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EFFECT OF CARDIOVASCULAR PREVENTION STRATEGIES ON INCIDENT CORONARY DISEASE HOSPITALISATION RATES IN SPAIN. AN ECOLOGICAL TIME SERIES ANALYSIS

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ABSTRACT

Objective: To assess the overall population impact of primary prevention strategies (promotion of healthy lifestyles, prevention of smoking and use of vascular risk drug therapy) of coronary disease in Spain.

Design: Ecological time series analysis, 1982 to 2009.

Setting: All public and private hospitals in Spain.

Participants: General population.

Outcome: Incident coronary disease hospitalization as derived from official hospital discharge data.

Methods: Annual hospitalisation rates were modelled according to nationwide use of statins, antihypertensive, antidiabetic and antiplatelet drugs, and prevalences of smoking, obesity and overweight. Additive generalised models and mixed Poisson regression models were used for the purpose, taking year as the random-effect variable and adjusting for age, sex, prevalence of vascular risk factors, and hospital beds in intensive and coronary care units.

Results: Across 28 years and 671.5 million persons-year of observation, there were 2,986,834 hospitalisations due to coronary disease; of these, 1,441,980 (48.28%) were classified as incident. Hospitalisation rates increased from 1982 to 1996, with an inflection point in 1997 and a subsequent 52% decrease until 2009. Prevalences of smoking, obesity, overweight and use of vascular risk drug therapy were significantly associated with hospitalisation rates ($p<0.001$): incidence rates ratios (95% CI) for the fourth versus the first quartile were 1.46 (1.42-1.50), 1.80 (1.78-1.83), 1.58 (1.55-1.60) and 0.57 (0.51-0.63) respectively. These variables accounted for 92% of interannual variability.

Conclusion: After decades of continuous rises, hospitalisation due to incident IHD has been cut by half, an achievement associated with the decline in smoking and the increase in vascular risk drug therapy. These results indicate that these two primary prevention strategies have been effective at a population level, thanks to an appropriate balance between financial and health goals, something that should be left intact despite the current economic crisis. Future strategies ought to lay special stress on excessive body weight prevention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study shows that the decline in coronary disease in Spain was associated with the exponential increase in pharmacological treatment of vascular risk, together with the decline in active smoking that followed the strong interventions against tobacco use implemented in mid and late '90s. This decrease in IHD hospitalisation rates could have been even greater, had it not been for the frequency of excessive weight, which not only failed to decline but actually rose.

- The exposure-effect associations found: 1- are of great magnitude; 2- show a strong dose-response relationship; 3-show a correct temporality; 4- are biologically plausible; and 5- are consistent with similar studies in other countries, with trends in other tobacco-related diseases and with the increase in the rates of detection, treatment and control of vascular risk factors in Spain.

- The results are relevant as some of these measures (i.e. broad use of statins in general population) are still controversial. Moreover, the results may substantially affect public health policy, especially in a context of financial crisis.

- This is an ecological study based on health indicators and targeted at the assessment of public health; its results should not be interpreted as outcomes of intervention trials, even though they may nuance the latter insofar as they provide an illustration of their external validity.

INTRODUCTION

Ischaemic heart disease (IHD) is a severe disease, is lethal in its acute form in 20%-30% of cases [1] – indeed, it is the leading cause of death in men and the second leading cause of death in women in Spain [2]- and is chronically incapacitating in a great proportion of survivors. Its frequency in the Spanish population is high, with population incidence being estimated at 207 and 45/100,000 in men and women respectively, and hospitalisations at 140,000 cases annually.[3] Consequently, this situation became a public health priority and the target of specific health-planning strategies at a national level.[4]

The main vascular risk factors (excessive body weight, smoking habit, hypercholesterolaemia, arterial hypertension and diabetes mellitus) can be modified by changes in lifestyle or therapeutic interventions. In recent years, cardiovascular disease prevention has therefore been the focus of a major collective effort, in which health professionals as well as scientific societies, the pharmaceutical industry and health administrations have all taken part. The pillars of IHD prevention have been prevention of smoking, promotion of healthy lifestyles, and detection, treatment and medical control of arterial hypertension, hypercholesterolaemia, diabetes mellitus and platelet aggregation in high risk patients.[4,5] These strategies have been generally implemented throughout the Spanish National Health System, as a result of recommendations made by the respective health authorities,[4] prevention guidelines drawn up by experts and scientific societies both domestic and international,[5-7] and the development of risk functions which not only enable patients to be stratified according to their individual coronary risk, estimated on the basis of vascular risk factors taken jointly,[8,9] but also serve as a guide when it comes to making therapeutic decisions about controlling vascular risk.

The promotion of healthy habits has specifically centred on diet and physical exercise.[10] Prevalence of obesity and overweight is regarded as an indicator of inadequate diet and physical activity.[4,11] With respect to smoking, the impact of anti-smoking interventions on coronary risk has been comprehensively described at both an individual and a population level. Hence, assessment of epidemiological anti-smoking legislation in a number of countries has shown its effectiveness in terms of IHD mortality and morbidity.[12,13] Lastly, the use of cardiovascular disease prevention drug therapy in healthy persons has demonstrated its effectiveness at an individual level in many clinical trials, though it is not known whether this effectiveness has been reflected at a population level, i.e., its epidemiological impact. Clinical trials are conducted under controlled experimental conditions and the patients included are selected on the basis of strict inclusion and exclusion criteria. Consequently, such studies do not represent the general population and their results may possibly not be seen at a population level (external validity).[14]

To our knowledge, there is no study that has assessed the joint impact of these cardiovascular disease prevention measures on IHD incidence. Epidemiological studies undertaken in different countries,[15-20] including Spain,[21] have linked the decrease in cardiovascular and ischaemic heart disease mortality to the decline in population levels of vascular risk factors. In Spain, 50% of the reduction in coronary mortality is estimated to be due to changes in risk factors, essentially total cholesterol (close on 31% of the fall in

mortality) and systolic blood pressure (15%).[21] Most of these studies have, however, been based on IMPACT methodology,[17,18] which was designed to assess changes in mortality but has not been adapted to the task of assessing morbidity. Recent studies in the USA,[22,23] Italy [24] and Australia [25] have reported a decrease in IHD-related hospital morbidity, which was linked to anti-smoking legislation and the use of cardioprotective medication, though these associations were not statistically proved. Lastly, a recent population-based observational study in Israel [26] assessed the effect of continued use of statins on the incidence of acute infarction and coronary revascularisation but did not consider the effect of use of antihypertensive, antiplatelet or antidiabetic drugs.

Accordingly, the aim of this study was to describe the time trend in hospital incident-IHD-related morbidity rates and assess the impact of smoking prevention, promotion of healthy lifestyles and the use of cardiovascular disease prevention drug therapy, using the following as indicators: population prevalence of smoking; prevalence of obesity and overweight; and use of statins and antihypertensive, antiplatelet and antidiabetic drugs.

METHODS

We conducted an epidemiological assessment study into the impact of preventive measures using regression analysis and time-series modelling and, for study purposes, including the total Spanish population over 29 years of age. The period considered in the description of the time series was 1982 to 2009, avoiding the years preceding the entry into force of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). In the analysis of related factors, the series was restricted to the period 1996–2006, since this was the period for which data on all the explanatory variables were available.

1- Principal and secondary variables. Data-sources.

The outcome variable was frequency of hospitalisation due to incident IHD (ICD-9-CM codes 410-414, with four digits), expressed in the form of annual age-adjusted rates according to the Standard European Population. Data on hospital discharges due to this cause were drawn from anonymised MBDS microfiches (Minimum Basic Data Set/*Conjunto Mínimo Básico de Datos*, the official nation-wide administrative and statistical database which includes clinical and demographic data on every hospital discharge, obtained from the pertinent medical records), and were completed with a patient discharge sample from some private hospitals that were not included in the MBDS. The fiches were supplied by the National Statistics Institute (NSI) (*Instituto Nacional de Estadística*) under a data loan agreement containing an undertaking of confidentiality and respect for statistical secrecy. Population data for calculating the rates for each year, sex and age group were obtained from NSI intercensal estimates.

An incident event was defined as that in which the following two conditions were fulfilled: a) diagnosis at discharge of acute IHD, acute myocardial infarction, intermediate coronary syndrome (unstable angina) or angina pectoris (ICD 410, 411 or 413); and, b) first admission due to IHD, as shown by a check for duplicate

entries based on the fields, "sex", "date of birth" and "province of residence". Events for which control for duplicates could not be performed for lack of any record of the patient's complete date of birth (n= 91,176, 3.1%), were excluded.

The method used to control for duplicates was validated by comparing the results against data on 30,205 hospitalisations in eight cities for which patient identification codes were available, yielding a sensitivity of 97.88% and specificity of 88.73. The distribution by age, sex and diagnostic category of this validation sample did not differ from that of the study population.

The variables considered as potentially explanatory of the trend in IHD hospitalisation rates in the population were:

- use of statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin);
- use of antihypertensive drugs (angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, betablockers, diuretics, calcium channel blockers and others);
- use of platelet aggregation inhibitors (aspirin, carbasalate, clopidogrel, dipyridamol, citazol, ticlopidine and triflusal);
- use of antidiabetic drugs (insulins, biguanides, sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones and combinations of these).
  The use of these drugs was expressed in Defined Daily Doses (DDDs) per 1,000 inhabitants per day (DHDs), for the period 1996-2006. These data were drawn from reports issued by the Spanish Medications & Health Products Agency on the basis of data on packages dispensed under and charged to the National Health System.[27] The methodology used is described in detail in these publications. DHDs divided by 10 were introduced into the models, with the estimators having to be interpreted as the effect for every increase of 10 units in the DHD.
- prevalence, with a breakdown by year, sex and age, of smoking, overweight, obesity, arterial hypertension, hypercholesterolaemia and diabetes mellitus obtained from self-report data in the 1987,1993, 1995, 1997, 2001, 2003 and 2006 National Health Surveys,[28] with data for the intermediate years being estimated by means of linear interpolation of data for the pivotal years.
- Number of physically available hospital beds in intensive care and coronary care units per 1,000 inhabitants.[28]

2- Data-analysis

Weightings specified by the NSI were used for the calculation of the number of cases. Age-adjusted incident IHD hospitalisation rates (Standard European Population) were calculated for each year and sex. The rates were depicted graphically, as were the frequency measures of the remaining explanatory variables for each year.

