

Original article

Analyzing the Coronary Heart Disease Mortality Decline in a Mediterranean Population: Spain 1988–2005

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ABSTRACT

Introduction and objectives: To examine the extent to which the decrease in mortality rates in Spain between 1988 and 2005 could be explained by changes in cardiovascular risk factors and by the use of medical and surgical treatments.

Methods: We used the previously validated IMPACT model to examine the contributions of exposure factors (risk factors and treatments) to the main outcome, changes in the mortality rates of death from coronary heart disease, among adults 35 to 74 years of age. Main data sources included official mortality statistics, results of longitudinal studies, national surveys, randomized controlled trials, and meta-analyses. The difference between observed and expected coronary heart disease deaths in 2005 was then partitioned between treatments and risk factors.

Results: From 1988 to 2005, the age-adjusted coronary heart disease mortality rates fell by almost 40%, resulting in 8530 fewer coronary heart disease deaths in 2005. Approximately 47% of the fall in deaths was attributed to treatments. The major treatment contributions came from initial therapy for acute coronary syndromes (11%), secondary prevention (10%), and heart failure (9%).

About 50% of the fall in mortality was attributed to changes in risk factors. The largest mortality benefit came from changes in total cholesterol (about 31% of the mortality fall) and in systolic blood pressure (about 15%). However, some substantial gender differences were observed in risk factor trends with an increase in diabetes and obesity in men and an increase in smoking in young women. These generated additional deaths.

Conclusions: Approximately half of the coronary heart disease mortality fall in Spain was attributable to reductions in major risk factors, and half to evidence-based therapies. These results increase understanding of past trends and will help to inform planning for future prevention and treatment strategies in low-risk populations.

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Análisis de la disminución de la mortalidad por enfermedad coronaria en una población mediterránea: España 1988-2005

RESUMEN

Introducción y objetivos: Examinar el grado en que la disminución de las tasas de mortalidad por cardiopatía isquémica en España entre 1988 y 2005 podría explicarse por cambios en los factores de riesgo cardiovascular y por el uso de tratamientos médicos y quirúrgicos.

Métodos: Se utilizó el modelo IMPACT previamente validado para combinar y analizar datos de las tendencias en la prevalencia de factores de riesgo y el uso y la efectividad de tratamientos cardíacos basados en la evidencia, entre varones y mujeres adultos de 35–74 años de edad. Las principales fuentes de datos incluyeron estadísticas oficiales de mortalidad, resultados de estudios longitudinales, encuestas nacionales, ensayos clínicos aleatorizados y metaanálisis. La diferencia entre las muertes coronarias observadas y esperadas en 2005 se distribuyó entre los tratamientos y los factores de riesgo.

Resultados: Desde 1988 a 2005, la tasa de mortalidad ajustada por edad cayó un 40%, y hubo 8.530 muertes menos en 2005. Aproximadamente el 47% de la caída en la mortalidad se ha atribuido a los

Palabras clave:

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tratamientos. Los abordajes que contribuyeron en mayor medida fueron el tratamiento en fase aguda de los síndromes coronarios (11%), la prevención secundaria (10%) y el tratamiento de la insuficiencia cardiaca (9%). El 50% de la reducción de la mortalidad se ha atribuido a cambios en los factores de riesgo. El mayor beneficio en la mortalidad viene de los cambios en el colesterol total (cerca de un 31% de la caída de la mortalidad) y de la presión arterial sistólica (cerca de un 15%). Pero se observaron importantes diferencias entre sexos en las tendencias de los factores de riesgo: se incrementó la diabetes mellitus y la obesidad entre los varones y la prevalencia del consumo de tabaco entre las mujeres jóvenes, lo cual produjo muertes adicionales.

Conclusiones: Aproximadamente la mitad del descenso en la mortalidad coronaria en España se ha atribuido a la reducción de los principales factores de riesgo y la otra mitad, a los tratamientos basados en la evidencia. Estos resultados incrementan la comprensión de tendencias pasadas y ayudarán a planificar futuras estrategias preventivas y de tratamientos en poblaciones con bajo riesgo.

