain). In France, participants were recruited as part of the GENES Study (Génétique et Environnement en Europe du Sud), a case-control study designed to assess the role of gene-environment interactions in the occurrence of CHD. Participants were men living in the Toulouse area (Southwestern France, bordering on Spain) and were included from 2001 to 2004. For the present analysis, only cases with a history of prior AMI were taken into account. Eligible participants were stable French male CHD patients, aged 45 to 74, living in the area of Toulouse and hospitalized in the Toulouse University Hospital for stable CHD follow-up. Prior AMI had to be documented in the medical file and determined from evidence of new pathological Q-waves on electrocardiogram (ECG), or from imaging evidence of healed AMI or a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause. Patients with confirmed AMI, ECG changes or rise in cardiac enzymes (>1.5 the upper limit) in the past two months, were excluded.

In Spain, the REGICOR Project (Registre Gironi del Cor) registries all AMIs occurring in local inhabitants in six counties in Gerona. This province is located in Northeastern Spain and bordering on France. Registry process is done prospectively, regarding those admitted to the only referral hospital in the area. In order to be eligible, subjects had to be clinically diagnosed with AMI. Once identified, patients were classified according to the MONICA (MONItoring of trends and determinants in CArdiovascular diseases) project algorithm, which takes into account type of symptoms, ECG findings, and enzymes[xviii]. Selected patients were part of the definite non-fatal AMI group identified as: (1) Definite ECG or (2) symptoms typical or atypical or inadequately described, together with probable ECG and abnor-

mal enzymes, or (3) symptoms typical and abnormal enzymes with ischaemic or non-codable ECG or ECG not available[xviii, xix]. A 6-month follow-up was done in order to measure blood lipid levels in patients in stable status.

In summary, men, aged 45 to 74, with stable CHD, who reported a previous history of AMI were selected in both studies for the purpose of our analysis. The sample size (420 and 562 individuals in France and Spain, respectively), allowed us to detect differences between centers greater than 10 percent points in CRF prevalence, with a statistical power of 87.5%, at least. Authorization from the local ethics committees was obtained in accordance with the French and Spanish laws and the Declaration of Helsinki. All participants were informed about the aim of the study and informed consent was signed by each subject.

Questionnaires

Age and socioeconomic variables were collected by means of standardized interviews. Smoking status was classified as smokers (current smokers or smokers who had quit for less than a year), former smokers (those who had quit for more than a year) and non-smokers. All medications taken were also recorded. Antiplatelet agents, β-blockers, nitrates, calcium inhibitors, angiotensin-converting enzyme (ACE) inhibitors, diuretics, angiotensin II receptor antagonists (ARA II), and lipid-lowering treatments were taken into account for the purposes of the study. For the last two drugs, information was available in the REGICOR Study only from 2001.

Clinical measurements

Examinations were performed by a team of trained nurses, physicians and interviewers who used equivalent standard questionnaires and measurement methods in both surveys [18]. Anthropometrical measurements, including height and body weight were taken according to standardized procedures. Body mass index (BMI) was determined as weight divided by squared height (kg/m^2). Participants were classified in three groups according to BMI: 1) *normal weight:* BMI <25 kg/m^2; 2) *overweight:* BMI ≥25 and <30; 3) *obesity:* BMI ≥30. Blood pressure was measured with a periodically calibrated mercury sphygmomanometer in Spain and an automatic sphygmomanometer (OMRON 705 CP) in France. A cuff adapted to the upper arm perimeter was selected for each participant. Measurements were performed after a five-minute rest, at least. Two measurements were taken and the lower value was recorded for the analysis. The cut-off points to define hypertension followed the criteria used in the Second Joint Task Force of European and Other Societies on Coronary Heart Disease Prevention in Clinical Practice[xx] and in

the 2000 recommendations from the French Health Product Safety Agency[xxi]. These guidelines were chosen as they were currently used in Spain and France, respectively, when inclusions were carried out. The following definitions were considered regarding hypertension and its treatment and control: 1) *history of hypertension:* when participants reported a previous diagnosis or treatment for hypertension; 2) *real hypertension:* history of hypertension or systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg; 3) *treated hypertension:* patients with a history of hypertension on drug treatment; and 4) *controlled hypertension:* SBP <140 and DBP <90 mmHg among treated patients. Reference values were SBP <130 and DBP <80 mmHg for diabetic participants.

Blood sample collection and biological analyses

Blood was withdrawn after a 10 to 14 hour fast, with less than 60 seconds duration, in both centres at least two months after AMI (six months in Spain). Serum sample aliquots were stored at -80ºC. Briefly, total cholesterol, glucose and triglyceride concentrations were determined enzymatically.

High-density lipoprotein (HDL) cholesterol was measured as cholesterol after precipitation of apoprotein B-containing lipoproteins with phosphotungstic-Mg^{++}. Low-density lipoprotein (LDL) cholesterol was calculated in both centres, by the Friedewald equation whenever triglycerides were lower than 3.4 mmol/l[xxii] (389 and 544 individuals in France and Spain, respectively). Biological measurements were performed in a core laboratory in Barcelona for Spanish participants[xxiii] and in a core laboratory in the Toulouse University Hospital for French subjects[xxiv]. The cut-off points to define dyslipidaemia followed the criteria used in the Second Joint Task Force of European and Other Societies on Coronary Heart Disease Prevention in Clinical Practice (LDL cholesterol ≥3.0 mmol/l or HDL cholesterol ≤1.0 mmol/l) in Spain [20]; and the 2000 recommendations from the French Health Product Safety Agency (LDL cholesterol ≥3.4 mmol/l or HDL cholesterol ≤1.0 mmol/l) in France [21].

Glucose metabolism disturbances were classified as follows: 1) *history of diabetes:* participants already diagnosed by a physician; 2) *impaired fasting glycaemia:* fasting glycaemia ranging from 6.1 to 6.9 mmol/l in participants not previously diagnosed with diabetes; and 3) *real diabetes*: participants with a history of diabetes or with fasting glycaemia ≥7 mmol/l; 4) *treated diabetes:* patients with a *history of diabetes* under drug treatment.

Statistical analyses

The analyses were first performed on the whole sample, and secondly age-stratified analyses were done (45-59, 60-74 years).

	45-59 years			60-74 years			All		
	GENES n=222	REGICOR n=272	p-value	GENES n=198	REGICOR n=290	P-value	GENES n=420	REGICOR n=562	p-value
Body Mass Index (BMI) (kg/m²)	27.2 (4.1)	27.4 (4.0)	0.718	27.0 (3.8)	27.3 (3.8)	0.370	27.1 (4.0)	27.3 (3.8)	0.395
Overweight and Obesity, n (%)			0.556			0.137			0.770
BMI <25 kg/m²	67 (30.2)	65 (28.3)		58 (29.3)	70 (29.2)		125 (29.8)	135 (28.7)	
25≤ BMI <30 kg/m²	100 (45.1)	115 (50.0)		106 (53.5)	111 (46.3)		206 (49.1)	226 (48.1)	
BMI ≥30 kg/m²	55 (24.8)	50 (21.7)		34 (17.2)	59 (24.6)		89 (21.2)	109 (23.2)	
Smoking, n (%)			<0.001			<0.001			<0.001
Non-smokers	48 (21.6)	36 (13.3)		46 (23.2)	67 (23.3)		94 (22.4)	103 (18.5)	
Smokers	78 (35.1)	199 (73.7)		24 (12.1)	107 (37.2)		102 (24.3)	306 (54.8)	
Former smokers	96 (43.2)	35 (13.0)		128 (64.7)	114 (39.6)		224 (53.3)	149 (26.7)	
Systolic Blood Pressure (mmHg)	129 (20)	112 (16)	<0.001	139 (22)	115 (19)	<0.001	134 (21)	114 (18)	<0.001
Diastolic Blood Pressure (mmHg)	82 (11)	66 (12)	<0.001	82 (10)	66 (12)	<0.001	82 (10)	66 (11)	<0.001
History of hypertension, n (%)	82 (36.9)	107 (41.0)	0.362	85 (42.9)	162 (57.5)	0.002	167 (39.8)	269 (49.5)	0.003
Real hypertension, n (%) [a]	133 (59.9)	114 (42.5)	<0.001	147 (74.2)	172 (59.3)	0.001	280 (66.7)	286 (51.3)	<0.001
Treated hypertension, n (%) [b]	78 (95.1)	102 (98.1)	0.257	84 (100.0)	158 (97.5)	0.146	162 (97.6)	260 (97.7)	0.918
Controlled hypertension, n (%) [c]	38 (48.7)	70 (68.6)	0.007	30 (35.7)	118 (74.7)	<0.001	68 (42.0)	188 (72.3)	<0.001

Results are given as mean (standard deviation) or n (%); a History of hypertension or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (≥130/80 mmHg in diabetics); b Patients with a history of hypertension on drug treatment; c Systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg (<130/80 in diabetics) among treated patients.