The effect of the explanatory variables on incident IHD morbidity was estimated on the basis of incidence rates ratios (IRRs) derived from mixed Poisson regression models of fixed and random effects, with year

being introduced as the random-effect variable. This approach enables one to control for both temporal autocorrelation and overdispersion, measure interannual variability explained by the preventive measures, and minimise the risk of residual confounding. The dependent variable was the number of incident hospitalisations in each sex and age stratum, and the national population figure of each stratum was introduced as the exposed population. The explanatory variables were sequentially introduced, successively obtaining age- and sex-adjusted estimators and multivariate estimators. We considered the concurrent effect across time of the explanatory variables and hospitalisation, plus the effect with lags of one, two and three years, so as to take into account the possible latency between exposure and its effect, and assess the temporality of the associations.

The effect of drug therapy for control of vascular risk was analysed for each type of drug (statins, and antihypertensive, antiplatelet and antidiabetic drugs), both individually and jointly, using the variable "drug use for control of vascular risk" obtained by adding together the respective usages of each type to avoid the strong collinearity that characterises the consumption of such drugs (correlation coefficients of 0.97 to 0.99). The explanatory variables categorised in quartiles were included in the models for dose-response analysis. These models were used to measure the interannual variability explained by the variables, calculated as 1 minus the ratio between the variance of the random term in the complete model and the variance of the random term in the model without explanatory variables.

Lastly, the incidence time series was analysed and plotted graphically with the aid of non-parametric generalised additive models (GAMs) implemented in the mgcv library of the R statistical package version 2.15.0 (2012-03-30).[29] The rates were modelled and smoothed by reference to time, and the smoothed age- and sex-adjusted series were depicted graphically. The explanatory variables were subsequently included in these models.

RESULTS

Across the 28 years and 671.5 million persons-year of observation, there were 2,986,834 hospitalisations in Spain due to IHD; and of these, 1,441,980 (66.7% men and 33.3% women), accounting for 48.28% of the total, were classified as incident. Mean age at admission was 65.9 ± 12.8 years, with a higher frequency in the 60- to 74-year age group (41.9%). Diagnosis at discharge was acute infarction in 55%, unstable angina in 14.7%, and stable angina in 30.3% of cases. Women's mean age was 5 years older ($p<0.001$), and the over-74-year age group was far more frequent among women than among men (data not shown in tables).

The annual age-adjusted incident IHD hospitalisation rates per 100,000, which are depicted graphically in Figure 1, show a rise from 1982 to 1996, a sharp inflection in 1997 and a subsequent cumulative decrease of 52.0% until 2009 (53.5% and 49.6% in men and women respectively). The decline was constant throughout the period, save for a slight increase in 2000, coinciding with the change in the definition of ischaemic heart disease. The distribution by sex of the incidence rates changed across the study period, with a decrease in

the male/female ratio from 3.3 to 2.4.

Of the total study period (1982-2009), data on indicators of cardiovascular disease prevention (prevalence of smoking, prevalence of obesity and overweight, and use of drug therapy for control of vascular risk) were available for the period 1996-2006. These years witnessed a rise in the use of statins (948.9%) and antihypertensive (95.4%), antiplatelet (105%) and antidiabetic drugs (142%), and a decline in smoking prevalence (6.8% in women and 23.8% in men). Prevalence of obesity increased by 40% (Figure 1).

Consumption of statins and antihypertensive, antiplatelet and antidiabetic drugs, individually considered, displayed an inverse and statistically significant relationship with incident IHD hospitalisation rates in models adjusted for age, sex and prevalences of smoking, obesity and overweight (Table 1), and this association became progressively greater when growing lags were taken into account. Similarly, the use of drugs considered jointly was inversely associated (IRR 0.97, 95% CI 0.97-0.98) with IHD incidence. The greater magnitude of the effect of drug use when considered individually rather than jointly should not be construed as a discrepancy: instead, this is attributable both to the difference in scale, and to drug associations and the lack of adjustment among the individual drug usages due to collinearity. In contrast, prevalence of smoking and that of obesity and overweight were both positively associated with incidence of hospitalisation due to IHD. In the models in which adjustment was additionally made for prevalences of arterial hypertension, hypercholesterolaemia and diabetes mellitus, and for the number of physically available beds in intensive and coronary care units, the above associations were not substantially modified, i.e., the effect of frequency of smoking was not modified, the effect of frequency of obesity and overweight was slightly attenuated, and the inverse association with drug use was slightly accentuated, both when the respective types of drugs were considered individually and when they were considered jointly.

Furthermore, these associations displayed a statistically significant dose-response relationship in the models adjusted for sex, age, the variables in the table, and year as a random-effect variable (Table 2): whereas the IRR of smoking prevalence in the fourth versus the first quartile was 1.46 (95%CI 1.42-1.50) and the IRRs for prevalence of obesity and overweight were 1.80 (1.78-1.83) and 1.58 (1.55-1.60) respectively, the IRR for cardiovascular disease prevention drug therapy was 0.57 (0.51-0.63). The linear trend was statistically significant for all four variables. The protective effect of cardiovascular disease prevention drug therapy was slightly attenuated when the growing lags between exposure and effect were taken into account (IRR lag 0= 0.57 (0.51-0.63) / IRR lag 3=0.61 (0.57-0.66)). Similarly, while the association with prevalence of overweight was attenuated over time, the association was not modified when the growing lags between exposure and effect for prevalences of obesity and smoking habit were taken into account.

The interannual variability in hospitalisation rates explained by the models considering the four variables simultaneously (continuous scale) and adjusting for age and sex was: 92% for no lag between exposure and effect; 95% for a lag of one year; 97% for a lag of two years; and 94% for a lag of three years (data not shown in tables).

Table 1. Effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates on annual incident ischaemic heart disease hospitalisation rates 1996-2006. Models for exposure-effect lags of 0, 1, 2 and 3 years.

	Lag0		Lag1		Lag2		Lag3	
	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
1. Adjustment for age, sex, year (random variable) and specified variables								
% Smokers	1.02	(1.01-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)
% Obesity	1.05	(1.04-1.05)	1.05	(1.05-1.05)	1.05	(1.05-1.05)	1.06	(1.05-1.06)
% Overweight	1.04	(1.04-1.04)	1.04	(1.04-1.04)	1.03	(1.03-1.04)	1.03	(1.03-1.03)
Drug use (x10 DHDs*)¶	0.97	(0.97-0.98)	0.97	(0.97-0.97)	0.97	(0.97-0.97)	0.97	(0.96-0.97)
Statins¶	0.92	(0.91-0.93)	0.91	(0.90-0.92)	0.90	(0.88-0.91)	0.87	(0.85-0.90)
Antihypertensive drugs¶	0.95	(0.94-0.95)	0.94	(0.94-0.95)	0.94	(0.94-0.94)	0.93	(0.93-0.94)
Antidiabetic drugs¶	0.81	(0.79-0.83)	0.81	(0.79-0.83)	0.80	(0.79-0.81)	0.78	(0.77-0.79)
Antiplatelet drugs¶	0.77	(0.76-0.79)	0.77	(0.75-0.79)	0.75	(0.74-0.77)	0.72	(0.70-0.74)
*2. Multivariate adjustment:***								
% Smokers	1.01	(1.01-1.01)	1.02	(1.01-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)
% Obesity	1.03	(1.03-1.03)	1.03	(1.03-1.04)	1.03	(1.03-1.04)	1.03	(1.03-1.04)
% Overweight	1.03	(1.03-1.03)	1.03	(1.03-1.03)	1.03	(1.02-1.03)	1.03	(1.03-1.03)
Drug use (10 DHDs*)¶	0.96	(0.96-0.97)	0.96	(0.96-0.97)	0.96	(0.96-0.96)	0.96	(0.96-0.96)
Statins¶	0.90	(0.89-0.91)	0.89	(0.88-0.90)	0.87	(0.86-0.89)	0.85	(0.83-0.87)
Antihypertensive drugs¶	0.92	(0.91-0.93)	0.92	(0.91-0.93)	0.92	(0.92-0.93)	0.92	(0.92-0.93)
Antidiabetic drugs¶	0.73	(0.68-0.77)	0.74	(0.71-0.77)	0.75	(0.73-0.77)	0.75	(0.74-0.75)
Antiplatelet drugs¶	0.70	(0.66-0.73)	0.70	(0.67-0.73)	0.70	(0.68-0.71)	0.68	(0.67-0.70)

* DHDs: No. of Defined Daily Doses per 1000 inhabitants per day.** Adjusted for variables specified in the table plus age, sex, year of discharge as a random-effect variable, prevalence (%) of arterial hypertension, prevalence (%) of hypercholesterolaemia, prevalence (%) of mellitus diabetes, and number of hospital beds in intensive care and coronary care units.¶ Not adjusted among themselves because collinearity.

Table 2. Dose-response analysis of the effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates. Models for exposure-effect lags of 0, 1, 2 and 3 years.