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Abbreviations

AMI: acute myocardial infarction

CHD: coronary heart disease

INTRODUCTION

Coronary heart disease (CHD) incidence and mortality rates in southern Europe have been consistently three-fold lower than those observed in the rest of Europe or the United States, in spite of similar levels of cardiovascular risk factors. This reflects the so-called “Mediterranean Paradox”.^{1,2} Furthermore, age-adjusted CHD death rates in people aged 35 to 74 have steeply decreased in Spain, by 40% since about 1980.³

This mortality decline could be explained in terms of risk factor trends or the use of evidence-based treatments, or a combination. For example, in Spain there were important recent improvements in cholesterol levels, hypertension treatments, and blood pressure control.⁴ The widespread use of effective evidence-based treatments has also improved, with decreases in acute myocardial infarction (AMI) 28-day case fatality observed since the 1990s.⁵

However, quantifying the relative contributions of these two contrasting components is a complex task. The use of epidemiological models is therefore becoming an increasingly important tool to address these difficult questions, by integrating data on risk factor trends and treatment effectiveness.⁶

Our objective was therefore to examine trends from CHD deaths in Spain between 1988 and 2005 by using IMPACT, a comprehensive CHD policy model now validated in over a dozen countries.^{6–11}

METHODS

To examine the contributions of various factors to the changes in mortality rates of death from CHD among Spanish adults aged 35 to 74 years, we used an updated version of the IMPACT policy model. This model has been previously validated in diverse populations of other countries in Europe, the United States, New Zealand, China,^{6–9,11} and—crucially—in another “Mediterranean” population, Italy.¹²

The IMPACT model methodology has been described in detail elsewhere.⁶ In brief, it is comprehensive, incorporating the major population risk factors for CHD (smoking, high blood pressure, elevated total cholesterol, obesity, diabetes, and physical inactivity) and all the usual medical and surgical treatments for CHD.

Wherever possible, data sources specific to the Spanish population were used to construct the Spanish IMPACT model

(Table 1). When more than one data source was available, we selected the most recent, representative, and least biased source.

Deaths Prevented or Postponed

Data for 1988 and 2005 on the total Spanish population and age distribution, and on deaths associated with CHD, all stratified by age and sex, were obtained from the Spanish Statistical Office.³ We then used internal standardization to estimate the number of CHD deaths that would have been expected in 2005 if the mortality rates in 1988 had remained unchanged. The age-specific mortality rates for 1988 were multiplied by the population for each 10-year age stratum in 2005 (thus accounting for population aging and growth). Three-year averages were employed to further reduce random variation.

Subtracting the number of deaths actually observed in 2005 from the number expected yielded the fall in the number of deaths in 2005 compared with the 1988 baseline that the model would have to explain.

Treatment and Mortality Reductions

The number of patients with CHD categorized by diagnosis was obtained from the Spanish Hospital Morbidity Survey.³ The estimated frequency of use of specific treatments, the case fatality rate, and the risk reduction due to treatment, all stratified by age and sex, were obtained from published sources (Supplementary material).

The number of deaths prevented or postponed as a result of each intervention in each group of patients in 2005, stratified by age, was then calculated. The number of people in each diagnostic group of patients in 2005 was multiplied by the proportion of those patients who received a particular treatment, by their case fatality rate over a period of 1 year, and by the relative reduction in the 1-year case fatality rate reported for that treatment in the largest and most recent meta-analysis.⁶

For example, about 10 752 men aged 55 to 64 years were hospitalized with AMI in Spain in 2005. The expected age-specific 1-year case-fatality rate was approximately 5.4%. Approximately 79% were prescribed acetylsalicylic acid,¹³ with an expected mortality reduction of 15%. The number of deaths prevented or postponed for at least a year by the use of acetylsalicylic acid among men aged 55–64 were then calculated as:

$$10\,752 \times 79\% \times 15\% \times 5.4\% = 69 \text{ deaths prevented or postponed.}$$

To address the potential effect on the relative reduction in the case fatality rate for individual patients receiving multiple treatments, we used the Mant and Hicks cumulative-relative-benefit approach¹⁴:

Table 1
Main Data Sources for the Parameters Used in the Spanish IMPACT Model for 1988 and 2005