	45-59 years			60-74 years			All		
	GENES n=222	REGICOR n=272	p-value	GENES n=198	REGICOR n=290	P-value	GENES n=420	REGICOR n=562	p-value
Total cholesterol (mmol/l)	5.3 (1.1)	4.9 (1.0)	<0.001	5.1 (1.2)	4.6 (1.0)	<0.001	5.2 (1.1)	4.7 (1.0)	<0.001
Total cholesterol ≥4.9 mmol/l, n (%)	131 (59.0)	123 (45.4)	0.003	106 (53.5)	97 (33.5)	<0.001	237 (56.4)	220 (39.2)	<0.001
HDL cholesterol (mmol/l)	1.1 (0.3)	1.1 (0.3)	0.835	1.1 (0.3)	1.1 (0.3)	0.094	1.1 (0.3)	1.1 (0.3)	0.351
HDL cholesterol ≤1.0 mmol/l, n (%)	129 (58.1)	142 (52.4)	0.205	90 (45.5)	141 (48.8)	0.469	219 (52.1)	283 (50.5)	0.618
LDL cholesterol (mmol/l)	3.3 (1.0)	3.1 (1.0)	0.053	3.2 (1.0)	2.9 (0.9)	<0.001	3.2 (1.0)	3.0 (1.0)	<0.001
LDL cholesterol ≥3.0 mmol/l, n (%)	116 (59.2)	139 (53.98)	0.259	109 (56.5)	119 (41.6)	0.001	225 (57.8)	258 (47.4)	0.002
LDL cholesterol ≥3.4 mmol/l, n (%)	82 (41.8)	94 (36.4)	0.242	72 (37.3)	83 (29.0)	0.057	154 (39.6)	177 (32.5)	0.026
Dyslipidaemia, n (%) [a]	147 (75.0)	196 (76.0)	0.812	127 (65.8)	195 (68.2)	0.586	274 (70.4)	391 (71.9)	0.632
Triglycerides (mmol/l)	2.2 (1.4)	1.6 (0.9)	<0.001	1.7 (0.9)	1.3 (0.6)	<0.001	1.9 (1.2)	1.4 (0.7)	<0.001[e]
Triglycerides ≥2.0 mmol/l, n (%)	93 (41.9)	46 (17.0)	<0.001	47 (23.7)	32 (11.1)	<0.001	140 (33.3)	78 (13.9)	<0.001
Glycaemia (mmol/l)	6.2 (2.4)	5.9 (1.8)	0.293	6.1 (2.5)	6.2 (2.2)	0.370	6.2 (2.5)	6.1 (2.1)	0.940[e]
Impaired fasting glycaemia, n (%) [b]	21 (11.3)	23 (10.5)	0.800	14 (8.8)	21 (9.1)	0.933	35 (10.1)	44 (9.8)	0.856
History of diabetes, n (%)	43 (19.4)	60 (24.2)	0.207	62 (31.3)	73 (26.4)	0.237	105 (25.0)	133 (25.3)	0.907
Real diabetes, n (%) [c]	78 (35.1)	81 (31.8)	0.436	87 (43.9)	97 (34.9)	0.046	165 (39.3)	178 (33.4)	0.060
Treated diabetes, n (%) [d]	39 (90.7)	33 (68.8)	0.010	62 (100.0)	51 (76.1)	<0.001	101 (96.2)	84 (73.0)	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein. Results are given as mean (standard deviation) or n (%); a LDL cholesterol ≥3.0 mmol/l (Spain), ≥3.4 mmol/l (France) or HDL cholesterol ≥1 mmol/l; b Glycaemia ranging from 6.1 to 6.9 mmol/l in patients not previously diagnosed with diabetes; c History of diabetes or glycaemia ≤7 mmol/l; d Patients with a history of diabetes on drug treatment; e Computed from log-transformed values.

Table 1.
Prevalence of obesity, smoking, and hypertension, by age and centre

Table 2.
Prevalence of dyslipidaemia and diabetes, by age and centre

Continuous variables are summarized as means and standard deviations, and categorical variables as proportions. Student-t test was used to compare means of continuous variables. A logarithmic transformation was done to compute p-value for variables whose distribution departed from normal (e.g., glycaemia, triglycerides). χ^2 test was used to compare proportions. Statistical analysis was done with STATA Software (Stata Corp. College Station, Tx, version 9.2).

Results

We included 982 individuals aged 45-74 (420 French and 562 Spanish participants). Mean age was 60 years-old. The percentage of smokers was higher in Spanish participants whereas French subjects showed a higher prorpotion of former-smokers. On the other hand, the prevalence of obesity did not signifi-

cantly differ between France and Spain (Table 1). SBP and DBP were significantly higher in French participants in all age strata. Real hypertension was significantly higher among French participants. In addition, French subjects treated for hypertension showed a significantly lower percentage of people with blood pressure levels under those recommended.

Total and LDL cholesterol and triglyceride average levels were significantly higher in French participants and the proportion of subjects with LDL cholesterol above 3.4 mmol/l was greater in France (table 2). However, when dyslipidaemia was defined according to the guidelines used in both countries (i.e. LDL cholesterol ≥3.4 mmol/l in France, ≥3 mmol/l in Spain, or HDL cholesterol ≤1 mmol/l) the percentage of dyslipidaemic subjects was not significantly different between France and Spain. No significant difference was observed in HDL cholesterol levels. The percentage of participants with diagnosed diabetes did not significantly differ between the two countries, but diabetic participants were significantly more frequently treated in France.

French participants were more frequently treated with antiplatelet drugs, calcium inhibitors (especially in younger subjects), and diuretics. The percentage of Spanish participants on lipid-lowering treatment or under antihypertensive drugs acting on the renin-angiotensin system (ACE-Inhibitors or ARA II) were significantly higher (Table 3).

Figure 1 shows the distribution of major CRF: real hypertension, dyslipidaemia (LDL cholesterol ≥3.0 mmol/l (Panel A) or ≥3.4 mmol/l (Panel B), HDL ≤1 mmol/l), real diabetes, smoking, and obesity, among French and Spanish participants. Only 2.6% and 2.8% (panel A) of the French and Spanish participants, respectively, lack any major CRF (less than 5% according to panel B).

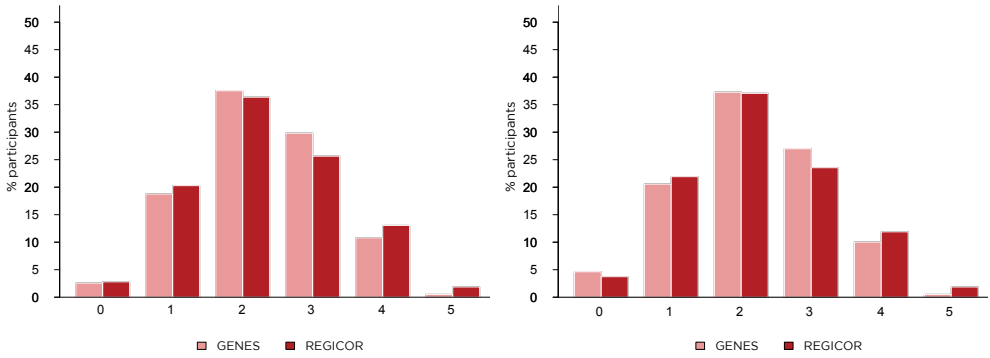
Discussion

Our results show a high prevalence of major CRF in CHD patients both in Gerona (Spain) and Toulouse (France). Indeed, 97.4% and 97.2% of the French and Spanish participants presented with at least one of the five major CRF (hypertension, dyslipidaemia, diabetes, smoking, or obesity).

Previous international studies have shown that the overall pattern of CRF exists irrespectively of geographic origin [9,11]. Despite similarities between Toulouse and Gerona areas (two regions close from a geographic point of view, belonging to the South-West of Europe and characterized by a low CHD incidence[xiv,xv]), our study shows significant differences between the two countries regarding CRF levels, treatment and control.

	45-59 years			60-74 years			All		
	GENES n=222	REGICOR n=272	P-value	GENES n=198	REGICOR n=290	P-value	GENES n=420	REGICOR n=562	p-value
Antiplatelet agents, n (%)	192 (87.2)	193 (75.7)	0.001	170 (85.9)	201 (71.8)	<0.001	362 (86.6)	394 (73.6)	<0.001
β-blockers, n (%)	150 (67.6)	190 (74.2)	0.110	120 (60.6)	162 (57.9)	0.547	270 (64.3)	352 (65.7)	0.656
Nitrates, n (%)	54 (24.6)	42 (16.5)	0.029	57 (28.8)	68 (24.4)	0.280	111 (26.6)	110 (20.6)	0.031
Calcium Inhibitors, n (%)	45 (20.4)	18 (7.4)	<0.001	48 (24.2)	66 (24.4)	0.978	93 (22.2)	84 (16.3)	0.022
ACE-Inhibitors, n (%)	100 (45.1)	130 (50.8)	0.211	81 (40.9)	154 (55.0)	0.002	181 (43.1)	284 (53.0)	0.002
ARA II, n (%) [a]	14 (6.4)	0 (0.0)	0.011	7 (3.5)	4 (4.9)	0.585	21 (5.0)	4 (2.3)	0.124
ACE-Inhibitors or ARA II, n (%)	114 (51.4)	130 (54.6)	0.482	87 (43.9)	158 (61.5)	<0.001	201 (47.9)	288 (58.2)	0.002
Diuretics, n (%)	26 (11.8)	15 (5.8)	0.019	48 (24.2)	50 (17.7)	0.078	74 (17.7)	65 (12.0)	0.013
Lipid-lowering drugs, n (%) [a]	155 (70.5)	144 (92.9)	<0.001	127 (64.8)	141 (78.3)	0.004	282 (67.8)	285 (85.1)	<0.001
4 drug combined therapy, n (%) [b]	57 (25.1)	64 (30.2)	0.322	29 (14.7)	47 (19.2)	0.208	86 (20.6)	111 (24.3)	0.189
3 drug combined therapy, n (%) [c]	99 (45.0)	106 (46.9)	0.687	70 (35.5)	77 (29.6)	0.180	169 (40.5)	183 (37.7)	0.377

Results are given as n (%); ACE, Angiotensin converting enzyme; ARAII, Angiotensin II receptor antagonist; a available only from 2001 to 2004 in the REGICOR Study; b Antiplatelet & β-blocker & Lipid-lowering drug & (ACE-Inhibitor or ARA II); c Antiplatelet & b-blocker & Lipid-lowering drug.