	Lag0		Lag1		Lag2		Lag3	
	IRR**	95%CI	IRR**	95%CI	IRR**	95%CI	IRR**	95%CI
% Smokers								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	0.92	(0.91-0.93)	0.91	(0.90-0.93)	0.92	(0.91-0.94)	0.93	(0.91-0.94)
3rd quartile	1.23	(1.21-1.25)	1.21	(1.19-1.23)	1.20	(1.18-1.22)	1.18	(1.15-1.20)
4th quartile	1.46	(1.42-1.50)	1.48	(1.44-1.52)	1.50	(1.46-1.55)	1.49	(1.45-1.54)
P trend	*<0.001*		*<.0001*		*< 0.001*		*< 0.001*	
% Obesity								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	1.46	(1.44-1.47)	1.45	(1.43-1.46)	1.34	(1.33-1.36)	1.32	(1.30-1.33)
3rd quartile	1.71	(1.69-1.73)	1.65	(1.63-1.67)	1.53	(1.51-1.55)	1.48	(1.46-1.50)
4th quartile	1.80	(1.78-1.83)	1.82	(1.79-1.85)	1.75	(1.73-1.79)	1.86	(1.78-1.90)
P trend	*<0.001*		*<0.001*		*<0.001*		*<0.001*	
% Overweight								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	1.23	(1.22-1.24)	1.21	(1.19-1.22)	1.14	(1.13-1.16)	1.06	(1.05-1.08)
3rd quartile	1.41	(1.39-1.43)	1.35	(1.33-1.37)	1.30	(1.28-1.31)	1.22	(1.20-1.24)
4th quartile	1.58	(1.55-1.60)	1.50	(1.47-1.52)	1.43	(1.41-1.45)	1.33	(1.31-1.36)
P trend	*<0.001*		*<0.001*		*<0.001*		*<0.001*	
Use of drugs (x10 DHDs*)								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	0.85	(0.76-0.93)	0.87	(0.80-0.94)	0.83	(0.78-0.88)	0.84	(0.78-0.90)
3rd quartile	0.71	(0.65-0.79)	0.73	(0.68-0.79)	0.71	(0.67-0.75)	0.70	(0.65-0.75)
4th quartile	0.57	(0.51-0.63)	0.59	(0.55-0.64)	0.62	(0.58-0.66)	0.61	(0.57-0.66)
P trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	

* DHDs: No. of Defined Daily Doses per 1000 inhabitants per day. ** IRR adjusted for variables specified in the table plus age, sex and year of discharge as a random-effect variable. Four independent models, each including the variable of interest on a categorical scale adjusted for the others on a continuous scale.

Lastly, the downward trend in the annual age-and sex-adjusted incidence rates (Figure 2, left plot) disappeared after additionally adjusting for the four explanatory variables (Figure 2, right plot), which shows that the decrease was due to the effect of these same variables. From 2004 onwards, however, the declining trend remained in evidence even after adjustment was made for use of preventive drug therapy and prevalence of smoking, obesity and overweight.

DISCUSSION

The results show that, after decades of continuous rises, hospitalisation due to incident IHD in the Spanish adult population fell after 1997, a drop that was associated with the decline in smoking and, in equal measure, with the increase in pharmacological treatment of vascular risk. This decrease in IHD hospitalisation rates could have been even greater, had it not been for the frequency of excessive weight, which not only failed to decline but actually rose. Overall, the factors analysed accounted for over 90% of the decrease in incident IHD hospitalisation rates. The decline occurred despite the increased sensitivity of diagnostic tests and the ensuing change in the IHD-definition criteria.[30]

The accuracy of the results is reinforced because the associations show a strong dose-response relationship and a correct temporality, with the effect being maintained in response to growing lags between exposure and disease. The associations found are biologically plausible, since both the role of smoking in the aetiology of coronary disease and the effect of drugs on vascular risk have been sufficiently proved by *in vitro* studies and clinical trials. Lastly, the results are in line with: what has been published with respect to the decreases in IHD mortality [15-21] and hospital morbidity recorded in other countries;[22-26] the decline in Spain in the incidence of smoking-related diseases such as asthma and lung cancer;[28] the reduction in mean population levels of serum cholesterol and systolic blood pressure;[21] and the increase in the rates of detection, treatment and control of vascular risk as documented by cross-sectional studies on the Spanish population.[31]

The study shows the success of the smoking control strategies implemented in the 1990s,[32] based on legislative measures targeted at restricting the sale, raising the price and placing limitations on the advertising of cigarettes, information programmes about smoking-related risks, and anti-smoking campaigns. These measures were followed by a considerable decline in the frequency of active smoking, principally among light and moderate smokers.[28] The most recent legislative measures, aimed at preventing passive smoking, have not achieved such a marked decrease in active smoking prevalence. Our results suggest, however, that part of the decline in IHD incidence in the lattermost years of the study is not accounted for by the factors analysed, indicating, in turn, that this may be due to the decline in passive smoking resulting, not only from the cumulative reduction in active smoking itself in the years preceding the entry into force of these

measures, but also from the direct impact of the first Anti-smoking Act. Different studies undertaken in Spain [33,34] and other countries [12,13] have shown the effect on IHD mortality and morbidity of a legal ban on smoking in the workplace.

The results support a primary prevention strategy based on pharmacological control of vascular risk. Evidence of the effectiveness of this strategy at a population level, which implies the mass use of medication, is especially important in an adverse economic context, and more so when the use of drugs for cardiovascular disease prevention in healthy persons has been the subject of controversy.[35] Specifically, in the case of the various statins, meta-analyses of clinical trials have yielded contradictory results,[36-40] with some authors being of the opinion that it is preferable to change the lifestyles of these patients. While this study does not purport to assess the clinical effect of these drugs, its results nonetheless show a statistically significant decrease in the age- and sex-adjusted hospitalisation rate associated with the use of both statins and hypertensive, antiplatelet and antidiabetic drugs. Although the presence of strong collinearity ruled out any analysis of the independent effect of each of these drugs with adjustment for remainder, their use considered jointly *did* show a strong protective effect, regardless of the effect of sex, age, smoking prevalence and excessive weight, a finding in line with the consideration that vascular risk is multifactorial and cannot be corrected by controlling the respective risk factors in isolation.[7] The appropriate balance between economic and health objectives by policies aimed at reducing pharmaceutical costs, such as those fostering the use of generic drugs or a gradual reduction in profit margins for producers and distributors,[41] have been decisive factors in this public health success. Even so, recent studies reveal that there is still much room for improvement in the detection, treatment and control of vascular risk.[31]

In contrast with smoking and control of vascular risk, prevalences of overweight and obesity, positively associated with incident IHD hospitalisation rates, increased across the study period, indicating that prevention based on promoting a healthy diet and physical exercise and changing obesogenic lifestyles is proving inadequate or ineffective, probably because the effects of these policies will only be seen in the longer term.[10] Without ignoring smoking prevention or therapeutic control of vascular risk, our results indicate that, from a public health stance, treatment and prevention of excess weight should be made a priority. Community interventions aimed at changing the prevalence of obesity and sedentarism are multidisciplinary, going beyond the strict scope of health care and involving multiple levels, such as education, the food sector, town planning and administration, provision of sports facilities, transport policy, etc.[11] Moreover, with the change of lifestyles many treatments could be avoided -and in this respect our sympathies are with those who advocate this- but, until such a time as a cost-effective means of changing the prevalence of obesity and sedentarism becomes available, the use of vascular prevention drug therapy is an inevitable strategy.

In the correct interpretation of the results of this study, some limitations must be borne in mind. Firstly, this study was based on health indicators and targeted at the assessment of public health; its results should not be extrapolated to the clinical sphere, i.e., to the clinical management of individual patients, and are thus not

interpretable as outcomes of clinical or intervention trials, even though they may nuance the latter insofar as they provide an illustration of their external validity. Secondly, the results are exclusively applicable to cases of hospitalised incident IHD; having said this, however, the possibility that the decline in hospitalisations might be due to increases in pre-admission mortality can be conclusively ruled out because mortality rates due to sudden death or poorly defined causes not only decreased across the study period but they actually decreased to a greater extent.[2] Errors of measurement that are inherent in the ecological design and limit causal inference are of little relevance in this study, in view of the fact that, in all the factors considered, causality was clearly shown. Identification of incident cases was based on an estimate but the method used was validated, with high sensitivity and specificity values being obtained. What is more, the proportion of cases of acute infarction with previous clinical history in our series (26.6%) agrees with the results of the PRIAMHO II Registry,[42] in which 24% of cases were shown to have a history of previous infarction or revascularisation.

The remaining potential study limitations stem from the nature of the available data and, were they to have some impact, would in all cases bias the results towards the null hypothesis and so tend to underestimate the effect. With respect to the exposure data studied, these were drawn from a self-report questionnaire without any objective measures of smoking, weight and height; and, while self-reported smoking data are regarded as valid, those on obesity and overweight may be underestimated. The data relating to drug use refer to total use: these drugs are prescribed, not only for primary prevention, but also for secondary prevention and treatment of other conditions, such as arrhythmias and heart failure. Nevertheless the frequency of these diseases is infinitely lower than the prevalence of vascular risk in the general adult population, and is indeed almost negligible in comparison. At all events, the error would, yet again, tend more towards overestimating exposure and, by extension, underestimating the effect. Lastly, specific dietary factors (i.e., fish, vegetables or alcoholic beverages), nutritional factors (i.e. fats) and physical activity factors were not analysed for reasons of parsimony; instead, the frequency of obesity and overweight was used as an indicator of quality of diet and physical activity as a whole.

In conclusion, after decades of continuous rises, incidence of IHD hospitalisation fell from 1997 onwards, a decline that was associated with the decrease in smoking and, in equal measure, with the increase in vascular risk drug therapy. The cumulative decline of 52% over 13 years might have been even greater if there had not been a concomitant increase in the prevalence of excessive weight, also associated with incidence. These results indicate that current IHD primary prevention strategies have been effective at a population level, thanks to an appropriate balance between financial and health goals, something that should be left intact despite the current economic crisis. Future strategies should lay special stress on the prevention and treatment of excessive weight.

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Competing Interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Annual trends in explanatory variables and incident ischaemic heart disease hospitalisation rates.

Figure 2. Time series of incidence analysed using non-parametric generalised additive models. Left plot: smoothed series adjusted for age and sex. Right plot: smoothed series adjusted for age, sex, prevalence of smoking, obesity and overweight, and use of cardiovascular disease prevention drug therapy.

Author Contributions

MJM conceived of the study, its design and coordinated the research team. MJM, EA-C, CO, and IG performed the statistical analysis and interpretation of data and prepared the draft manuscript. All authors participated in the design of the study and in critical review of the manuscript. All authors read and approved the final manuscript.

Data sharing

Technical appendix and supplementary material available on request from the corresponding author for scientific non-commercial use. Individual patient datasets are protected by Spanish regulations; these may be obtained from the Spanish Ministry of Health and the National Institute of Statistics under specific data loan agreements.