	1988	2005
Population, deaths, CHD Mortality	National Statistics Institute	National Statistics Institute
Number of patients admitted yearly: MI, AP, HF	Hospital Morbidity Survey	Hospital Morbidity Survey
Number of CABG patients	Assume zero	Revista Española de Cardiología
PTCA	Assume zero	
Cardiopulmonary resuscitation in the community	IBERICA, REGICOR	IBERICA, REGICOR
AMI	Assume zero	REGICOR, MASCARA
Unstable angina pectoris	Assume zero	MASCARA, EMMA Researchers personal communication
Secondary prevention following AMI	Assume zero	REGICOR, EMMA Researchers personal communication
Secondary prevention following CABG or PTCA	Assume zero	REGICOR, EMMA Researchers personal communication
Congestive heart failure	Assume zero	EPISERVE Study; The PRICE Study
Treatment for chronic angina	Assume zero	REGICOR
Community angina pectoris: total	PANES	EMMA Researchers personal communication
Community chronic heart failure		
Prevalence	Literature review	EMMA Researchers personal communication
Medication (ACE inhibitors, beta blockers, spironolactone, acetylsalicylic acid, statins)	Assume zero	EMMA Researchers personal communication
Hypertension	Banegas ²⁴	REGICOR
Statins for primary-prevention		HERMES
Population risk factor prevalence		
Current smoking	National Health Survey	National Health Survey
Systolic blood pressure	CINDI Study	Baena Díez et al ³⁷
Cholesterol	MONICA-Cat	HERMES
Physical activity	National Health Survey	National Health Survey
Obesity (BMI)	MONICA-Cat	REGICOR
Diabetes	National Health Survey	National Health Survey

ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; AP, angina pectoris; BMI, body mass index; CABG, coronary artery bypass grafts surgery; CHD, coronary heart disease; HF, heart failure; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Relative benefit = $1 - (1 - \text{relative reduction in case fatality rate for treatment A}) \times (1 - \text{relative reduction in case fatality rate for treatment B}) \times (1 - \text{relative reduction in case fatality rate for treatment N})$.

We assumed that adherence, or the proportion of treated patients actually taking therapeutically effective levels of medication, was 100% among hospitalized patients, 70% among symptomatic patients in the community, and 50% among asymptomatic patients in the community.^{15,16} To avoid double counting of patients treated, we identified potential overlaps between different groups of patients and made appropriate adjustments.

Risk Factors and Mortality Reductions

Two approaches were used to calculate the number of deaths prevented or postponed as a result of changes in specific risk factors.

We used a regression approach for systolic blood pressure, total cholesterol, and body mass index. The number of deaths prevented or postponed as a result of the change in the mean value for each of these risk factors was estimated as the product of 3 variables: the number of deaths from CHD in 1988 (the base year), the subsequent reduction in that risk factor, and the regression coefficient quantifying the change in mortality from CHD per unit of absolute change in the risk factor (obtained from a large, recent meta-analysis).

For example, in 1988, there were 3028 CHD deaths among 2 035 451 men aged 55–64 years. Mean systolic blood pressure in this group decreased by 2.4 mmHg between 1988 and 2005. The

largest metaanalysis reports an estimated age- and sex-specific reduction in mortality of 2.5% for every 1 mmHg reduction in systolic blood pressure, thereby generating a logarithmic coefficient of -0.035 .¹⁷

$$= (1 - (\text{EXP}(\text{coefficient} \times \text{change}))) \times \text{deaths in 1988}$$

$$= 1 - (\text{EXP}(-0.035 \times 0.56) \times 3,028) = 246 \text{ deaths prevented or postponed}$$

The population-attributable risk fraction approach was used to determine the effect of changes in the prevalence of smoking, diabetes, and physical inactivity.¹⁸ This is detailed in the [Supplementary material](#).

The number of deaths prevented or postponed as a result of changes in risk factors was systematically quantified for each specific patient group to account for potential differences in effect.

We assumed that lag times between the change in the risk factor rate and the change in the event rate would be relatively unimportant over a period of 17 years.

Because independent regression coefficients and relative risks for each risk factor were obtained from multivariate analyses, we assumed that there was no further synergy between the treatment and risk-factor sections of the model or among the major risk factors.

Comparison of Estimated and Observed Mortality Changes

The model estimates for the total number of deaths prevented or postponed by each risk-factor change were then summed and

compared with the observed changes in mortality for men and women in each age group. Any shortfall in the overall model estimate was then presumed to be attributable either to inaccuracies in our calculations or to other unmeasured risk factors. All estimates were rounded to the nearest multiple.

Sensitivity Analysis

We tested all the above assumptions and variables in a multiple-way sensitivity analysis, using the analysis-of-extremes method.¹⁹ For each variable in the model, we assigned a lower value and an upper value, using 95% confidence intervals when available and otherwise using $\pm 20\%$ (for the number of patients, treatment use, and compliance).^{13,20}

Detailed information on methods and data sources is shown in the [Supplementary material](#).