Number of cardiovascular risk factors per individual, in each centre, according to the Second Joint Task Force of European and Other Societies on Coronary Heart Disease Prevention in Clinical Practice[xx] (left) or the 2000 recommendations from the French Health Products Safety Agency[xxi] (right). Cardiovascular risk factors taken into account: (a) Real hypertension: History of hypertension or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (130/80 mmHg in diabetics); (b) Dyslipidaemia: Low-Density Lipoprotein (LDL) cholesterol ≥3.0 mmol/l or High-Density Lipoprotein (HDL) cholesterol ≤1.0 mmol/l (above, panel A) or (b) Dyslipidaemia: LDL cholesterol ≥3.4 mmol/l or HDL cholesterol ≤1.0 mmol/l (below, panel B); (c) Real diabetes: History of diabetes or glycaemia ≤7 mmol/l; (d) Smoking; (e) Obesity: Body Mass Index ≥30 kg/m2.

Table 3.
Distribution of treatments, by age and centre.

Figure 1.
Number of cardiovascular risk factors per individual, in each centre.

The most prevalent CRF in both regions was consistently dyslipidaemia. However, the lipid profile in French participants was more unfavourable than in Spanish subjects and the use of lipid-lowering drugs was significantly higher in the latter. Consistently with the EUROASPIRE II (European Action on Secondary Prevention by Intervention to Reduce Events II) findings [13], lipid control was poor in the GENES and REGICOR studies. About half of the participants did not reach the European goal established for LDL cholesterol in secondary prevention of CHD [20] and one third remained above the threshold used in French guidelines (3.4 mmol/l)[xxi].

More than half of the patients showed low HDL cholesterol levels (≤1 mmol/l). CHD-free individuals from the same populations

(France and Spain) have been shown to have higher HDL cholesterol levels than stable CHD individuals[xxiii, xxv]. HDL-cholesterol could play an important role in the development of CHD in these populations but raising HDL-cholesterol levels still remains difficult [26]. On the one hand, lifestyle modifications (i.e. diet, exercise, weight loss, and smoking cessation) have been shown to have a favourable impact on HDL cholesterol levels. On the other hand, the evidence of the clinical efficacy of drugs raising HDL cholesterol, is far less abundant than for statins, which mainly act by lowering LDL cholesterol[xxvii].

Hypertension was the second most prevalent CRF in both populations (66.7% and 51.3%, in France and Spain respectively). The percentage of treated patients among those who reported a previous history of hypertension was close to 100%, nevertheless, blood pressure control remained poor, especially in French participants. This failure has been extensively described in other studies previously published[xii, xiii, xvi] and has been attributed by the investigators of the EUROASPIRE II Study to low-dose treatment prescriptions, at first, and secondly to poor patients' compliance[xiii]. Despite of the development of numerous antihypertensive drugs, blood pressure control still remains a problem of crucial importance to reduce the risk of recurrence in CHD patients.

Diabetes markedly increases the risk of CHD and non-fatal recurrent coronary events in patients with clinically established CHD[xxviii]. A quarter of patients enrolled in the GENES and REGICOR Studies were aware to be diabetics. An additional 10% (14% in France and 8% in Spain) had fasting plasma glucose levels ≥7 mmol/l, which could be compatible with the diagnosis of diabetes.

Results from a previous study showed that CHD events in the Spanish population could be firstly attributed to an excess of weight in both sexes, then followed by smoking in men[xxix]. Despite the design of our study did not allow computing population attributable risk fractions, our results show that smoking prevalence is significantly higher in Spanish participants, being the most prevalent CRF in participants younger than 60 years old. These results highlight the need to reinforce all measures that could help to permanently quit smoking, consistently with all current recommendations on cardiovascular prevention[xxx]. From a population point of view, laws aimed at forbidding smoking in public areas have been recently reinforced in France and Spain and could have a favourable impact on the prevalence of smoking in CHD patients.

No difference was found in the percentage of French and Spanish participants who were treated with a combination of the four drugs recommended in secondary prevention: statins, antiplatelet agents, beta-blockers, and ACE-inhibitors. This drug combination has been shown to improve survival in high risk patients with CHD[xxxi] and is recommended by the European Guidelines for Cardiovascular Prevention[xx, xxx]. However, the role of ACE inhibitors in CHD patients without a history of heart failure remains controversial[xxxi-xxxiii]. According to a previous study, heart failure is the main determinant of the use of ACE inhibitors in France[x].

We have found that less than 3% of the examined CHD patients in these two countries with low CHD incidence lacked any of the five major CRF. However, the distribution of major CRF was different in the two countries. It has been previously shown that less than a half of CHD-free individuals have optimum risk factors levels[xxii, xxv]. Despite this situation, France and Spain have shown a CHD mortality rate unexpectedly low[xxxiv]. This observation suggests that CHD development might be different in these two countries at low incidence for CHD as compared to high incidence countries. Therefore, CHD prevention should also be adapted to local characteristics, since the underlying causes of CHD are widely dependent on socio-economic and cultural factors which determine unhealthy lifestyles[i, xxx].

Several limitations should be pointed out in our analysis. First, the GENES Study included individuals with first or recurrent AMI whereas participants in the REGICOR Study were all recruited after a first AMI. Second, the fact that the period of recruitment was different in the two studies (2001-2004 for the GENES Study and 1995-2004 for the REGICOR Study) may have primarily affected treatment patterns. However, participants in the REGICOR study were mainly recruited after 2001 (less than 25% were recruited before 2001). Finally, the design of the study did not allow the investigation of differences in CRF prevalence between AMI survivors and non-survivors in France and Spain and the assessment of potential regional differences in the impact of CRF on AMI recurrence.

The strength of the study lies in the comparison of CRF prevalence in two different countries, with different lifestyle habits and health care systems, based on extensive clinical and biological CRF evaluations. We have shown that CRF prevalence is high among French and Spanish CHD patients. Particularly, French participants show higher lipid and blood pressure levels whereas Spanish patients show a higher smoking prevalence. As

in previous published studies, the control of CRF is too often inadequate.

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5. ANNEX

5.2 Supplementary Material II

Grau M, Subirana I, Elosua R, Fitó M, Covas MI, Sala J, Masiá R, Ramos R, Solanas P, Cordon F, Nieto FJ, Marrugat J on behalf of the REGICOR Investigators.

Sources of variation of population attributable fractions for cardiovascular disease.

SOURCES OF VARIATION IN POPULATION ATTRIBUTABLE FRACTIONS FOR CARDIOVASCULAR DISEASE

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Abstract

The population attributable fraction (PAF) combines the magnitude of the relative risk of cardiovascular disease (CVD) associated to a risk factor with its distribution in the studied population. The aim of this analysis was to determine the effect of age and study period on coronary heart disease (CHD) risk attributable to cardiovascular risk factors. A cohort of CVD-free randomly selected participants aged 35-74 years was followed for an average of 6.9 years. Smoking, hypertension, diabetes, sedentary lifestyle, obesity, total cholesterol ≥240mg/dl, low-density lipoprotein (LDL) cholesterol ≥160mg/dl, and high-density lipoprotein (HDL) cholesterol<40mg/dl were the risk factors considered. The composite end-point included acute myocardial infarction, angina pectoris, and CHD death. LDL cholesterol had the highest potential for CHD prevention between 35 and 74 years [41% (95%Confidence interval: 24, 54)]. The PAF for smoking was 64% (28, 81) in subjects <55 years, whereas among those ≥55 years, the PAF for hypertension was 36% (27, 71) and for HDL cholesterol 23% (9, 36). The decrease observed between 1995 and 2005 in the population's mean LDL cholesterol level has led to a reduction in its PAF in all age groups. Therefore, periodic recalculation of the PAF in different age groups may be required to adequately monitor population trends in world regions.

Introduction

In public health, decisions about resource allocation, prevention, and patient care are closely tied to the availability of information on prevalence, incidence, mortality, and case-fatality to address the illnesses with the greatest impact on the population and their determinant risk factors. One example of the importance of access to quality information is our need to understand cardiovascular diseases (CVD), the main cause of death in the developed world, and the associated risk factors[i].

The population attributable fraction (PAF) is the proportion of disease incidence in the population that can be attributed to a risk factor. It combines the concepts of incidence (or alternatively the relative risk or the hazard ratio) of a disease and its risk factor prevalence[ii]. The assumptions underlying valid PAF estimation include a causal relationship between the risk factors and the disease; the immediate risk reduction among the exposed when the risk factor is eliminated from a population, to that of the non-exposed; and independence of the considered risk factors from other factors that influence disease occurrence[iii, iv].