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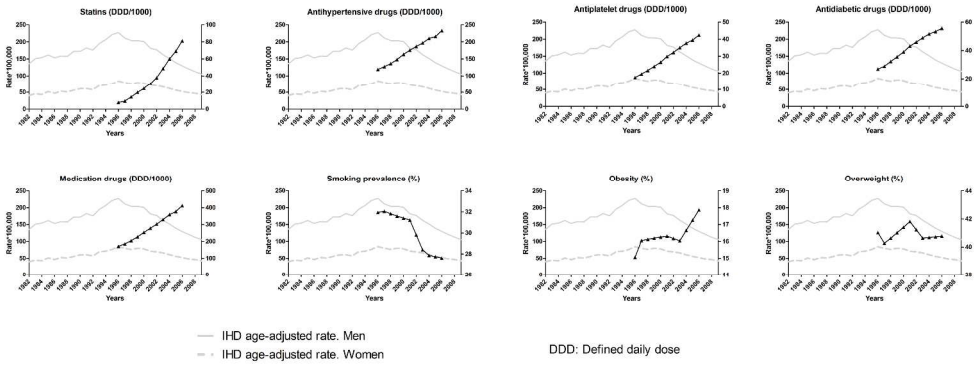

Figure 1. Annual trends in explanatory variables and incident ischaemic heart disease hospitalisation rates.
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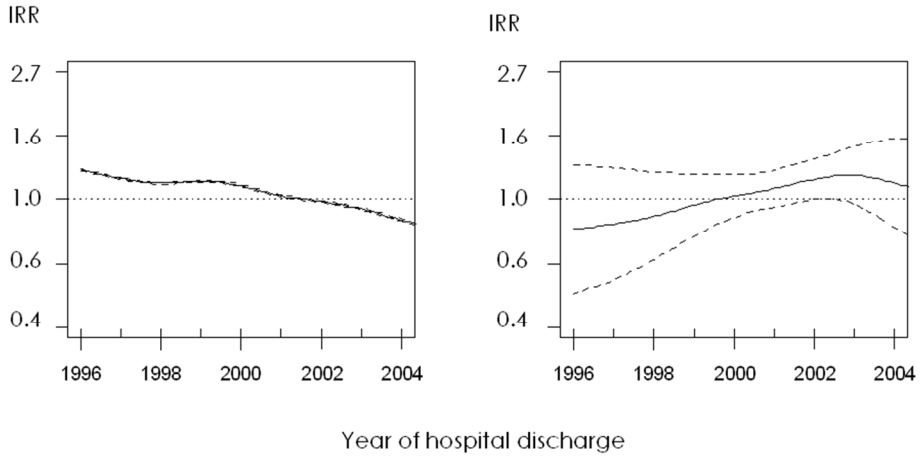

Figure 2. Time series of incidence analysed using non-parametric generalised additive models. Left plot: smoothed series adjusted for age and sex. Right plot: smoothed series adjusted for age, sex, prevalence of smoking, obesity and overweight, and use of cardiovascular disease prevention drug therapy.
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EFFECT OF CARDIOVASCULAR PREVENTION STRATEGIES ON INCIDENT CORONARY DISEASE HOSPITALISATION RATES IN SPAIN. AN ECOLOGICAL TIME SERIES ANALYSIS

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EFFECT OF CARDIOVASCULAR PREVENTION STRATEGIES ON INCIDENT CORONARY DISEASE HOSPITALISATION RATES IN SPAIN. AN ECOLOGICAL TIME SERIES ANALYSIS

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ABSTRACT

Objective: To assess the overall population impact of primary prevention strategies (promotion of healthy lifestyles, prevention of smoking and use of vascular risk drug therapy) of coronary disease in Spain.

Design: Ecological time series analysis, 1982 to 2009.

Setting: All public and private hospitals in Spain.

Participants: General population.

Outcome: Incident coronary disease hospitalization as derived from official hospital discharge data.

Methods: Annual hospitalisation rates were modelled according to nationwide use of statins, antihypertensive, antidiabetic and antiplatelet drugs, and prevalences of smoking, obesity and overweight. Additive generalised models and mixed Poisson regression models were used for the purpose, taking year as the random-effect variable and adjusting for age, sex, prevalence of vascular risk factors, and hospital beds in intensive and coronary care units.

Results: Across 28 years and 671.5 million persons-year of observation, there were 2,986,834 hospitalisations due to coronary disease; of these, 1,441,980 (48.28%) were classified as incident. Hospitalisation rates increased from 1982 to 1996, with an inflection point in 1997 and a subsequent 52% decrease until 2009. Prevalences of smoking, obesity, overweight and use of vascular risk drug therapy were significantly associated with hospitalisation rates ($p<0.001$): incidence rates ratios (95% CI) for the fourth versus the first quartile were 1.46 (1.42-1.50), 1.80 (1.78-1.83), 1.58 (1.55-1.60) and 0.57 (0.51-0.63) respectively. These variables accounted for 92% of interannual variability.

Conclusion: After decades of continuous rises, hospitalisation due to incident IHD has been cut by half, an achievement associated with the decline in smoking and the increase in vascular risk drug therapy. These results indicate that these two primary prevention strategies have been effective at a population level, thanks to an appropriate balance between financial and health goals, something that should be left intact despite the current economic crisis. Future strategies ought to lay special stress on excessive body weight prevention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study shows that the decline in coronary disease in Spain was associated with the exponential increase in pharmacological treatment of vascular risk, together with the decline in active smoking that followed the strong interventions against tobacco use implemented in mid and late '90s. This decrease in IHD hospitalisation rates could have been even greater, had it not been for the frequency of excessive weight, which not only failed to decline but actually rose.

- The exposure-effect associations found: 1- are of great magnitude; 2- show a strong dose-response relationship; 3-show a correct temporality; 4- are biologically plausible; and 5- are consistent with similar studies in other countries, with trends in other tobacco-related diseases and with the increase in the rates of detection, treatment and control of vascular risk factors in Spain.

- The results are relevant as some of these measures (i.e. broad use of statins in general population) are still controversial. Moreover, the results may substantially affect public health policy, especially in a context of financial crisis.

- This is an ecological study based on health indicators and targeted at the assessment of public health; its results should not be interpreted as outcomes of intervention trials, even though they may nuance the latter insofar as they provide an illustration of their external validity.

INTRODUCTION

Ischaemic heart disease (IHD) is a severe disease, is lethal in its acute form in 20%-30% of cases [1] – indeed, it is the leading cause of death in men and the second leading cause of death in women in Spain [2]- and is chronically incapacitating in a great proportion of survivors. Its frequency in the Spanish population is high, with population incidence being estimated at 207 and 45/100,000 in men and women respectively, and hospitalisations at 140,000 cases annually.[3] Consequently, this situation became a public health priority and the target of specific health-planning strategies at a national level.[4]

The main vascular risk factors (excessive body weight, smoking habit, hypercholesterolaemia, arterial hypertension and diabetes mellitus) can be modified by changes in lifestyle or therapeutic interventions. In recent years, cardiovascular disease prevention has therefore been the focus of a major collective effort, in which health professionals as well as scientific societies, the pharmaceutical industry and health administrations have all taken part. The pillars of IHD prevention have been prevention of smoking, promotion of healthy lifestyles, and detection, treatment and medical control of arterial hypertension, hypercholesterolaemia, diabetes mellitus and platelet aggregation in high risk patients.[4,5] These strategies have been generally implemented throughout the Spanish National Health System, as a result of recommendations made by the respective health authorities,[4] prevention guidelines drawn up by experts and scientific societies both domestic and international,[5-7] and the development of risk functions which not only enable patients to be stratified according to their individual coronary risk, estimated on the basis of vascular risk factors taken jointly,[8,9] but also serve as a guide when it comes to making therapeutic decisions about controlling vascular risk.

The promotion of healthy habits has specifically centred on diet and physical exercise.[10] Prevalence of obesity and overweight is regarded as an indicator of inadequate diet and physical activity.[4,11] With respect to smoking, the impact of anti-smoking interventions on coronary risk has been comprehensively described at both an individual and a population level. Hence, assessment of epidemiological anti-smoking legislation in a number of countries has shown its effectiveness in terms of IHD mortality and morbidity.[12,13] Lastly, the use of cardiovascular disease prevention drug therapy in healthy persons has demonstrated its effectiveness at an individual level in many clinical trials, though it is not known whether this effectiveness has been reflected at a population level, i.e., its epidemiological impact. Clinical trials are conducted under controlled experimental conditions and the patients included are selected on the basis of strict inclusion and exclusion criteria. Consequently, such studies do not represent the general population and their results may possibly not be seen at a population level (external validity).[14]

To our knowledge, there is no study that has assessed the joint impact of these cardiovascular disease prevention measures on IHD incidence. Epidemiological studies undertaken in different countries,[15-20] including Spain,[21] have linked the decrease in cardiovascular and ischaemic heart disease mortality to the decline in population levels of vascular risk factors. In Spain, 50% of the reduction in coronary mortality is estimated to be due to changes in risk factors, essentially total cholesterol (close on 31% of the fall in

mortality) and systolic blood pressure (15%).[21] Most of these studies have, however, been based on IMPACT methodology,[17,18] which was designed to assess changes in mortality but has not been adapted to the task of assessing morbidity. Recent studies in the USA,[22,23] Italy [24] and Australia [25] have reported a decrease in IHD-related hospital morbidity, which was linked to anti-smoking legislation and the use of cardioprotective medication, though these associations were not statistically proved. Lastly, a recent population-based observational study in Israel [26] assessed the effect of continued use of statins on the incidence of acute infarction and coronary revascularisation but did not consider the effect of use of antihypertensive, antiplatelet or antidiabetic drugs.

Accordingly, the aim of this study was to describe the time trend in hospital incident-IHD-related morbidity rates and assess the impact of smoking prevention, promotion of healthy lifestyles and the use of cardiovascular disease prevention drug therapy, using the following as indicators: population prevalence of smoking; prevalence of obesity and overweight; and use of statins and antihypertensive, antiplatelet and antidiabetic drugs.

METHODS

We conducted an epidemiological assessment study into the impact of preventive measures using regression analysis and time-series modelling and, for study purposes, including the total Spanish population over 29 years of age. The period considered in the description of the time series was 1982 to 2009, avoiding the years preceding the entry into force of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). In the analysis of related factors, the series was restricted to the period 1996–2006, since this was the period for which data on all the explanatory variables were available.