RESULTS

From 1988 to 2005, the age-adjusted mortality rate of CHD fell from 148.2 to 92.1 cases per 100 000 population among men aged 35 to 74 years and from 46.7 to 24.2 among women aged 35 to 74 years. This resulted in 8530 fewer deaths in 2005 compared with the expected number if the rates in 1988 had persisted (20 610 expected minus 12 080 observed).

The Spain IMPACT model explained approximately 8310 (97%) of this 8530 decrease. Under the assumptions of the sensitivity analysis, the extreme minimum and the maximum number of deaths from CHD that were explained was 5045 (59%) and 13 830 (162%).

Medical and Surgical Treatments

Approximately 3990 (47%) fewer CHD deaths were attributable to medical therapies (*minimum estimate 1650, maximum estimate 8625*) (Table 2). The largest mortality reductions came from the use of secondary prevention medications (after post-myocardial infarction or after percutaneous transluminal coronary angioplasty/coronary artery bypass grafts surgery, approximately 855 fewer deaths) and initial treatments for AMI or unstable angina (approximately 975 deaths), followed by the treatments of heart failure and hypertension, statins for primary prevention, and medical treatments for chronic angina. Revascularization for chronic angina resulted in approximately 170 fewer deaths in 2005 compared with 1988, or approximately 2% of the total mortality fall (Table 2).

Risk Factors

Approximately 4320 fewer CHD deaths were attributable to changes in risk factors (*minimum estimate 3395, maximum estimate 5205, Table 3*). Decreases in total cholesterol concentration (-0.3 mmol/L), systolic blood pressure (-3.3 mmHg), and smoking prevalence (-3.9%), were estimated to have prevented or postponed approximately 3130, 2045, and 1385 deaths, respectively. The 7.7% decrease in physical inactivity prevented or postponed approximately 195 deaths. In contrast, the 0.4 kg/m² increase in body mass index and 0.6% increase in diabetes prevalence resulted overall in approximately 535 and 640 additional deaths, respectively (Table 3).

Risk factor trends were different in men and women. In men, there were increases in body mass index (1.5 kg/m²), diabetes prevalence (2.2%), and physical inactivity (2%). In women, overall

diabetes prevalence apparently decreased slightly, paralleling a modest decrease in obesity. More worryingly, an important increase in smoking prevalence (from 9% to 19.7%) was observed in women, adding 345 extra deaths and thus negating some of the gains obtained with the favorable trends in other risk factors.

Sensitivity Analyses: Proportional Contributions to the Fall in Coronary Heart Disease Deaths

The proportional contributions of specific treatments and risk factor changes to the overall fall in CHD deaths in 2005 remained relatively consistent in the sensitivity analyses (Fig. 1). Thus, all initial treatments for AMI together accounted for 7.7% of the total 8530 decrease in deaths. The minimum estimated contribution was 4.4% and the maximum was 15.6%. The contribution of AMI treatments therefore remained consistently smaller than that of secondary prevention or heart failure therapies, irrespective of whether best, minimum or maximum estimates were compared (Fig. 1).

The model estimates also showed reasonable agreement with the observed reduction in CHD deaths across specific age groups in men and women (Fig. 2).

DISCUSSION

We examined CHD trends in Spain, a Mediterranean population where cardiovascular mortality rates are far lower than in Northern Europe or the United States.

CHD mortality rates fell by almost 40% between 1988 and 2005. Approximately half the fall was attributable to evidence-based medical therapies and half to reductions in major risk factors. Even though CHD mortality rates fell substantially between 1988 and 2005 in Spain, the burden of CHD in Spain remains an important public health issue. CHD still accounts for 32% of all deaths²¹ and also causes substantial disability, long-term dependence on health services and medications, and loss of quality of life.²² Furthermore, CHD is an important factor contributing to stroke occurrence at older ages. In the 17 years of the study there has been rapid growth in costly medical technology and pharmaceutical treatments for CHD, as well as substantial public health efforts to reduce the levels of major cardiovascular risk factors. Establishing the relative contributions of these contrasting approaches is therefore of considerable importance.

This is only the second time that the IMPACT Model has been applied to a Mediterranean country, characterized by substantially lower CHD mortality rates compared with Northern European countries^{9,11} and the United States⁶ given similar levels of the main cardiovascular risk factors in the population (the “Mediterranean paradox”).¹² In Italy, we found that age-adjusted CHD mortality rates also fell by approximately 40% among persons aged 25–84 years between 1980 and 2000.¹² Approximately 40% of this decrease was attributed to treatments, and approximately 55% to changes in risk factors. Decreases in systolic blood pressure (-5.3 mmHg), total cholesterol concentration (-0.35 mmol/L), and smoking prevalence (-4.0%) were estimated to have accounted for approximately 25%, 23%, and 4% of the mortality fall, respectively. Increases in diabetes and body mass index were smaller than in Spain in 2005, resulting in only approximately 2% additional deaths.