PAF magnitude varies with age and region, which are known to modify the risk factors' prevalence[v, vi]. Moreover, secular changes in the prevalence of risk factors also have an effect on the PAF value[vi, vii]. For some risk factors, the relative risk or hazard

ratio have been shown to vary based on length of follow-up[viii,ix], which may in turn slightly influence the PAF estimates.

Estimates of relative risk and risk factor prevalence are typically obtained from a variety of sources, including published data on different populations, regions and time periods[x,xi]. It is important to use relative risk and risk factor prevalence data from the same population to obtain accurate PAF estimates.

The aim of this analysis was to determine the effect of age and study period on 10-year CHD risk attributable to cardiovascular risk factors in a population-based study.

Materials and methods

Design

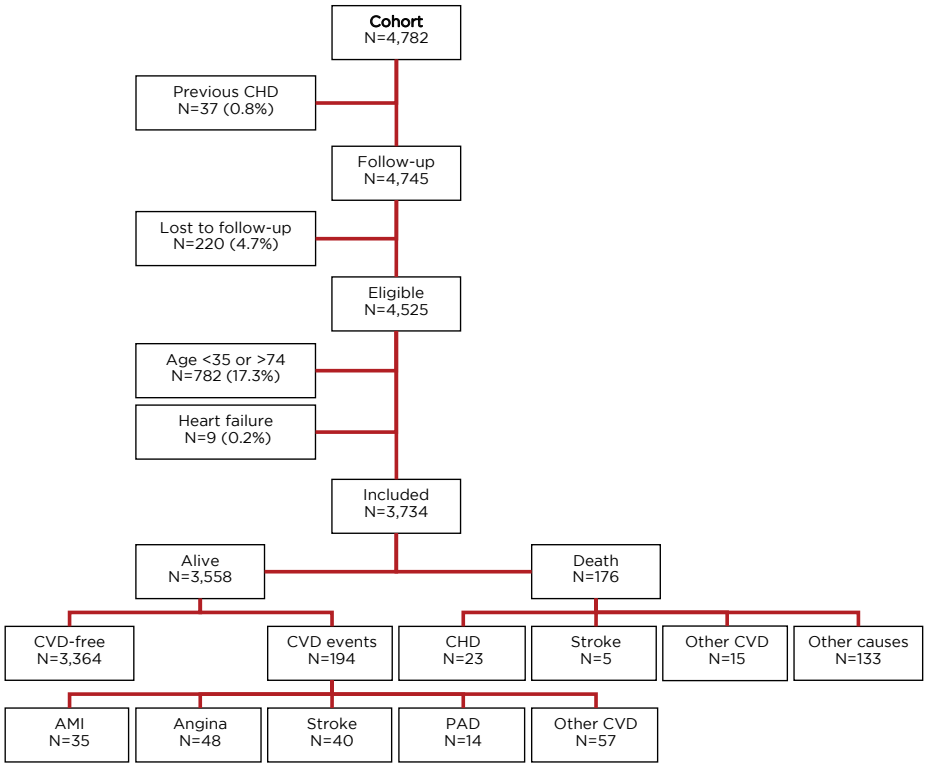
A cohort study was conducted in northeast Spain. Participants aged 35 to 74 years were randomly recruited from the census of Girona in two surveys: 1995 and 2000, which have been used to determine the 10-year hazard ratios and the PAF of CHD for the different risk factors by age groups.

Baseline examinations at recruitment of these participants and another survey conducted in the same area in 2005 have permitted the analysis of the PAF of CHD modifications over a 10-year period. Inclusion criteria and recruitment methodology have been described in detail elsewhere[vii]. Only participants free of CVD at baseline were included in the present analyses. We also excluded patients who developed heart failure of non-CHD origin during follow-up. All participants were duly informed and signed their consent to participate. The surveys and methods were approved by the local ethics committee and the results of the examination were sent to participants. Participation in all three surveys was >72%.

Risk factor measurement

Examinations were performed by a team of trained nurses and interviewers who used the same standard questionnaires and measurement methods in all three surveys.

Participants underwent standardized anthropometric measurements to determine waist circumference, height and weight. Body mass index (BMI) was calculated as weight (kg) divided by height (cm) squared. Cigarette smoking (current/ex/never) was ascertained using an administered questionnaire. Blood pressure was determined from the average of 2 separate readings taken at least 5 minutes apart, as described previously[vii]. The Minnesota leisure-time physical activity questionnaire vali-



AMI, Acute myocardial infarction; CHD, Coronary Heart Disease; CVD, Cardiovascular disease; PAD, Peripheral artery disease.

Figure 1
Participation and Follow-up Flow Chart

dated for the Spanish population was used to assess leisure activities during the previous year[xii, xiii].

Blood was withdrawn within 60 seconds, after 10-14 hours fasting. Serum sample aliquots were stored at -80Cº. Total cholesterol and triglyceride concentrations were determined enzymatically (Roche Diagnostics, Basel, Switzerland). High-density lipoprotein (HDL) cholesterol was measured as a soluble HDL-cholesterol determined by an accelerator selective detergent method (ABXHoriba Diagnostics, Montpellier, France). Analyses were performed in a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Basel, Switzerland). The calibration mode and internal and external quality controls were established to guarantee the transferability of the results among surveys. Quality control was performed with External Quality Assessment-WHO Lipid Program (WHO, Prague, Czech Republic) and Monitrol-Quality Control Program (Baxter Diagnostics, Dudingen, Switzerland). Interassay coefficients of variation were 2.5, 4.5, and 3.2% for total cholesterol, HDL cholesterol, and triglycerides, respectively.

Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation whenever triglycerides were <300mg/dl.

Exposure Criteria

Current smoking was defined as active smoking within the year preceding the examination. Hypertension was defined by the use of antihypertensive agents or the presence of systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90[xiv]. Diabetes was defined by the use of insulin or hypoglycemic agents or a fasting blood glucose >125 mg/dl. Lifestyle was considered sedentary when the weekly average energy expenditure in moderate to high intensity physical activity was below 1000 kcal. Obesity markers were BMI ≥30kg/m^2 for both men and women, and waist circumference ≥102cm for men and ≥88 for women, considered separately. The exposure cut-points to define abnormal lipid levels were total cholesterol ≥240mg/dl, LDL ≥160mg/dl, and HDL<40mg/dl, according to the National Cholesterol Education Program III (NCEP III)[xv].

Case ascertainment

Non-fatal events during follow-up were ascertained by telephone questionnaire and review of medical records. Fatal events were identified from regional and national mortality registers. Primary composite end-point event was defined by the occurrence of acute myocardial infarction, angina pectoris, or death from CHD. Secondary composite end-point was CVD events: fatal and non-fatal acute myocardial infarction, angina pectoris, fatal and non-fatal stroke and peripheral artery disease. All deaths and suspected CVD events were adjudicated by a panel of 2 physicians who applied established criteria in their review.

Statistical analysis

Analyses were done in the whole sample and stratified by age groups (35-54, 55-74 years). Age was summarized as mean and standard deviation, and categorical variables as proportions.

Cox proportional hazards models were fitted to estimate the crude and adjusted risk of CHD for cardiovascular risk factors, with two models for each factor: first a crude model, and a second adjusted for age, sex and the cardiovascular risk factors that were found to differ between event and non-event participants.

PAFs were estimated for each factor, with the following formula (4):

$$PAF = 1 - \sum_c P(D \mid \overline{E}, C) \;/\; P(D)$$

Where:

$P(D)$ = Average probability of disease (D) in the population (containing both exposed and unexposed individuals),
$P(D|\bar{E},C)$ = Marginal conditional probability of disease (D) given no exposure ($\bar{E}$), averaged over strata of potential confounders (C).
The Bootstrap method was used to estimate the confidence intervals of PAF point estimates with this formula.

The same two models were also used in a secondary analysis to estimate the hazard ratios and the PAF of CVD events.

Given the fact that we have not yet begun the 2005 cross-sectional study follow-up, to ensure comparability we estimated the non-adjusted PAF in the 1995, 2000, and 2005 surveys according to the Levin formula, which does not require incidence rates and uses unadjusted HR[iv]:

$$PAF = [(HR - 1) \times Pr] / [1 + (HR - 1) \times Pr]$$

Where,
HR = Unadjusted hazard ratio obtained with the cohort follow-up,
Pr = Cardiovascular risk factor prevalence in general population.

The prevalence estimates of cardiovascular risk factors in 1995, 2000, and 2005 used in our PAF estimations have been previously published (7, 16) and are shown in table 1.

Statistical analysis was performed with R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria, Version 2.0).

Results

We followed 1,806 men and 1,937 women for 25,701 person-years, with 6.9 years mean follow-up. During follow-up, 220 participants (4.7%) were lost, 107 participants suffered an incident event, and 133 died of other causes (Figure 1). The acute myocardial infarction age-standardized incidence rate was 294 and 88/100,000 men and women, respectively.

Characteristics of the participants are given in Table 1 for men and women according to age strata. The prevalence of baseline hypertension, diabetes, and obesity (as indicated by either BMI or waist circumference) increased with age. In contrast, the prevalence of smoking at baseline was lower in older participants.