1- Principal and secondary variables. Data-sources.

The outcome variable was frequency of hospitalisation due to incident IHD (ICD-9-CM codes 410-414, with four digits), expressed in descriptive analyses in the form of annual age-adjusted rates according to the Standard European Population. Data on hospital discharges due to this cause were drawn from anonymised MBDS microfiches (Minimum Basic Data Set/*Conjunto Mínimo Básico de Datos*, the official nation-wide administrative and statistical database which includes clinical and demographic data on every hospital discharge, obtained from the pertinent medical records), and were completed with a patient discharge sample from some private hospitals that were not included in the MBDS. The fiches were supplied by the National Statistics Institute (NSI) (*Instituto Nacional de Estadística*) under a data loan agreement containing an undertaking of confidentiality and respect for statistical secrecy. Population data for calculating the rates for each year, sex and age group were obtained from NSI intercensal estimates. The age strata were 5-year age groups starting from 30 to 85 and older.

An incident event was defined as that in which the following two conditions were fulfilled: a) diagnosis at discharge of acute IHD, acute myocardial infarction, intermediate coronary syndrome (unstable angina) or

angina pectoris (ICD 410, 411 or 413); and, b) first admission due to IHD, as shown by a check for duplicate entries based on the fields, "sex", "date of birth" and "province of residence". Events for which control for duplicates could not be performed for lack of any record of the patient's complete date of birth (n= 91,176, 3.1%), were excluded.

The method used to control for duplicates was validated by comparing the results against data on 30,205 hospitalisations in eight cities for which patient identification codes were available, yielding a sensitivity of 97.88% and specificity of 88.73. The distribution by age, sex and diagnostic category of this validation sample did not differ from that of the study population.

The variables considered as potentially explanatory of the trend in IHD hospitalisation rates in the population were:

- use of statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin);
- use of antihypertensive drugs (angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, betablockers, diuretics, calcium channel blockers and others);
- use of platelet aggregation inhibitors (aspirin, carbasalate, clopidogrel, dipyridamol, citazol, ticlopidine and triflusal);
- use of antidiabetic drugs (insulins, biguanides, sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones and combinations of these).

  The use of these drugs was expressed in Defined Daily Doses (DDDs) per 1,000 inhabitants per day (DHDs), for the period 1996-2006. These data were drawn from reports issued by the Spanish Medications & Health Products Agency on the basis of data on packages dispensed under and charged to the National Health System.[27] The methodology used is described in detail in these publications. DHDs divided by 10 were introduced into the models, with the estimators having to be interpreted as the effect for every increase of 10 units in the DHD.
- prevalence, with a breakdown by year, sex and age, of smoking, overweight, obesity, arterial hypertension, hypercholesterolaemia and diabetes mellitus obtained from self-report data in the 1987,1993, 1995, 1997, 2001, 2003 and 2006 National Health Surveys,[28] with data for the intermediate years being estimated by means of linear interpolation of data for the pivotal years.
- Number of physically available hospital beds in intensive care and coronary care units per 1,000 inhabitants.[28]

2- Data-analysis

Weightings specified by the NSI were used for the calculation of the number of cases. In descriptive analyses, age-adjusted incident IHD hospitalisation rates (Standard European Population) were calculated for each year and sex. These rates were depicted graphically, as were the frequency measures of the remaining explanatory variables for each year.

The effect of the explanatory variables on incident IHD morbidity was estimated on the basis of incidence

rates ratios (IRRs) derived from mixed Poisson regression models of fixed and random effects, with year being introduced as the random-effect variable, usingy the command 'xtmepoisson' implemented in Stata, that fits mixed-effects models for count responses assuming a Poisson distribution of the data.This approach enables one to control for both temporal autocorrelation and overdispersion, measure interannual variability explained by the preventive measures, and minimise the risk of residual confounding. The dependent variable was the number of incident hospitalisations in each sex and age stratum, and the national population figure of each stratum was introduced as the exposed population. This is equivalent to modelling of rates. The explanatory variables were sequentially introduced, successively obtaining age- and sex-adjusted estimators and multivariate estimators. We considered the concurrent effect across time of the explanatory variables and hospitalisation, plus the effect with lags of one, two and three years, so as to take into account the possible latency between exposure and its effect, and assess the temporality of the associations.

The effect of drug therapy for control of vascular risk was analysed for each type of drug (statins, and antihypertensive, antiplatelet and antidiabetic drugs), both individually and jointly, using the variable "drug use for control of vascular risk" obtained by adding together the respective usages of each type to avoid the strong collinearity that characterises the consumption of such drugs (correlation coefficients of 0.97 to 0.99). The explanatory variables categorised in quartiles were included in the models for dose-response analysis. These models were used to measure the interannual variability explained by the variables, calculated as 1 minus the ratio between the variance of the random term in the complete model, and the variance of the random term in the model without prevention explanatory variables and in the model adjusted for age and sex.

Lastly, the incidence time series was analysed and plotted graphically with the aid of Poisson non-parametric generalised additive models (GAMs) implemented in the mgcv library of the R statistical package version 2.15.0 (2012-03-30).[29] GAM models allow to graphically depict the relationship including both smoothing and also a non-parametric fit, with no a priori assumptions on the actual relationship between response and predictor. As time is used as the predictor, the result is a smoothed time series of the response. The rates were modelled and smoothed by reference to time, and the smoothed age- and sex-adjusted series were depicted graphically. The explanatory variables were subsequently included in these models to depict the trends not due to these variables.

(See technical appendix in supplementary material for theoretical basis of models and technical details)

RESULTS

Across the 28 years and 671.5 million persons-year of observation, there were 2,986,834 hospitalisations in Spain due to IHD; and of these, 1,441,980 (66.7% men and 33.3% women), accounting for 48.28% of the total, were classified as incident. Mean age at admission was 65.9 ± 12.8 years, with a higher frequency in the 60- to 74-year age group (41.9%). Diagnosis at discharge was acute infarction in 55%, unstable angina

in 14.7%, and stable angina in 30.3% of cases. Women's mean age was 5 years older (p<0.001), and the over-74-year age group was far more frequent among women than among men (data not shown in tables).

The annual age-adjusted incident IHD hospitalisation rates per 100,000, which are depicted graphically in Figure 1, show a rise from 1982 to 1996, a sharp inflection in 1997 and a subsequent cumulative decrease of 52.0% until 2009 (53.5% and 49.6% in men and women respectively). The decline was constant throughout the period, save for a slight increase in 2000, coinciding with the change in the definition of ischaemic heart disease. The distribution by sex of the incidence rates changed across the study period, with a decrease in the male/female ratio from 3.3 to 2.4.

Of the total study period (1982-2009), data on indicators of cardiovascular disease prevention (prevalence of smoking, prevalence of obesity and overweight, and use of drug therapy for control of vascular risk) were available for the period 1996-2006. These years witnessed a rise in the use of statins (948.9%) and antihypertensive (95.4%), antiplatelet (105%) and antidiabetic drugs (142%), and a decline in smoking prevalence (6.8% in women and 23.8% in men). Prevalence of obesity increased by 40% (Table 1, Figure 1).

Table 1. Annual trends in explanatory variables in Spanish general population.

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Proportion (%) Smokers	31,9	32,0	31,8	31,6	31,4	31,2	29,8	28,4	27,9	27,8	27,6
Proportion (%) Obesity	15,1	16,1	16,1	16,2	16,3	16,3	16,2	16,0	16,7	17,3	17,9
Proportion (%) Overweight	41,0	40,3	40,6	41,0	41,4	41,8	41,2	40,6	40,7	40,7	40,8
Drugs for control of vascular risk. No. of Defined Daily Doses* per 1000 inhabitants per day (x10).											
Total	171,5	185,6	204,9	227,7	253,8	279,2	303,0	329,7	359,6	377,7	412,3
Statins	7,8	9,4	14,3	19,7	24,4	30,4	38,0	48,7	60,1	69,2	81,3
Antihypertensive drugs	119,2	127,6	136,6	148,4	163,8	175,7	186,9	197,1	210,2	215,7	232,9
Antidiabetic drugs	27,0	28,9	32,3	35,6	39,1	43,2	46,0	48,9	51,7	53,3	55,7
Antiplatelet drugs	17,5	19,6	21,7	24,0	26,6	29,9	32,2	35,0	37,6	39,5	42,4

DDD: number of doses (adult average maintenance dose per day) prescribed and sold in the National Health System

Consumption of statins and antihypertensive, antiplatelet and antidiabetic drugs, individually considered, displayed an inverse and statistically significant relationship with incident IHD hospitalisation rates in models adjusted for age, sex and prevalences of smoking, obesity and overweight (Table 2), and this association became progressively greater when growing lags were taken into account. Similarly, the use of drugs

considered jointly was inversely associated (IRR 0.97, 95% CI 0.97-0.98) with IHD incidence. The greater magnitude of the effect of drug use when considered individually rather than jointly should not be construed as a discrepancy: instead, this is attributable both to the difference in scale, and to drug associations and the lack of adjustment among the individual drug usages due to collinearity. In contrast, prevalence of smoking and that of obesity and overweight were both positively associated with incidence of hospitalisation due to IHD. In the models in which adjustment was additionally made for prevalences of arterial hypertension, hypercholesterolaemia and diabetes mellitus, and for the number of physically available beds in intensive and coronary care units, the above associations were not substantially modified, i.e., the effect of frequency of smoking was not modified, the effect of frequency of obesity and overweight was slightly attenuated, and the inverse association with drug use was slightly accentuated, both when the respective types of drugs were considered individually and when they were considered jointly.

Furthermore, these associations displayed a statistically significant dose-response relationship in the models adjusted for sex, age, the variables in the table, and year as a random-effect variable (Table 3): whereas the IRR of smoking prevalence in the fourth versus the first quartile was 1.46 (95%CI 1.42-1.50) and the IRRs for prevalence of obesity and overweight were 1.80 (1.78-1.83) and 1.58 (1.55-1.60) respectively, the IRR for cardiovascular disease prevention drug therapy was 0.57 (0.51-0.63). The linear trend was statistically significant for all four variables. The protective effect of cardiovascular disease prevention drug therapy was slightly attenuated when the growing lags between exposure and effect were taken into account (IRR lag 0= 0.57 (0.51-0.63) / IRR lag 3=0.61 (0.57-0.66)). Similarly, while the association with prevalence of overweight was attenuated over time, the association was not modified when the growing lags between exposure and effect for prevalences of obesity and smoking habit were taken into account.