Previous studies using the IMPACT methodology in Northern European or United States populations have all consistently shown a greater contribution from reduction in population risk factor levels than from treatments.^{7–10,12} In Spain, we found that improvements in major risk factors accounted for approximately

Table 2
Estimated Attributable Effect of Treatments on the 8530 Coronary Heart Disease Deaths Prevented or Postponed in Spain in 2005

	Patients eligible	Treatment uptake (%)	Relative risk reduction	Mean case-fatality	Deaths Prevented or Postponed			
					Best estimate	Minimum estimate	Maximum estimate	% of total
Acute phase disease management								
<i>Acute myocardial infarction</i>								
Community CPR	13 672	3	0.08	0.066	20	16	55	0.3
Hospital CPR	892	100	0.33	0.066	275	69	375	3.2
Thrombolysis	44 617	30	0.27	0.066	205	163	245	2.4
Acetylsalicylic acid	44 617	78	0.15	0.066	215	171	620	2.5
Primary PTCA	44 617	3	0.28	0.066	25	17	57	0.3
Beta blocker	44 617	20	0.04	0.066	40	-30	125	0.5
ACE inhibitor	44 617	13	0.07	0.066	40	5	59	0.5
Primary CABG	44 617	1	0.39	0.066	10	5	16	0.1
Treatment effect already existing in 1988	—	—	—	—	-170	-38	-225	-2.0
Total AMI	44 617	—	—	0.066	660	378	1327	7.7
<i>Unstable angina</i>								
Acetylsalicylic acid and Heparin	—	67	0.33	0.184	195	62	208	2.3
Acetylsalicylic acid alone	—	20	0.15	0.184	15	8	28	0.2
GP IIB/IIA	—	18	0.09	0.184	10	5	16	0.1
Primary CABG	—	20	0.43	0.184	50	24	81	0.6
Primary PTCA	—	30	0.28	0.184	45	24	79	0.5
Total unstable angina	14 151	—	—	0.184	315	123	412	3.7
Total AMI+ unstable angina	—	—	—	—	975	501	1739	11.4
Secondary prevention								
<i>Myocardial infarction</i>								
Acetylsalicylic acid	—	74	0.15	0.037	160	65	327	1.8
Beta blocker	—	41	0.23	0.037	170	72	365	2.1
ACE inhibitor	—	42	0.20	0.037	145	60	301	1.7
Statin	—	64	0.22	0.037	165	67	341	1.9
Warfarin	—	6	0.22	0.037	35	11	58	0.4
Rehabilitation	—	7	0.26	0.037	5	3	16	0.1
Treatment effect already existing in 1988	—	—	—	—	-10	-5	-20	—
Total myocardial infarction	268 545	—	—	0.037	670	280	1405	7.9
<i>Post-CABG surgery/PTCA</i>								
Acetylsalicylic acid	—	80	0.15	0.015	45	19	97	0.5
Beta blocker	—	44	0.23	0.015	35	15	75	0.4
ACE inhibitor	—	42	0.20	0.015	30	12	62	0.3
Statin	—	63	0.22	0.015	50	20	102	0.6
Warfarin	—	6	0.22	0.015	5	2	11	0.1
Rehabilitation	—	3	0.26	0.015	5	1	6	0.1
Total post-CABG surgery/PTCA	66 808	—	—	—	170	69	353	2.0
Total AMI+total post-CABG surgery/PTCA	—	—	—	—	855	347	1761	10.0
Chronic angina								
CABG surgery 1995-2005, minus 1988	65 054	100	0.15	0.016	170	155	806	2.0
Angioplasty 1995-2005	0	100	0.13	0.003	0	0	0	0
Acetylsalicylic acid in community	441 255	78	0.15	0.0103	200	82	414	2.3
Statins in community	441 255	69	0.23	0.0103	200	82	417	2.3
Total chronic angina	441 255	—	—	—	570	319	1637	6.7
Heart failure (hospital management)								
ACE inhibitor	—	48	0.20	0.213	120	52	261	1.4
Beta blocker	—	28	0.35	0.213	125	53	267	1.5
Spirolactone	—	6	0.30	0.213	25	10	50	0.3
Acetylsalicylic acid	—	38	0.15	0.213	60	31	155	0.7
Total heart failure (hospital management)	9735	—	—	—	330	146	733	3.9
Heart failure (community management)								
ACE inhibitor	—	30	0.20	0.078	95	37	233	1.1