	35-54 years		55-74 years		35-74 years	
	Men N=925	Women N=1005	Men N=881	Women N=932	Men N=1806	Women N=1937
Age *	45 (6)	45 (6)	64 (6)	64 (6)	54 (11)	54 (11)
Total cholesterol ≥240 mg/dl	310 (35.9%)	268 (28.4%)	255 (31.3%)	413 (47.5%)	565 (33.7%)	681 (37.6%)
LDL cholesterol ≥160 mg/dl	344 (42.2%)	274 (30.3%)	326 (41.1%)	425 (50.1%)	670 (41.6%)	699 (39.9%)
HDL cholesterol <40 mg/dl	262 (30.5%)	87 (9.34%)	231 (28.4%)	110 (12.7%)	493 (29.5%)	197 (11.0%)
Hypertension	325 (35.2%)	225 (22.5%)	563 (64.1%)	618 (66.5%)	888 (49.3%)	843 (43.6%)
Diabetes	99 (11.4%)	63 (6.65%)	204 (24.8%)	177 (20.0%)	303 (17.9%)	240 (13.1%)
Smoking	377 (41.5%)	236 (23.8%)	179 (20.8%)	35 (3.81%)	556 (31.4%)	271 (14.2%)
Body mass index ≥30	183 (19.9%)	181 (18.2%)	260 (29.9%)	328 (35.5%)	443 (24.7%)	509 (26.6%)
Waist circumference ≥102 or ≥88 cm	190 (20.7%)	304 (30.6%)	352 (40.3%)	551 (59.6%)	542 (30.2%)	855 (44.6%)
Sedentary	464 (51.5%)	641 (65.0%)	427 (49.8%)	674 (73.9%)	891 (50.7%)	1315 (69.3%)
Non-fatal Coronary Heart Disease	19 (2.1%)	3 (0.3%)	39 (4.43%)	27 (2.9%)	58 (3.2%)	30 (1.6%)
Non-fatal Cardiovascular Disease	39 (4.2%)	15 (1.5%)	98 (11.3%)	72 (7.8%)	137 (7.6%)	87 (4.5%)
Coronary Heart Disease 10-year mortality	3 (0.3%)	0 (0.0%)	13 (1.5%)	8 (0.9%)	16 (0.9%)	8 (0.4%)
Cardiovascular Disease 10-year mortality	3 (0.3%)	0 (0.0%)	15 (1.7%)	11 (1.2%)	18 (1.0%)	11 (0.6%)
All-cause 10-year mortality	17 (1.8%)	4 (0.4%)	104 (11.8%)	61 (6.6%)	121 (6.7%)	65 (3.4%)

HDL, high-density lipoprotein; LDL, low-density lipoprotein. *Mean (Standard Deviation)

Table 1.
Cardiovascular Risk Factors at Recruitment and Number of Events during Follow-up in the Population of Girona.

	35-54 years			55-74 years			35-74 years		
	Events during follow-up			Events during follow-up			Events during follow-up		
	No N=1875	Yes N=23	p value	No N=1621	Yes N=84	p value	No N=3496	Yes N=107	p value
Age*	45 (6)	47 (5)	0.064	64 (6)	66 (6)	<0.001	53 (11)	62 (10)	<0.001
Total cholesterol ≥ 240 mg/dl	552 (31.4%)	14 (70.0%)	<0.001	592 (39.2%)	40 (52.6%)	0.020	1144 (35.0%)	54 (56.2%)	<0.001
LDL cholesterol ≥ 160 mg/dl	593 (35.3%)	13 (81.2%)	<0.001	669 (45.3%)	46 (64.8%)	0.001	1262 (40.0%)	59 (67.8%)	<0.001
HDL cholesterol < 40 mg/dl	329 (18.9%)	7 (36.8%)	0.071	280 (18.6%)	31 (40.8%)	<0.001	609 (18.8%)	38 (40.0%)	<0.001
Hypertension	524 (28.0%)	14 (63.6%)	<0.001	1028 (63.5%)	68 (81.9%)	0.001	1552 (44.5%)	82 (78.1%)	<0.001
Diabetes	151 (8.54%)	7 (33.3%)	0.001	327 (21.5%)	21 (26.6%)	0.281	478 (14.5%)	28 (28.0%)	<0.001
Smoking	588 (31.9%)	16 (69.6%)	<0.001	189 (11.9%)	12 (14.3%)	0.510	777 (22.6%)	28 (26.2%)	0.387
Body mass index ≥30	348 (18.7%)	5 (22.7%)	0.587	518 (32.3%)	28 (34.1%)	0.721	866 (25.0%)	33 (31.7%)	0.119
Waist circumference ≥102 or ≥88 cm	475 (25.5%)	6 (27.3%)	0.853	802 (49.9%)	41 (49.4%)	0.932	1277 (36.8%)	47 (44.8%)	0.097
Sedentary	1077 (58.7%)	12 (57.1%)	0.884	982 (61.9%)	50 (61.7%)	0.973	2059 (60.2%)	62 (60.8%)	0.906

HDL, high-density lipoprotein; LDL, low-density lipoprotein. *Mean (Standard Deviation)

Table 2.
Cardiovascular Risk Factors at Recruitment According to Acute Myocardial Infarction or Angina Pectoris Occurrence, or Death From Coronary Heart Disease during Follow-up in Population of Girona.

Participants aged 35-54 years who presented a CHD event during follow-up had significantly higher prevalence of hypertension, diabetes, and smoking, and higher total and LDL cholesterol levels. On the other hand, those aged 54-74 years who presented a CHD event were significantly older, more often hypertensive, and presented higher total and LDL cholesterol levels and lower HDL cholesterol levels. When we considered the whole sample (35-74 years), participants with a CHD event were significantly older, more frequently hypertensive, diabetic and smokers, and had higher total and LDL cholesterol levels and lower HDL cholesterol levels (Table 2).

Age, male sex, total and LDL cholesterol, hypertension, diabetes and smoking were significant predictors of CHD events in people aged 35-54 years. However, hypertension was no longer significant after adjustment for potential confounders (Table 3). Total and LDL cholesterol and smoking were the only cardiovascular risk factors with significant adjusted PAF in this age stratum (Table 4).

	35-54 years				55-74 years				35-74 years			
	HR	95%CI	HR*	95%CI	HR	95%CI	HR**	95%CI	HR	95%CI	HR †	95%CI
Age (1 year)	1.1	1.0, 1.2	1.1	1.0, 1.2	1.1	1.0, 1.1	1.1	1.0, 1.1	1.1	1.1, 1.1	1.1	1.1, 1.1
Sex (women)	0.1	0.0, 0.4	0.1	0.0, 0.9	0.6	0.4, 0.9	0.5	0.3, 0.9	0.4	0.3, 0.7	0.5	0.3, 0.7
Total cholesterol ≥ 240 mg/dl‡	4.9	1.9, 12.7	3.2	1.2, 8.5	1.5	1.0, 2.4	1.7	1.1, 2.8	2.2	1.5, 3.3	2.1	1.4, 3.1
LDL cholesterol ≥ 160 mg/dl	7.8	2.2, 27.2	5.4	1.5, 19.0	2.0	1.2, 3.3	2.2	1.4, 3.7	3.0	1.9, 4.7	2.7	1.7, 4.2
HDL cholesterol < 40 mg/dl	2.6	1.0, 6.5	0.9	0.3, 2.7	3.0	1.9, 4.8	2.5	1.5, 4.2	2.9	2.0, 4.4	2.1	1.3, 3.3
Hypertension	4.6	1.9, 11.0	1.9	0.7, 5.4	2.7	1.5, 4.6	2.0	1.1, 3.7	4.6	2.9, 7.2	2.1	1.2, 3.5
Diabetes	5.1	2.1, 12.8	3.2	1.0, 9.8	1.3	0.8, 2.2	1.2	0.7, 2.1	2.3	1.5, 3.5	1.4	0.9, 2.4
Smoking	4.9	2.0, 11.9	7.0	2.2, 22.5	1.2	0.6, 2.2	1.2	0.6, 2.3	1.2	0.8, 1.8	1.8	1.1, 3.1
Body mass index ≥30	1.3	0.5, 3.5	0.2	0.0, 1.7	1.2	0.8, 1.9	1.1	0.7, 1.8	1.5	1.0, 2.2	0.9	0.6, 1.5
Waist circumference ≥102 or ≥88 cm	1.1	0.4, 2.8	0.7	0.2, 2.3	1.1	0.7, 1.6	1.0	0.6, 1.6	1.4	1.0, 2.1	0.9	0.6, 1.5
Sedentary	0.8	0.4, 2.0	0.9	0.3, 2.6	1.0	0.6, 1.5	0.9	0.6, 1.5	0.9	0.6, 1.4	0.9	0.6, 1.5

HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein. * Model adjusted for sex, age, LDL cholesterol, hypertension, diabetes, and smoking. **Model adjusted for sex, age, LDL cholesterol, HDL cholesterol, and hypertension. † Model adjusted for sex, age, LDL cholesterol, HDL Cholesterol, hypertension, diabetes, and smoking. ‡ Total cholesterol was not adjusted for LDL cholesterol.