The interannual variability in hospitalisation rates explained by the models considering the four variables simultaneously (continuous scale) was: 92% for no lag between exposure and effect; 95% for a lag of one year; 97% for a lag of two years; and 94% for a lag of three years (data not shown in tables). The proportion of variability in annual rates explained by prevention variables raised from 92% with respect to the empty model, to 97% when calculated with respect to the model adjusted by age and sex, thus meaning a 5% variability in hospitalisation rates due to changes in age-sex population structure from 1996 to 2006.

Table 2. Effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates on annual incident ischaemic heart disease hospitalisation rates 1996-2006. Models for exposure-effect lags of 0, 1, 2 and 3 years.

	Lag0		Lag1		Lag2		Lag3	
	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
1. Adjustment for age, sex, year (random variable) and specified variables								
% Smokers	1.02	(1.01-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)
% Obesity	1.05	(1.04-1.05)	1.05	(1.05-1.05)	1.05	(1.05-1.05)	1.06	(1.05-1.06)
% Overweight	1.04	(1.04-1.04)	1.04	(1.04-1.04)	1.03	(1.03-1.04)	1.03	(1.03-1.03)
Drug use (x10 DHDs*)¶	0.97	(0.97-0.98)	0.97	(0.97-0.97)	0.97	(0.97-0.97)	0.97	(0.96-0.97)
Statins¶	0.92	(0.91-0.93)	0.91	(0.90-0.92)	0.90	(0.88-0.91)	0.87	(0.85-0.90)
Antihypertensive drugs¶	0.95	(0.94-0.95)	0.94	(0.94-0.95)	0.94	(0.94-0.94)	0.93	(0.93-0.94)
Antidiabetic drugs¶	0.81	(0.79-0.83)	0.81	(0.79-0.83)	0.80	(0.79-0.81)	0.78	(0.77-0.79)
Antiplatelet drugs¶	0.77	(0.76-0.79)	0.77	(0.75-0.79)	0.75	(0.74-0.77)	0.72	(0.70-0.74)
*2. Multivariate adjustment:***								
% Smokers	1.01	(1.01-1.01)	1.02	(1.01-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)
% Obesity	1.03	(1.03-1.03)	1.03	(1.03-1.04)	1.03	(1.03-1.04)	1.03	(1.03-1.04)
% Overweight	1.03	(1.03-1.03)	1.03	(1.03-1.03)	1.03	(1.02-1.03)	1.03	(1.03-1.03)
Drug use (10 DHDs*)¶	0.96	(0.96-0.97)	0.96	(0.96-0.97)	0.96	(0.96-0.96)	0.96	(0.96-0.96)
Statins¶	0.90	(0.89-0.91)	0.89	(0.88-0.90)	0.87	(0.86-0.89)	0.85	(0.83-0.87)
Antihypertensive drugs¶	0.92	(0.91-0.93)	0.92	(0.91-0.93)	0.92	(0.92-0.93)	0.92	(0.92-0.93)
Antidiabetic drugs¶	0.73	(0.68-0.77)	0.74	(0.71-0.77)	0.75	(0.73-0.77)	0.75	(0.74-0.75)
Antiplatelet drugs¶	0.70	(0.66-0.73)	0.70	(0.67-0.73)	0.70	(0.68-0.71)	0.68	(0.67-0.70)

* DHDs: No. of Defined Daily Doses per 1000 inhabitants per day.** Adjusted for variables specified in the table plus age, sex, year of discharge as a random-effect variable, prevalence (%) of arterial hypertension, prevalence (%) of hypercholesterolaemia, prevalence (%) of mellitus diabetes, and number of hospital beds in intensive care and coronary care units.¶ Not adjusted among themselves because collinearity.

Table 3. Dose-response analysis of the effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates. Models for exposure-effect lags of 0, 1, 2 and 3 years.

	Lag0		Lag1		Lag2		Lag3	
	IRR**	95%CI	IRR**	95%CI	IRR**	95%CI	IRR**	95%CI
% Smokers								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	0.92	(0.91-0.93)	0.91	(0.90-0.93)	0.92	(0.91-0.94)	0.93	(0.91-0.94)
3rd quartile	1.23	(1.21-1.25)	1.21	(1.19-1.23)	1.20	(1.18-1.22)	1.18	(1.15-1.20)
4th quartile	1.46	(1.42-1.50)	1.48	(1.44-1.52)	1.50	(1.46-1.55)	1.49	(1.45-1.54)
P trend	*<0.001*		*<.0001*		*< 0.001*		*< 0.001*	
% Obesity								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	1.46	(1.44-1.47)	1.45	(1.43-1.46)	1.34	(1.33-1.36)	1.32	(1.30-1.33)
3rd quartile	1.71	(1.69-1.73)	1.65	(1.63-1.67)	1.53	(1.51-1.55)	1.48	(1.46-1.50)
4th quartile	1.80	(1.78-1.83)	1.82	(1.79-1.85)	1.75	(1.73-1.79)	1.86	(1.78-1.90)
P trend	*<0.001*		*<0.001*		*<0.001*		*<0.001*	
% Overweight								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	1.23	(1.22-1.24)	1.21	(1.19-1.22)	1.14	(1.13-1.16)	1.06	(1.05-1.08)
3rd quartile	1.41	(1.39-1.43)	1.35	(1.33-1.37)	1.30	(1.28-1.31)	1.22	(1.20-1.24)
4th quartile	1.58	(1.55-1.60)	1.50	(1.47-1.52)	1.43	(1.41-1.45)	1.33	(1.31-1.36)
P trend	*<0.001*		*<0.001*		*<0.001*		*<0.001*	
Use of drugs (x10 DHDs*)								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	0.85	(0.76-0.93)	0.87	(0.80-0.94)	0.83	(0.78-0.88)	0.84	(0.78-0.90)
3rd quartile	0.71	(0.65-0.79)	0.73	(0.68-0.79)	0.71	(0.67-0.75)	0.70	(0.65-0.75)
4th quartile	0.57	(0.51-0.63)	0.59	(0.55-0.64)	0.62	(0.58-0.66)	0.61	(0.57-0.66)
P trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	

* DHDs: No. of Defined Daily Doses per 1000 inhabitants per day. ** IRR adjusted for variables specified in the table plus age, sex and year of discharge as a random-effect variable. Four independent models, each including the variable of interest on a categorical scale adjusted for the others on a continuous scale.

Lastly, figure 2 describes the time series of incidence analysed using Poisson non-parametric generalised additive models. Left plot displays the downward trend in the annual age-and sex-adjusted incidence rates, which shows very narrow confidence interval because the very large size of the study population. This downward trend disappeared after additionally adjusting for the four explanatory variables (Figure 2, right plot), which shows that the decrease was due to the effect of these same variables. From 2004 onwards, however, the declining trend remained in evidence even after adjustment was made for use of preventive drug therapy and prevalence of smoking, obesity and overweight.

DISCUSSION

The results show that, after decades of continuous rises, hospitalisation due to incident IHD in the Spanish adult population fell after 1997, a drop that was associated with the decline in smoking and, in equal measure, with the increase in pharmacological treatment of vascular risk. This decrease in IHD hospitalisation rates could have been even greater, had it not been for the frequency of excessive weight, which not only failed to decline but actually rose. Overall, the factors analysed accounted for over 90% of the decrease in incident IHD hospitalisation rates. The decline occurred despite the increased sensitivity of diagnostic tests and the ensuing change in the IHD-definition criteria.[30]

The accuracy of the results is reinforced because the associations show a strong dose-response relationship and a correct temporality, with the effect being maintained in response to growing lags between exposure and disease. The associations found are biologically plausible, since both the role of smoking in the aetiology of coronary disease and the effect of drugs on vascular risk have been sufficiently proved by *in vitro* studies and clinical trials. Lastly, the results are in line with: what has been published with respect to the decreases in IHD mortality [15-21] and hospital morbidity recorded in other countries;[22-26] the decline in Spain in the incidence of smoking-related diseases such as asthma and lung cancer;[28] the reduction in mean population levels of serum cholesterol and systolic blood pressure;[21] and the increase in the rates of detection, treatment and control of vascular risk as documented by cross-sectional studies on the Spanish population.[31]

The study shows the success of the smoking control strategies implemented in the 1990s,[32] based on legislative measures targeted at restricting the sale, raising the price and placing limitations on the advertising of cigarettes, information programmes about smoking-related risks, and anti-smoking campaigns. These measures were followed by a considerable decline in the frequency of active smoking, principally among light and moderate smokers.[28] The most recent legislative measures, aimed at preventing passive smoking, have not achieved such a marked decrease in active smoking prevalence. Our results suggest,

however, that part of the decline in IHD incidence in the lattermost years of the study is not accounted for by the factors analysed, indicating, in turn, that this may be due to the decline in passive smoking resulting, not only from the cumulative reduction in active smoking itself in the years preceding the entry into force of these measures, but also from the direct impact of the first Anti-smoking Act. Different studies undertaken in Spain [33,34] and other countries [12,13] have shown the effect on IHD mortality and morbidity of a legal ban on smoking in the workplace.