Table 2 (continued)

	Patients eligible	Treatment uptake (%)	Relative risk reduction	Mean case-fatality	Deaths Prevented or Postponed			
					Best estimate	Minimum estimate	Maximum estimate	% of total
<i>Beta blocker</i>	—	27	0.35	0.078	225	91	463	2.6
<i>Spirolactone</i>	—	4	0.36	0.078	25	10	52	0.3
<i>Acetylsalicylic acid</i>	—	23	0.15	0.078	85	48	243	1.0
<i>Total heart failure (community management)</i>	65 715	—	—	—	430	186	991	5.0
Primary prevention								
<i>Hypertension treatments</i>	7 735 137	43	0.13	0.002	775	125	1625	9.1
<i>Statins for primary prevention</i>	12 985 919	9	0.24	0.001	70	28	141	0.8
<i>Total primary prevention</i>	—	—	—	—	(845)	153	1764	9.9
Total treatments	—	—	—	—	3990	1650	8625	46.8

ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass grafts surgery; CPR, cardiopulmonary resuscitations; GP, glycoprotein; PTCA, percutaneous transluminal coronary angioplasty (with or without stent).

Numbers of eligible patients and category totals of deaths prevented or postponed were rounded to nearest 0 or 5; totals may therefore not always be exact. Additional details of data sources are described in the Supplementary material.

Table 3

Estimated Attributable Effect of Risk Factor changes on the 8530 Coronary Heart Disease Deaths Prevented or Postponed in Spain from 1988 to 2005

Risk Factor	Absolute level of risk factor		Absolute risk factor change	Regression coefficient	Deaths prevented or postponed			
	1988	2005			Best estimate	Minimum	Maximum	% of total ^a
<i>Systolic blood pressure (mmHg)</i>								
Men	133.8	130.2	-3.6	-0.033	1165	757	1644	13.6
Women	128.1	124.9	-3.2	-0.04	880	578	1221	10.2
Both sexes	130.8	127.5	-3.3	-0.033	2045	1335	2865	24.0
Minus treatment effect in 2005	—	—	—	—	-775	-125	1625	-9.1
<i>Smoking prevalence (%)</i>								
Men	52.5	32.5	-20.0	—	1730	1488	2233	20.3
Women	9.0	19.7	10.7	—	-345	-260	-629	-4.0
Both sexes	29.7	25.8	-3.9	—	1385	1069	1604	16.3
<i>Total cholesterol (mmol/L)</i>								
Men	5.7	5.4	-0.3	-0.762	2200	1485	3089	25.7
Women	5.8	5.5	-0.3	-0.762	930	615	1295	10.9
Both sexes	5.8	5.5	-0.3	-0.762	3130	2100	4380	36.7
Minus treatment effects in 2005	—	—	—	—	-480	-200	-1005	-5.6
<i>Body mass index (kg/m²)</i>								
Men	26.0	27.5	+1.5	0.028	-545	-304	-848	-6.4
Women	27.4	26.7	-0.7	0.028	10	6	17	0.2
Both sexes	26.7	27.1	+0.4	0.028	-535	-298	-831	-6.2
<i>Diabetes prevalence (%)</i>								
Men	8.3	10.5	+2.2	—	-485	-350	-631	-5.7
Women	10.1	9.3	-0.8	—	-155	-112	-198	-1.8
Both sexes	9.3	9.9	+0.6	—	-640	-460	-830	-7.5
<i>Physical Inactivity (%)</i>								
Men	36.6	38.6	+2.0	—	-90	-72	-108	-0.7
Women	55.7	39.2	-16.5	—	285	227	340	3.3
Both genders	46.6	38.9	-7.7	—	195	155	232	2.6
<i>Total</i>	—	—	—	—	4320	3395	5205	50.6

Numbers of deaths prevented or postponed were rounded to nearest 0 or 5.

Additional details of data sources are described in the Supplementary material.

Units are percent change in mortality rate per unit of risk factor as shown in column one

^a Results of subtracting the treatments from the best estimate.