	35-54 years				55-74 years				35-74 years			
	PAF%	95%CI	PAF%*	95%CI	PAF%	95%CI	PAF%**	95%CI	PAF%	95%CI	PAF%†	95%CI
Total cholesterol ≥ 240 mg/dl‡	55	24, 81	45	5, 78	17	0, 34	24	6, 41	30	15, 45	28	13, 44
LDL cholesterol ≥ 160 mg/dl	70	37, 86	64	26, 87	31	11, 50	36	18, 55	44	28, 59	41	24, 58
HDL cholesterol < 40 mg/dl	23	-5, 53	-3	-33, 30	27	14, 39	23	9, 36	26	14, 38	19	5, 31
Hypertension	50	22, 74	25	-29, 61	50	27, 71	36	5, 62	61	46, 76	35	9, 60
Diabetes	26	5, 50	18	-4, 45	6	-6, 19	2	-10, 14	15	6, 26	6	-5, 17
Smoking	55	28, 80	64	28, 81	2	-6, 10	1	-7, 11	4	-6, 15	10	0, 20
Body mass index ≥30	5	-14, 30	-19	-25, 3	6	-9, 21	1	-16, 17	11	-2, 23	-3	-18, 11
Waist circumference ≥102 or ≥88 cm	2	-21, 28	-10	-32, 15	2	-19, 24	-3	-26, 20	14	-2, 29	-5	-24, 15
Sedentary	-11	-58, 44	-5	-64, 59	-3	-29, 24	-9	-42, 21	-4	-28, 20	-7	-35, 19

HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein. * Model adjusted for sex, age, LDL cholesterol, hypertension, diabetes, and smoking. **Model adjusted for sex, age, LDL cholesterol, HDL Cholesterol, hypertension. †Model adjusted for sex, age, LDL cholesterol, HDL Cholesterol, hypertension, diabetes, and smoking. ‡Total cholesterol was not adjusted for LDL cholesterol.

Table3.
Age-Stratified Hazard Ratio of Acute Myocardial Infarction or Angina Pectoris Occurrence, or Death From Coronary Heart Disease for Various Cardiovascular Risk Factors in the Population of Girona.

Table 4.
Age-Stratified Population Attributable Fraction of Acute Myocardial Infarction or Angina Pectoris Occurrence, or Death From Coronary Heart Disease for Various Cardiovascular Risk Factors in Population of Girona at Recruitment.

The hazard ratios of CHD for age, female sex, LDL and HDL cholesterol and hypertension were significantly different from 1 in all adjusted models for people aged 55-74 years (Table 3). PAF for total, LDL and HDL cholesterol and hypertension had significant adjusted PAF in this age stratum and in the whole group (Table 4).

The adjusted PAF of CVD was significant for LDL cholesterol [31%; (95% Confidence Interval: 5, 54)], HDL cholesterol [22%; (2, 44)], and smoking [24%; (3, 46)] in participants aged 35-54 years, whereas in those aged 55-74 years HDL cholesterol [14%; (6, 22)] and hypertension [35%; (15, 54)] were the only risk factors with significant PAF.

In our cohort, the all-cause mortality in participants aged 35-54 years was 2.3% and 0.5% for smokers and non-smokers, respectively (P=0.001). However, this difference was not statistically significant in those aged 54-74 years (13.6% *vs.* 9.8%, P=0.100). PAF of all-cause mortality for smokers was 51% and 4% in participants aged 35-54 and 55-74 years, respectively.

The marked decrease in mean total and LDL cholesterol between the 1995 and 2005 surveys resulted in a reduction in the PAF of CHD for these risk factors in all age groups (Figure 2).

Discussion

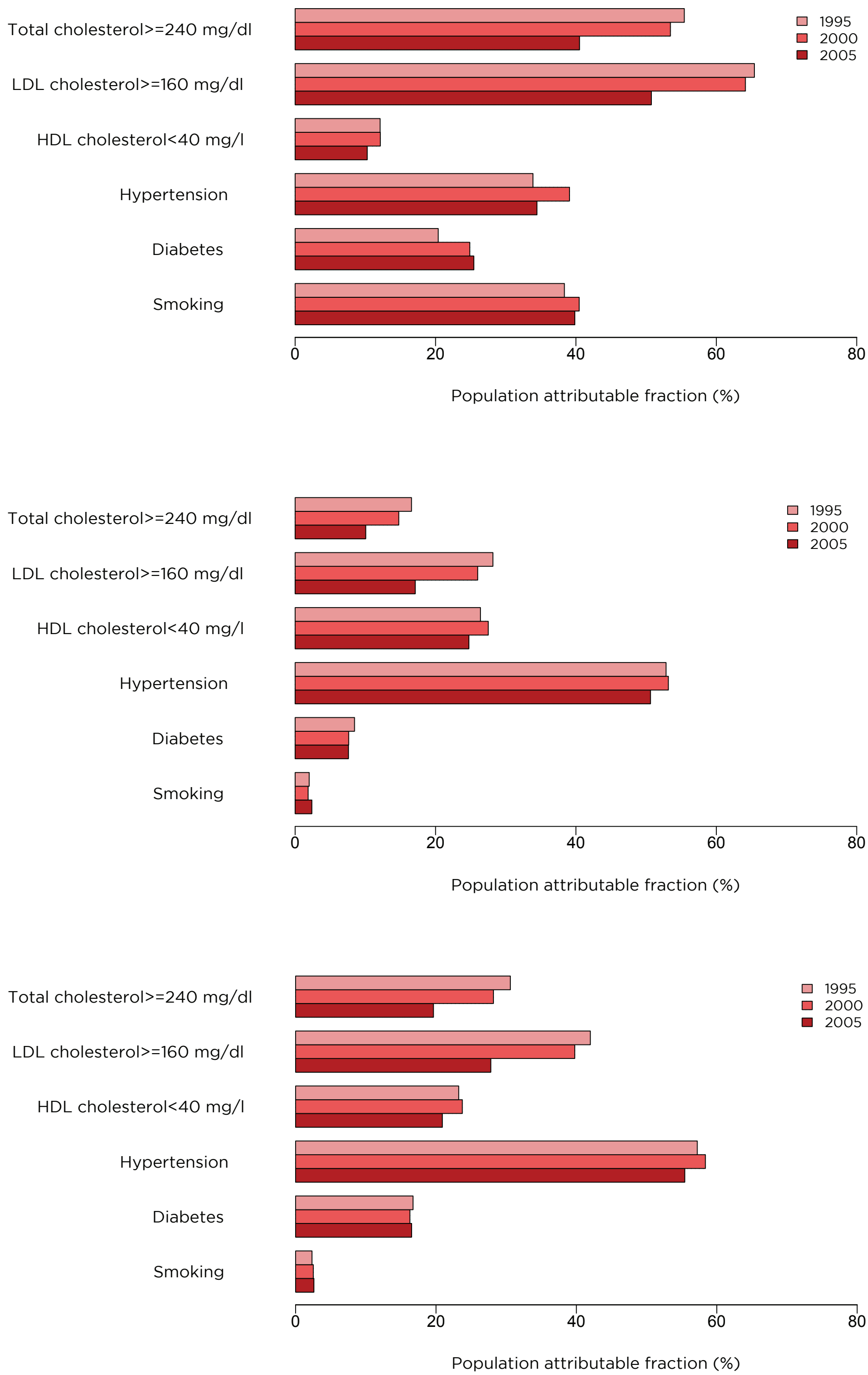
PAF magnitude depends on the size of the effect of the exposure to a risk factor and on this risk factor prevalence. Effect size depends in turn on time of follow-up, age group, and prevalence in the age group itself, period of time and region. Our study showed that age group and study period are important determinants of the magnitude of PAF of CHD for total, LDL, and HDL cholesterol, hypertension, diabetes and smoking. In our region, the risk factors with the highest population impact on CHD were, by order of importance, smoking and LDL cholesterol in the population aged 35-54 years; and hypertension, LDL cholesterol and HDL cholesterol in the group aged 55-74 years. PAFs for total and LDL cholesterol have experienced the most important change, owing to the decreasing prevalence observed in our region from 1995 to 2005[7]. Therefore, PAF should be calculated for different age groups and periodically by country or region to adequately monitor the population risk and identify the potential benefits of preventive public health initiatives in a timely manner.

Age and PAF estimates

Elevated LDL cholesterol was the risk factor with the highest potential impact on CHD prevention in our population. PAF estimates from the INTERHEART study using data from 52 countries, and some other local studies, showed similar results[xvii-xx]. However, our findings considerably differed from those previously observed in the Spanish population, which attributed the highest PAF of CHD to overweight[x]: we could not confirm this finding in our study. The discrepancy may stem from the fact that risk factor prevalence in the target population for the earlier study was estimated from a meta-analysis that did not consider age groups or take into account the different study periods when data were obtained[xxi]. In addition, risk factor prevalence in CHD cases, which is needed to estimate adjusted PAF, was taken from a national myocardial infarction registry in Spain, conducted in hospitals with a coronary care unit[xxii].

In our cohort, smokers younger than 55 years had significantly higher 10-year risk not only of developing a CHD event but also of dying from any cause: 4 times that of non-smokers of the same age. These findings concur with those of a young Swedish cohort, in which smoking was the risk factor with the highest impact on CHD[xxiii]. In fact, a previous publication already showed that PAF of dying from CHD because of smoking de-

Figure 2.
Age-stratified Population Attributable Risk for Classical Risk Factors According to Levin's Formula in 1995, 2000 and 2005 in the Population of Girona.