The results support a primary prevention strategy based on pharmacological control of vascular risk. Evidence of the effectiveness of this strategy at a population level, which implies the mass use of medication, is especially important in an adverse economic context, and more so when the use of drugs for cardiovascular disease prevention in healthy persons has been the subject of controversy.[35] Specifically, in the case of the various statins, meta-analyses of clinical trials have yielded contradictory results,[36-40] with some authors being of the opinion that it is preferable to change the lifestyles of these patients. While this study does not purport to assess the clinical effect of these drugs, its results nonetheless show a statistically significant decrease in the age- and sex-adjusted hospitalisation rate associated with the use of both statins and hypertensive, antiplatelet and antidiabetic drugs. Although the presence of strong collinearity ruled out any analysis of the independent effect of each of these drugs with adjustment for remainder, their use considered jointly *did* show a strong protective effect, regardless of the effect of sex, age, smoking prevalence and excessive weight, a finding in line with the consideration that vascular risk is multifactorial and cannot be corrected by controlling the respective risk factors in isolation.[7] The appropriate balance between economic and health objectives by policies aimed at reducing pharmaceutical costs, such as those fostering the use of generic drugs or a gradual reduction in profit margins for producers and distributors,[41] have been decisive factors in this public health success. Even so, recent studies reveal that there is still much room for improvement in the detection, treatment and control of vascular risk.[31]

In contrast with smoking and control of vascular risk, prevalences of overweight and obesity, positively associated with incident IHD hospitalisation rates, increased across the study period, indicating that prevention based on promoting a healthy diet and physical exercise and changing obesogenic lifestyles is proving inadequate or ineffective, probably because the effects of these policies will only be seen in the longer term.[10] Without ignoring smoking prevention or therapeutic control of vascular risk, our results indicate that, from a public health stance, treatment and prevention of excess weight should be made a priority. Community interventions aimed at changing the prevalence of obesity and sedentarism are multidisciplinary, going beyond the strict scope of health care and involving multiple levels, such as education, the food sector, town planning and administration, provision of sports facilities, transport policy, etc.[11] Moreover, with the change of lifestyles many treatments could be avoided -and in this respect our sympathies are with those who advocate this- but, until such a time as a cost-effective means of changing the prevalence of obesity and sedentarism becomes available, the use of vascular prevention drug therapy is an inevitable strategy.

In the correct interpretation of the results of this study, some limitations must be borne in mind. Firstly, this study was based on health indicators and targeted at the assessment of public health; its results should not be extrapolated to the clinical sphere, i.e., to the clinical management of individual patients, and are thus not interpretable as outcomes of clinical or intervention trials, even though they may nuance the latter insofar as they provide an illustration of their external validity. Secondly, the results are exclusively applicable to cases of hospitalised incident IHD; having said this, however, the possibility that the decline in hospitalisations might be due to increases in pre-admission mortality can be conclusively ruled out because mortality rates due to sudden death or poorly defined causes not only decreased across the study period but they actually decreased to a greater extent.[2] Errors of measurement that are inherent in the ecological design and limit causal inference are of little relevance in this study, in view of the fact that, in all the factors considered, causality was clearly shown. Identification of incident cases was based on an estimate but the method used was validated, with high sensitivity and specificity values being obtained. What is more, the proportion of cases of acute infarction with previous clinical history in our series (26.6%) agrees with the results of the PRIAMHO II Registry,[42] in which 24% of cases were shown to have a history of previous infarction or revascularisation.

The remaining potential study limitations stem from the nature of the available data and, were they to have some impact, would in all cases bias the results towards the null hypothesis and so tend to underestimate the effect. With respect to the exposure data studied, these were drawn from a self-report questionnaire without any objective measures of smoking, weight and height; and, while self-reported smoking data are regarded as valid, those on obesity and overweight may be underestimated. The data relating to drug use refer to total use: these drugs are prescribed, not only for primary prevention, but also for secondary prevention and treatment of other conditions, such as arrhythmias and heart failure. Nevertheless the frequency of these diseases is infinitely lower than the prevalence of vascular risk in the general adult population, and is indeed almost negligible in comparison. At all events, the error would, yet again, tend more towards overestimating exposure and, by extension, underestimating the effect. Lastly, specific dietary factors (i.e., fish, vegetables or alcoholic beverages), nutritional factors (i.e. fats) and physical activity factors were not analysed for reasons of parsimony; instead, the frequency of obesity and overweight was used as an indicator of quality of diet and physical activity as a whole.

In conclusion, after decades of continuous rises, incidence of IHD hospitalisation fell from 1997 onwards, a decline that was associated with the decrease in smoking and, in equal measure, with the increase in vascular risk drug therapy. The cumulative decline of 52% over 13 years might have been even greater if there had not been a concomitant increase in the prevalence of excessive weight, also associated with incidence. These results indicate that current IHD primary prevention strategies have been effective at a population level, thanks to an appropriate balance between financial and health goals, something that should

be left intact despite the current economic crisis. Future strategies should lay special stress on the prevention and treatment of excessive weight.

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Competing Interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Annual trends in explanatory variables and incident ischaemic heart disease hospitalisation rates.

Figure 2. Time series of incidence analysed using non-parametric generalised additive models. Left plot: smoothed series adjusted for age and sex. Right plot: smoothed series adjusted for age, sex, prevalence of smoking, obesity and overweight, and use of cardiovascular disease prevention drug therapy. Solid lines represent the incidence rate ratios (IRRs) and dashed lines are the upper and lower limits of its 95% confidence interval.

Author Contributions

MJM conceived of the study, its design and coordinated the research team. MJM, EA-C, CO, and IG performed the statistical analysis and interpretation of data and prepared the draft manuscript. All authors participated in the design of the study and in critical review of the manuscript. All authors read and approved the final manuscript.

Data sharing

Technical appendix and supplementary material available online. Individual patient datasets are protected by Spanish regulations; these may be obtained from the Spanish Ministry of Health and the National Institute of Statistics under specific data loan agreements.

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EFFECT OF CARDIOVASCULAR PREVENTION STRATEGIES ON INCIDENT CORONARY DISEASE HOSPITALISATION RATES IN SPAIN. AN ECOLOGICAL TIME SERIES ANALYSIS

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ABSTRACT

Objective: To assess the overall population impact of primary prevention strategies (promotion of healthy lifestyles, prevention of smoking and use of vascular risk drug therapy) of coronary disease in Spain.

Design: Ecological time series analysis, 1982 to 2009.

Setting: All public and private hospitals in Spain.

Participants: General population.

Outcome: Incident coronary disease hospitalization as derived from official hospital discharge data.

Methods: Annual hospitalisation rates were modelled according to nationwide use of statins, antihypertensive, antidiabetic and antiplatelet drugs, and prevalences of smoking, obesity and overweight. Additive generalised models and mixed Poisson regression models were used for the purpose, taking year as the random-effect variable and adjusting for age, sex, prevalence of vascular risk factors, and hospital beds in intensive and coronary care units.

Results: Across 28 years and 671.5 million persons-year of observation, there were 2,986,834 hospitalisations due to coronary disease; of these, 1,441,980 (48.28%) were classified as incident. Hospitalisation rates increased from 1982 to 1996, with an inflection point in 1997 and a subsequent 52% decrease until 2009. Prevalences of smoking, obesity, overweight and use of vascular risk drug therapy were significantly associated with hospitalisation rates ($p<0.001$): incidence rates ratios (95% CI) for the fourth versus the first quartile were 1.46 (1.42-1.50), 1.80 (1.78-1.83), 1.58 (1.55-1.60) and 0.57 (0.51-0.63) respectively. These variables accounted for 92% of interannual variability.

Conclusion: After decades of continuous rises, hospitalisation due to incident IHD has been cut by half, an achievement associated with the decline in smoking and the increase in vascular risk drug therapy. These results indicate that these two primary prevention strategies have been effective at a population level, thanks to an appropriate balance between financial and health goals, something that should be left intact despite the current economic crisis. Future strategies ought to lay special stress on excessive body weight prevention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study shows that the decline in coronary disease in Spain was associated with the exponential increase in pharmacological treatment of vascular risk, together with the decline in active smoking that followed the strong interventions against tobacco use implemented in mid and late '90s. This decrease in IHD hospitalisation rates could have been even greater, had it not been for the frequency of excessive weight, which not only failed to decline but actually rose.

- The exposure-effect associations found: 1- are of great magnitude; 2- show a strong dose-response relationship; 3-show a correct temporality; 4- are biologically plausible; and 5- are consistent with similar studies in other countries, with trends in other tobacco-related diseases and with the increase in the rates of detection, treatment and control of vascular risk factors in Spain.

- The results are relevant as some of these measures (i.e. broad use of statins in general population) are still controversial. Moreover, the results may substantially affect public health policy, especially in a context of financial crisis.

- This is an ecological study based on health indicators and targeted at the assessment of public health; its results should not be interpreted as outcomes of intervention trials, even though they may nuance the latter insofar as they provide an illustration of their external validity.

INTRODUCTION

Ischaemic heart disease (IHD) is a severe disease, is lethal in its acute form in 20%-30% of cases [1] – indeed, it is the leading cause of death in men and the second leading cause of death in women in Spain [2]- and is chronically incapacitating in a great proportion of survivors. Its frequency in the Spanish population is high, with population incidence being estimated at 207 and 45/100,000 in men and women respectively, and hospitalisations at 140,000 cases annually.[3] Consequently, this situation became a public health priority and the target of specific health-planning strategies at a national level.[4]

The main vascular risk factors (excessive body weight, smoking habit, hypercholesterolaemia, arterial hypertension and diabetes mellitus) can be modified by changes in lifestyle or therapeutic interventions. In recent years, cardiovascular disease prevention has therefore been the focus of a major collective effort, in which health professionals as well as scientific societies, the pharmaceutical industry and health administrations have all taken part. The pillars of IHD prevention have been prevention of smoking, promotion of healthy lifestyles, and detection, treatment and medical control of arterial hypertension, hypercholesterolaemia, diabetes mellitus and platelet aggregation in high risk patients.[4,5] These strategies have been generally implemented throughout the Spanish National Health System, as a result of recommendations made by the respective health authorities,[4] prevention guidelines drawn up by experts and scientific societies both domestic and international,[5-7] and the development of risk functions which not only enable patients to be stratified according to their individual coronary risk, estimated on the basis of vascular risk factors taken jointly,[8,9] but also serve as a guide when it comes to making therapeutic decisions about controlling vascular risk.