50% of the recent decrease in CHD deaths. The largest mortality benefit came from changes in total cholesterol (about 31% of the mortality fall) and in systolic blood pressure (about 9%). Cholesterol and blood pressure have been steadily decreasing over the past 20 years.^{4,23} The decline in systolic blood pressure was more evident in young men than in other groups. Indeed, the

proportion of treated hypertension rose to 70% by 2005, although only about 30% were adequately controlled.²⁴ A similar phenomenon could be described with cholesterol: almost 31% of the mortality decrease came from a moderate reduction (0.33 mmol/L) in serum cholesterol level, having separately quantified the effect of statins in primary prevention (barely 1%). Despite an unhealthy

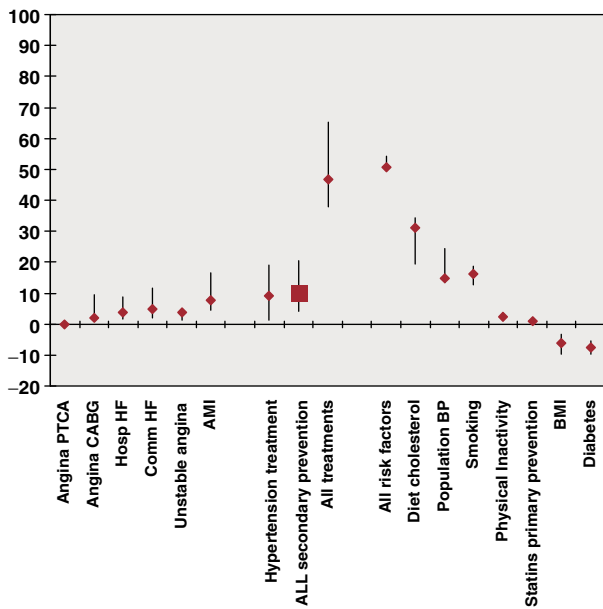


Figure 1. Sensitivity analysis. The proportional contributions of specific treatments and risk factor changes to the overall decrease in coronary heart disease mortality in Spain between 1988 and 2005. The squares and diamonds show the specific and total best-model estimates, respectively. The vertical lines show the extreme minimum and maximum estimates. AMI, Acute myocardial infarction; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafts surgery; HF, Heart failure; PTCA, percutaneous transluminal coronary angioplasty.

diet, other developed countries have also shown decreases in cholesterol levels.²⁵⁻²⁷

We found interesting differences in risk factor trends by sex. Although smoking prevalence among men fell from 52.5% to 32.6%, smoking prevalence among women rose distressingly from 9.1% to 19.1%,²⁸ resulting in over 340 additional coronary deaths. In spite of recent declines in smoking prevalence following the workplace

smoking ban in Spain in 2006 and 2010^{29,30} further interventions will clearly be essential.

Furthermore, whereas the body mass index in women apparently decreased from 27.4 kg/m² to 26.7 kg/m², the body mass index rise in men resulted in about 540 additional deaths. Similar results have been described previously in Spain.³¹ Furthermore, the increase in diabetes prevalence accounted for approximately 640 additional deaths from CHD in 2005.

These adverse trends are depressingly consistent with recent studies in Italy and other Mediterranean countries.¹² Stronger interventions are therefore needed in future measures to improve the public health.

As elsewhere, the largest contributions from medical therapies consistently came from secondary prevention, followed by treatment for hypertension, then AMI treatment. Revascularization by coronary artery bypass grafts surgery or coronary angioplasty for stable and unstable disease together accounted for approximately 3.5% of the overall fall in CHD deaths, even less than the 5% in previous studies in the United States and Europe.^{8,9,12,32,33} Furthermore, recent trial evidence now suggests that for patients with stable angina, percutaneous transluminal coronary angioplasty provides no mortality benefits compared with optimal medical treatment.^{8,9,12,32-34}

Modelling studies have a number of potential strengths, including the ability to transparently integrate and simultaneously consider huge amounts of data from many sources, and then test explicit assumptions by sensitivity analyses.

However, all modeling analyses have limitations. Models are dependent on the variable extent and quality of data available. Assumptions have to be made to fill the gaps, and robust sensitivity analysis using the analysis of extremes approach are therefore essential. However, the proportional contributions to the overall reductions in deaths from specific treatments and risk factor changes remained reasonably consistent, irrespective of whether best, minimum, or maximum estimates were considered (Tables 2 and 3). This was reassuring, as was the general consistency with studies performed elsewhere.^{35,36}

Results from different studies were used to estimate cholesterol level, blood pressure, and body mass index at the beginning and at