LDL, low-density lipoprotein; HDL, high-density lipoprotein.

creased with age[xxiv], which is fully corroborated in our cohort. Lloyd-Jones et al reported that smokers had CVD much earlier than non-smokers in the Framingham Heart Study[xxv]. However, lifetime risk for CVD was similar for smokers and non-smokers, due to the competing risk of death from other smoking-related causes[xxv, xxvi], illustrated in our study by the increased all-cause mortality among our younger participants. The potential beneficial effect of smoking cessation is more clearly seen in middle-aged adults in most world regions, even though it is also present in older people from some communities[xxvii-xxix].

Study periods and PAF estimates

Since the simultaneous presence of cardiovascular risk factors occurs in both men and women more frequently than could be expected by chance[xxx], it may be difficult to modify any level of exposure without influencing other risk factors[ii]. Therefore, the only purpose served by comparing the PAF for different risk factors is to prioritize interventions. The changes in the prevalence of one or various risk factors obtained by interventions will require PAF recalculation with the new information[xxxi]. This phenomenon is illustrated in our study by the fact that the dramatic decrease in population distribution of total and LDL cholesterol observed in our region[vii] resulted in substantial changes in PAF estimates between 1995 and 2005.

Time of follow-up and PAF estimates

The predictive power of cardiovascular risk factors varies slightly over time[viii, ix] and their maximum effects on mortality may be observed 10 or more years after exposure onset or measurement[xxxii, xxxiii]. In the context of the Framingham Heart Study, obesity has already been associated with an increased relative risk for the development of CVD in a population aged 35 to 75 years followed for 44 years[xxxiv]. More recently, Baker et al have shown that higher childhood BMI values elevated the risk of having a CHD as an adult[xxxv]. Therefore, the increase in BMI observed in our population in the last 10 years[vii] will take some time to translate into higher myocardial infarction incidence and mortality rates.

Implications for prevention of CHD

Prevention strategies are usually assessed using different cut-points to define risk factor prevalence. We followed the NCEP III recommendations to categorize total and LDL cholesterol for our PAF estimates[xv]. Had we used more recent European guidelines[xxxvi], i.e., total cholesterol <190mg/dl and LDL cholesterol <115 mg/dl, the prevalence of hypercholesterolemia would have reached more than 86%; we believe that it would be an unrealistic goal to tackle such a large portion of the general population.

Therefore, given the factors included in the PAF estimation, a situation with many individuals at small risk cannot be distinguished from one with few individuals at high risk. For cost-effectiveness, public health decisions will need to take into account relative risks to distinguish between these situations[ii, xxxvii].

Characteristics and limitations of the study

All PAF estimates in this paper should be interpreted with caution due to the following limitations: first, although the analysis was age-stratified, we did not stratify by sex despite the differences observed in risk factors prevalence[xxxiii]. The reason for combining both sexes for analysis was the low incidence of CHD events observed, particularly in women, which was, indeed, similar to that previously observed in our region[xxxviii].

Estimation of PAF with a composite CVD end-point would enable broader evaluation of the potential benefits of a comprehensive intervention. Despite the fact that both CHD and stroke have some risk factors in common, the effect size of these risk factors differs substantially[xxxix]. In addition, our cohort did not include participants at high risk of stroke, i.e., participants >74 years[xl]. For these reasons, we focused our attention on CHD end-points.

The dichotomization of all risk factor exposures might lead to non-differential misclassification[xxxvi, xli]. An alternative to dichotomization would be creating more than two groups (a gradient of exposure in three or more groups), as has been suggested by some authors[xlii]. The potential benefits expected under this assumption, expressed by PAF, would imply that an intervention on cholesterol levels would move all participants at risk to the recommended exposure levels: these expectations are probably unrealistic and do not take into account the limited effect of available dietary controls and the high costs of lipid-lowering drug interventions[xliii]. As this would have hampered our statistical power, we preferred to use cut-points that represented realistic population objectives while preserving the rule that the non-exposed group was in fact likely to be non-exposed[xv,xxxv].

Conclusions

Overall, LDL cholesterol levels had the highest potential for CHD prevention over 10 years in a Mediterranean population aged 35-74 years. In age-stratified analyses, PAF estimates were highest for smoking among participants <54 years old and for hypertension and low HDL cholesterol among those age 55 and older. PAF may need periodic age-stratified recalculation of prevalence to adequately monitor the population trends in world regions.

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6. DISCUSSION

The coexistence of low AMI incidence levels and high cardiovascular risk factor prevalence represents the so-called "southern Europe paradox"[53, 123]. When this paradox was described, AMI incidence in Spain was between one-half and one-fourth that found in north, east, and west European countries, the USA, and other English-speaking countries[32, 49]. Essentially, the results of the present study found no overall change in AMI incidence in the REGICOR region over the past decade. Nonetheless, men under age 65 –about half the total AMI population register cases– showed a significant reduction in incidence rates between 1990 and 1999, while the trend in men age 65-74 did not change significantly. The prevalence of risk factors in the Girona population was surprisingly similar to those countries with high AMI incidence[53, 123]. In addition, the major cardiovascular risk factors are present in more than 95% of IHD cases registered in Girona. The prevalence of cardiovascular risk factors, however, has undergone considerable change from the first cross-sectional study organized in this area in 1995 to the 2000 and 2005 studies. The most noteworthy aspects are improvements in participants' awareness, control and treatment of hypertension, and improvement in total and LDL cholesterol distribution.

Definitively, primary prevention must be adapted to local characteristics of cardiovascular risk factor prevalence, AMI mortal-

“The combination of primary and secondary prevention measures are postponing the age of AMI occurrence or recurence.

ity and incidence rates, and economic and cultural factors. The estimation of PAF, which represents an important link between causality and public health action, provides relevant information for such adaptation[181]. The PAF estimates in Girona showed that LDL cholesterol levels had the highest potential for IHD prevention in people aged 35 to 74 years, along with history of smoking for those younger than 55, and hypertension and HDL cholesterol for those age 55 and older. However, we observed that the PAF may require periodic recalculation in different age groups to adequately monitor the population trends in world regions.

6.1 Incidence, Mortality and Secondary Prevention of Ischemic Heart Disease

Girona, as in other areas of Spain and southern Europe, is among the regions with the lowest AMI attack and mortality rate in the world[32, 48-50]. In addition, the incidence rate in the male population aged 35-64 years improved since 1990. However, this finding has not been observed in those aged 65-74, suggesting that combined primary and secondary prevention measures are postponing the age of AMI occurrence or recurrence rather than achieving a reduction in the total number of cases[47]. The particularly low incidence rates observed in women in this area (the lowest in the world) may explain the absence of significant changes during the studied period. Certainly, the low incidence observed in the region makes a decline in mortality less statistically significant than in places with much higher rates in the early 1990s[32, 34, 193, 194].

A significant decrease in in-hospital case-fatality has also been observed. As more people live with IHD, the burden of prevalent disease with its assorted comorbid complications is increasing[47]. This fact may explain the increasing number of discharges for IHD observed in Spain and Catalonia[45], despite the fact that the overall recurrence rate of major events (i.e., AMI) has not varied significantly. First, the aging of the population has translated into an increase in AMI and unstable angina cases in Spain[41]. Second, improvements in medical technology have led to substantial changes in the treatment[61, 62] (e.g., thrombolysis[195], antiplatelet drugs[195-197], beta-blockers[198], angiotensine conversive enzyme inhibitors[199], and statins[200]) and management (e.g., coronary angiography and angioplasty[201, 202]) of AMI patients, which are more often used now than just a few years ago[203-205]. Indeed, following their introduction in the mid-80s, the use of proven life-saving drugs rapidly increased until it became relatively stable in new AMI cases[205]. Our study showed huge progress in the

use of anticoagulants, beta-blockers, coronary angioagraphy, and revascularization techniques between 1990 and 1999.

Compared with the risk in the general population, IHD patients have a 5- to 7-fold increased risk of recurrent AMI[57]. Thus, patients with clinically significant atherosclerosis warrant an aggressive approach to managing cardiovascular risk factors to reduce recurrent events and the need for interventional procedures, and to improve the quality of life[58]. However, our results showed that about half of stable IHD individuals from Girona and Toulouse did not reach the European goal established for LDL cholesterol in secondary prevention[206]. Moreover, despite the fact that close to 100% of patients who reported a history of hypertension were receiving treatment, the goal for blood pressure control (140/90 mmHg) was achieved only in 42% and 72% of the French and Spanish participants, respectively. Regarding LDL cholesterol, about half of the participants did not reach the European goal in secondary prevention. This failure has been extensively described in other studies previously published[207-210] and has been attributed by the European Action on Secondary Prevention by Intervention to Reduce Events II (EUROASPIRE II) Study authors first to the prescription of low-dose treatments and then to poor patient compliance[207].

Finally, only around 40% of stable IHD patients were treated with the drug combination (statins, antiplatelet agents, and beta-blockers) that has been shown to improve survival in IHD-patients[60, 206], the fraction of the population at highest CVD risk[211].

6.2 Reducing the Burden of Ischemic Heart Disease in Southern Europe

Since the PAF combines the concepts of incidence of a disease and its risk factor prevalence, estimates should be population-specific to identify the potential benefits of public health prevention efforts adapted to each region's characteristics[181].

In our population, LDL cholesterol was the risk factor with the highest potential impact on IHD prevention. PAF estimates from the INTERHEART study using data from 52 countries[16] and some other local studies[184, 185, 189] showed similar results. Indeed, LDL cholesterol levels experienced a dramatic decrease between 1995 and 2005 that has led to a shift to the left in the population distribution curves. Geoffrey Rose described this as one of the essential public health objectives, given the potential consequences for reducing CVD that are implicit in such a change[13,56] This dramatic decrease was also observed in other European

“Greater clinical benefit and economic efficiency in reducing the risk of IHD is attained in high incidence countries.

countries and the USA[212-216]. However, it cannot be attributed to better lipid-lowering treatment in our population, which did improve significantly, since a sensitivity analysis that excluded those under treatment also showed the same shift in the distribution. Therefore, we should assume that the population has experienced a growing interest in their health in the case of cholesterol.

The feasibility of medical treatment of dyslipemia in the primary prevention of IHD has been widely discussed. The first point is the potential costs involved in treating large segments of the population[217]. When setting therapy thresholds in Spain, we should also take into account that the main clinical trials were conducted in high-incidence countries[83, 171, 174], except for the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study, which was conducted in Japan, a low-incidence country[175]. The absolute risk reduction in the latter was much smaller than in other countries, even though blood lipid levels at baseline were similar[175]. At the population scale, greater clinical benefit and economic efficiency in reducing the risk of IHD is attained in high-incidence countries[141].

The second point discussed is the high-risk profile of participants in primary prevention trials[83, 171-175]. This selection was to some extent biased since they reflected a fairly small proportion of the general population[217]. For instance, 40% of men and 80% of women in the Framingham Heart Study had lipid profiles that did not meet eligibility criteria for inclusion in the large primary prevention trials[218]. Pragmatic clinical trials with higher external validity are desirable to establish more realistic population-based recommendations.

In contrast, HDL cholesterol, which plays a key role in lowering cardiovascular risk[78-81], remained unchanged over the 10-year period analyzed. This lipid fraction might contribute to the low IHD incidence found in Southern Europe populations[219]. In our study, although triglyceride, total and LDL cholesterol mean levels were quite similar between IHD-free and stable-IHD people in Girona, mean levels of HDL cholesterol differed between these two groups. PAF estimates showed that raising HDL cholesterol would have a potential impact on IHD prevention in people older than 54, which is in turn the age group with the highest IHD incidence. Up to now, lifestyle modifications with greater cardiovascular benefit (i.e., diet, exercise, weight loss, and smoking cessation) have shown a favourable impact on HDL cholesterol levels, whereas the clinical efficacy of drugs raising HDL choles-

terol is far less abundant than for statins[79], which mainly involve lowering LDL cholesterol[200, 220, 221].

A large number of placebo-controlled trials have conclusively demonstrated that, in patients with high blood pressure values (i.e., systolic values >160 mmHg or diastolic values >100 mmHg), blood pressure reduction lowers cardiovascular morbidity and mortality[222-225]. Indeed, hypertension was the second most prevalent risk factor in our region, with the highest potential impact on IHD prevention in people older than 54. Almost 50% of men and 40% of women were diagnosed with hypertension or had blood pressure measurements beyond the limits of hypertension; this prevalence reached 70% in participants aged 65 years or above. Primary care with universal coverage in Spain has probably improved the detection and purposeful treatment of hypertension, in addition to specific institutional prevention campaigns.

Smoking prevalence increased in women and remained steadily high in men over the period, together with a growth in the percentage of former smokers for both sexes, probably related to smoking ban policies developed in recent years in Spain. In addition, smoking was the most prevalent cardiovascular risk factor in stable-IHD individuals younger than 60 years. Younger smokers, but not those older than 54 years, had significantly higher risk (4 times) not only of developing an IHD event, but also of dying from any cause at 10 years than non-smokers of the same age in our cohort. Lloyd-Jones et al. reported that smokers had CVD much earlier than non-smokers in the Framingham Heart Study[226]. However, lifetime risk for CVD was similar for smokers and non-smokers, due to the competing risk of death from other smoking-related causes[226, 227].

Overweight and obesity have increased at an alarming rate in our region in recent years. Indeed, a decrease in overall diet quality has been described in the Girona population between 2000 and 2005[228]. Recent publications have underlined the considerable increase in the monetary cost of food, in particular of items associated with a low risk of obesity, over the last few years[229]. Moreover, frequent fast food consumption has been directly related to body mass index and the risk of obesity[230]. Despite obesity being a significant predictor of IHD in the Framingham cohort followed up to 44 years[116], our results did not show a significant association with this disease at 10 years. Therefore, the sustained increase in body mass index observed in our pop-

ulation will possibly take some time to translate into higher AMI incidence and mortality rates.

In summary, an overall approach to IHD prevention that takes multiple risk factors into consideration generally provides a more effective measure to substantiate treatment decisions than separate individual risk factor measurements[167].

6.3 Future Research

The findings in this research accurately depict the current situation of IHD epidemics in Spain. The determinants of IHD are multifactorial, and the impact of the different risk factors on incidence and fatalities might vary over time and geography[47]. The continued monitoring in a delimited area in South Europe has allowed detection of changes in the trends and their determinants and the evaluation of the effectiveness of public health strategies to fight IHD.

The next step in this line of research is to ascertain the potential role of primary and secondary prevention in the recent declines in IHD incidence and mortality in those younger than 74 years. The comprehensive IMPACT model, which has been already applied and validated in other countries[55, 231-236], will be adapted to the Spanish population for this purpose.

In addition, many issues regarding the epidemiology of IHD still remain unsolved. First, the role of potential protective factors in South Europe remains to be elucidated, such as the interaction between the environment, particularly diet and physical activity, and genetic characteristics of the population.

Second, although large randomized clinical trials have established the role of statins as effective medical therapy for the primary prevention of IHD events[83, 171, 175], the beneficial effects elicited by this class of drugs may be attributed to the diversity of their non-lipid-lowering pleiotropic effects[237]. Unless new evidence becomes available, advice on lifestyle, including smoking cessation, engaging in the maximum physical exercise possible for one's age and personal fitness, adopting a healthy diet, and controlling weight, is supported by robust scientific evidence, is the most widely accepted prevention strategy and should be systematically applied in IHD prevention regardless of the level of coronary risk[57, 60].

Third, the purpose of risk assessment is not to categorize individuals according to a test, but rather to identify and prioritize indi-

viduals who can be helped by preventive activities[141]. The Framingham function adapted to the Spanish population allows reliable and accurate coronary risk estimation and responds to the recommendation that prevention strategies should be adapted to local characteristics[59, 60]. The problem remains in those individuals classified in the intermediate risk group, among whom the greatest proportion of IHD events will occur. The new population screening strategies for atherosclerosis try to identify the "vulnerable patient": an individual who is likely to suffer IHD events, based on vulnerable plaque markers (unstable or high-risk), vulnerable blood (tendency to thrombosis), and vulnerable myocardium (electrically unstable or arrhythmogenic)[238].

7. CONCLUSIONS

7.1 Incidence and mortality rates due to AMI are low in Girona compared to northern, eastern and western Europe, the USA and other Anglo-Saxon countries. Almost half of patients with AMI die within 28 days following symptom onset, two-thirds of these without accessing hospital care. The improvements found in the attack, incidence and recurrence rates of AMI cases in males aged 35-64 years between 1990 and 1999 were not observed in those aged 65-74 years, possibly indicating a delay in age of AMI onset or recurrence. Attention in the acute phase of AMI has probably helped to reduce the number of fatal cases in hospitalized males, especially in those over 64 years. There are no changes in any indicator in females, who present extraordinarily low rates in the region.

7.2 The prevalence of classic cardiovascular risk factors in Girona is high despite the relatively low AMI incidence and death rates observed in this region. The cardiovascular risk factor prevalence change in Girona has been marked in the last decade by a shift of total cholesterol and LDL cholesterol distributions to the left, independent of the increase in lipid-lowering drug use, and by better hypertension control, accompanied by increased use of antihypertensive drugs.

7.3 Cardiovascular risk factor prevalence is high among French and Spanish stable-IHD patients. In particular, French participants showed higher lipid and blood pressure levels whereas Spanish patients had higher smoking prevalence. Overall, only one out of four patients reached the optimal blood pressure or lipid levels recommended in European guidelines on IHD prevention.

7.4 LDL cholesterol levels had the highest potential for IHD prevention in this population aged 35-74 years, along with smoking for those younger than 55 and hypertension and HDL cholesterol age 55 and older, according to PAF estimations. PAF may require periodic recalculation in different age groups and periods to adequately monitor the population trends in world regions.

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ABSTRACT

The primary prevention of cardiovascular disease must be adapted to local characteristics of cardiovascular risk factor prevalence, acute myocardial infarction mortality and incidence rates, and economic and cultural factors. Traditionally, acute myocardial infarction incidence in Spain has been lower than that found in north, east, and west European countries, the USA, and other English-speaking countries. However, the prevalence of risk factors in Spain was surprisingly similar to those countries with high acute myocardial infarction incidence. Essentially, no overall change in acute myocardial infarction incidence has been observed over the past decade. Nonetheless, men under age 65 showed a significant reduction in incidence rates, while the trend in men age 65-74 did not change significantly. The prevalence of cardiovascular risk factors, however, has undergone considerable change. The most noteworthy aspects are improvements in participants' awareness, control and treatment of hypertension, and improvement in total and low-density lipoprotein cholesterol distribution. In this context, the reduction of low-density lipoprotein cholesterol levels had the highest potential for ischemic heart disease prevention, along with smoking prevention for people younger than 55.