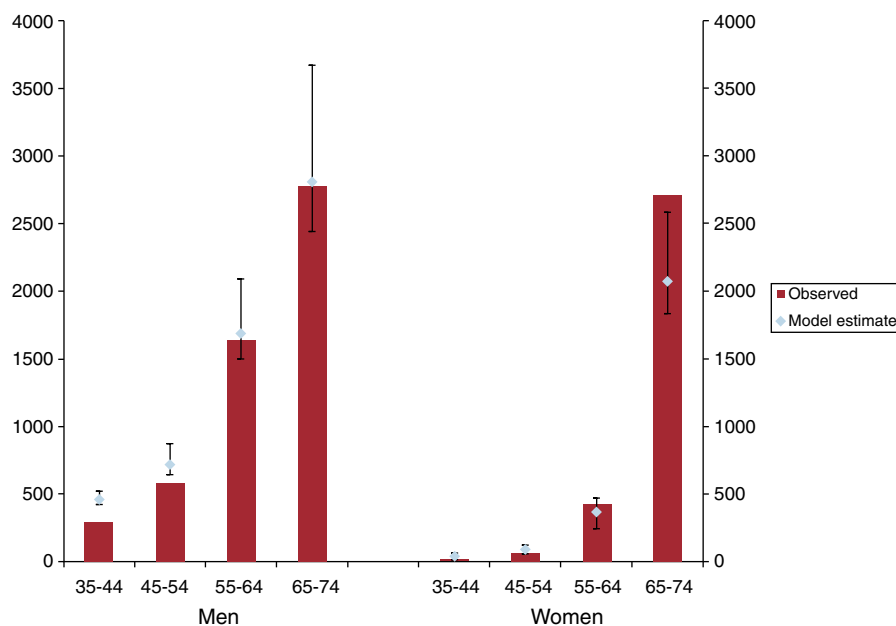


Figure 2. Model-estimated and observed reductions in coronary heart disease deaths in Spain between 1988 and 2005. The columns show the observed fall in deaths in each age group; the diamonds show the best model estimates and the vertical lines indicate the extreme minimum and maximum estimates.

the end of the study period.^{4,24,37,38} Variations due to different study designs, study populations, and study periods might therefore influence results. Even though unpublished original data were used together with published sources, publication bias might still be an issue.

Although previous publications have suggested the distribution of prevalence of cardiovascular risk factors may be not homogeneous,³⁹ little variation was observed between Autonomous communities in the population aged 35-74 years in a recent publication.⁴⁰ The trends in cardiovascular risk factors observed in some areas of Catalonia may also apply to the rest of Spain.

Still more worrisome is the fact that at least 8% of the persons are unaware that they have the disease (undiagnosed or unknown diabetes mellitus).⁴¹

The model included only those aged 35-74 years because very limited data was available in older groups. In addition, the model fit was poorer in the oldest women, explaining less of the observed decrease in CHD mortality in this age group compared with men. Elderly women have been shown to be underrepresented in many CHD clinical trials and surveys.⁴² Furthermore, death certification could be overestimating CHD mortality in elderly groups.

The risk factor estimates clearly remain imprecise. Furthermore, risk estimates were not necessarily fully independent from each other. However, the use of the sensitivity analyses with $\pm 20\%$ thresholds for each parameter, when 95% confidence intervals were not available, helps to give a robust range within which the real value will almost certainly fall. We also did not explicitly consider the effect of lag times; however, they may be relatively unimportant over a 17-year period.^{9,11,43} Although major efforts were made to address overlaps, residual double-counting of some individual patients remains possible. We also assumed that, after adjustments for lower dosing and imperfect compliance, the efficacy of treatments in randomized controlled trials could be generalized to population effectiveness in usual clinical practice.^{11,43,44} Both assumptions may have potentially overestimated the true treatment effect.

We therefore made explicit assumptions detailed in the **Supplementary material**. Moreover, we only analyzed the estimated fall in CHD deaths, not life years gained or quality of life⁹. These merit further work, as do economic analyses which would complement the mortality data and help determine priorities when planning future prevention and intervention strategies.

CONCLUSIONS

In conclusion, approximately half of the recent CHD mortality decrease in Spain was attributable to reductions in major risk factors, and half to medical and surgical therapies. Future CHD strategies should therefore actively promote primary prevention and maximize the population coverage of effective treatments.

DISCLAIMER

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the University of Liverpool or of the Spanish Institutions.

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CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY MATERIAL



Supplementary material associated with this article can be found, in the online version available, at [doi:10.1016/j.rec.2011.05.035](https://doi.org/10.1016/j.rec.2011.05.035).

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