The promotion of healthy habits has specifically centred on diet and physical exercise.[10] Prevalence of obesity and overweight is regarded as an indicator of inadequate diet and physical activity.[4,11] With respect to smoking, the impact of anti-smoking interventions on coronary risk has been comprehensively described at both an individual and a population level. Hence, assessment of epidemiological anti-smoking legislation in a number of countries has shown its effectiveness in terms of IHD mortality and morbidity.[12,13] Lastly, the use of cardiovascular disease prevention drug therapy in healthy persons has demonstrated its effectiveness at an individual level in many clinical trials, though it is not known whether this effectiveness has been reflected at a population level, i.e., its epidemiological impact. Clinical trials are conducted under controlled experimental conditions and the patients included are selected on the basis of strict inclusion and exclusion criteria. Consequently, such studies do not represent the general population and their results may possibly not be seen at a population level (external validity).[14]

To our knowledge, there is no study that has assessed the joint impact of these cardiovascular disease prevention measures on IHD incidence. Epidemiological studies undertaken in different countries,[15-20] including Spain,[21] have linked the decrease in cardiovascular and ischaemic heart disease mortality to the decline in population levels of vascular risk factors. In Spain, 50% of the reduction in coronary mortality is estimated to be due to changes in risk factors, essentially total cholesterol (close on 31% of the fall in

mortality) and systolic blood pressure (15%).[21] Most of these studies have, however, been based on IMPACT methodology,[17,18] which was designed to assess changes in mortality but has not been adapted to the task of assessing morbidity. Recent studies in the USA,[22,23] Italy [24] and Australia [25] have reported a decrease in IHD-related hospital morbidity, which was linked to anti-smoking legislation and the use of cardioprotective medication, though these associations were not statistically proved. Lastly, a recent population-based observational study in Israel [26] assessed the effect of continued use of statins on the incidence of acute infarction and coronary revascularisation but did not consider the effect of use of antihypertensive, antiplatelet or antidiabetic drugs.

Accordingly, the aim of this study was to describe the time trend in hospital incident-IHD-related morbidity rates and assess the impact of smoking prevention, promotion of healthy lifestyles and the use of cardiovascular disease prevention drug therapy, using the following as indicators: population prevalence of smoking; prevalence of obesity and overweight; and use of statins and antihypertensive, antiplatelet and antidiabetic drugs.

METHODS

We conducted an epidemiological assessment study into the impact of preventive measures using regression analysis and time-series modelling and, for study purposes, including the total Spanish population over 29 years of age. The period considered in the description of the time series was 1982 to 2009, avoiding the years preceding the entry into force of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). In the analysis of related factors, the series was restricted to the period 1996–2006, since this was the period for which data on all the explanatory variables were available.

1- Principal and secondary variables. Data-sources.

The outcome variable was frequency of hospitalisation due to incident IHD (ICD-9-CM codes 410-414, with four digits), expressed in descriptive analyses in the form of annual age-adjusted rates according to the Standard European Population. Data on hospital discharges due to this cause were drawn from anonymised MBDS microfiches (Minimum Basic Data Set/*Conjunto Mínimo Básico de Datos*, the official nation-wide administrative and statistical database which includes clinical and demographic data on every hospital discharge, obtained from the pertinent medical records), and were completed with a patient discharge sample from some private hospitals that were not included in the MBDS. The fiches were supplied by the National Statistics Institute (NSI) (*Instituto Nacional de Estadística*) under a data loan agreement containing an undertaking of confidentiality and respect for statistical secrecy. Population data for calculating the rates for each year, sex and age group were obtained from NSI intercensal estimates. The age strata were 5-year age groups starting from 30 to 85 and older.

An incident event was defined as that in which the following two conditions were fulfilled: a) diagnosis at discharge of acute IHD, acute myocardial infarction, intermediate coronary syndrome (unstable angina) or

angina pectoris (ICD 410, 411 or 413); and, b) first admission due to IHD, as shown by a check for duplicate entries based on the fields, "sex", "date of birth" and "province of residence". Events for which control for duplicates could not be performed for lack of any record of the patient's complete date of birth (n= 91,176, 3.1%), were excluded.

The method used to control for duplicates was validated by comparing the results against data on 30,205 hospitalisations in eight cities for which patient identification codes were available, yielding a sensitivity of 97.88% and specificity of 88.73. The distribution by age, sex and diagnostic category of this validation sample did not differ from that of the study population.

The variables considered as potentially explanatory of the trend in IHD hospitalisation rates in the population were:

- use of statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin);
- use of antihypertensive drugs (angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, betablockers, diuretics, calcium channel blockers and others);
- use of platelet aggregation inhibitors (aspirin, carbasalate, clopidogrel, dipyridamol, citazol, ticlopidine and triflusal);
- use of antidiabetic drugs (insulins, biguanides, sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones and combinations of these).

  The use of these drugs was expressed in Defined Daily Doses (DDDs) per 1,000 inhabitants per day (DHDs), for the period 1996-2006. These data were drawn from reports issued by the Spanish Medications & Health Products Agency on the basis of data on packages dispensed under and charged to the National Health System.[27] The methodology used is described in detail in these publications. DHDs divided by 10 were introduced into the models, with the estimators having to be interpreted as the effect for every increase of 10 units in the DHD.
- prevalence, with a breakdown by year, sex and age, of smoking, overweight, obesity, arterial hypertension, hypercholesterolaemia and diabetes mellitus obtained from self-report data in the 1987,1993, 1995, 1997, 2001, 2003 and 2006 National Health Surveys,[28] with data for the intermediate years being estimated by means of linear interpolation of data for the pivotal years.
- Number of physically available hospital beds in intensive care and coronary care units per 1,000 inhabitants.[28]

2- Data-analysis

Weightings specified by the NSI were used for the calculation of the number of cases. In descriptive analyses, age-adjusted incident IHD hospitalisation rates (Standard European Population) were calculated for each year and sex. These rates were depicted graphically, as were the frequency measures of the remaining explanatory variables for each year.

The effect of the explanatory variables on incident IHD morbidity was estimated on the basis of incidence

rates ratios (IRRs) derived from mixed Poisson regression models of fixed and random effects, with year being introduced as the random-effect variable, usingy the command 'xtmepoisson' implemented in Stata, that fits mixed-effects models for count responses assuming a Poisson distribution of the data.This approach enables one to control for both temporal autocorrelation and overdispersion, measure interannual variability explained by the preventive measures, and minimise the risk of residual confounding. The dependent variable was the number of incident hospitalisations in each sex and age stratum, and the national population figure of each stratum was introduced as the exposed population. This is equivalent to modelling of rates. The explanatory variables were sequentially introduced, successively obtaining age- and sex-adjusted estimators and multivariate estimators. We considered the concurrent effect across time of the explanatory variables and hospitalisation, plus the effect with lags of one, two and three years, so as to take into account the possible latency between exposure and its effect, and assess the temporality of the associations.

The effect of drug therapy for control of vascular risk was analysed for each type of drug (statins, and antihypertensive, antiplatelet and antidiabetic drugs), both individually and jointly, using the variable "drug use for control of vascular risk" obtained by adding together the respective usages of each type to avoid the strong collinearity that characterises the consumption of such drugs (correlation coefficients of 0.97 to 0.99). The explanatory variables categorised in quartiles were included in the models for dose-response analysis. These models were used to measure the interannual variability explained by the variables, calculated as 1 minus the ratio between the variance of the random term in the complete model, and the variance of the random term in the model without prevention explanatory variables and in the model adjusted for age and sex.

Lastly, the incidence time series was analysed and plotted graphically with the aid of Poisson non-parametric generalised additive models (GAMs) implemented in the mgcv library of the R statistical package version 2.15.0 (2012-03-30).[29] GAM models allow to graphically depict the relationship including both smoothing and also a non-parametric fit, with no a priori assumptions on the actual relationship between response and predictor. As time is used as the predictor, the result is a smoothed time series of the response. The rates were modelled and smoothed by reference to time, and the smoothed age- and sex-adjusted series were depicted graphically. The explanatory variables were subsequently included in these models to depict the trends not due to these variables.

(See technical appendix in supplementary material for theoretical basis of models and technical details)

RESULTS

Across the 28 years and 671.5 million persons-year of observation, there were 2,986,834 hospitalisations in Spain due to IHD; and of these, 1,441,980 (66.7% men and 33.3% women), accounting for 48.28% of the total, were classified as incident. Mean age at admission was 65.9 ± 12.8 years, with a higher frequency in the 60- to 74-year age group (41.9%). Diagnosis at discharge was acute infarction in 55%, unstable angina

in 14.7%, and stable angina in 30.3% of cases. Women's mean age was 5 years older (p<0.001), and the over-74-year age group was far more frequent among women than among men (data not shown in tables).

The annual age-adjusted incident IHD hospitalisation rates per 100,000, which are depicted graphically in Figure 1, show a rise from 1982 to 1996, a sharp inflection in 1997 and a subsequent cumulative decrease of 52.0% until 2009 (53.5% and 49.6% in men and women respectively). The decline was constant throughout the period, save for a slight increase in 2000, coinciding with the change in the definition of ischaemic heart disease. The distribution by sex of the incidence rates changed across the study period, with a decrease in the male/female ratio from 3.3 to 2.4.

Of the total study period (1982-2009), data on indicators of cardiovascular disease prevention (prevalence of smoking, prevalence of obesity and overweight, and use of drug therapy for control of vascular risk) were available for the period 1996-2006. These years witnessed a rise in the use of statins (948.9%) and antihypertensive (95.4%), antiplatelet (105%) and antidiabetic drugs (142%), and a decline in smoking prevalence (6.8% in women and 23.8% in men). Prevalence of obesity increased by 40% (Table 1, Figure 1).

Table 1. Annual trends in explanatory variables in Spanish general population.

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Proportion (%) Smokers	31,9	32,0	31,8	31,6	31,4	31,2	29,8	28,4	27,9	27,8	27,6
Proportion (%) Obesity	15,1	16,1	16,1	16,2	16,3	16,3	16,2	16,0	16,7	17,3	17,9
Proportion (%) Overweight	41,0	40,3	40,6	41,0	41,4	41,8	41,2	40,6	40,7	40,7	40,8
Drugs for control of vascular risk. No. of Defined Daily Doses* per 1000 inhabitants per day (x10).											
Total	171,5	185,6	204,9	227,7	253,8	279,2	303,0	329,7	359,6	377,7	412,3
Statins	7,8	9,4	14,3	19,7	24,4	30,4	38,0	48,7	60,1	69,2	81,3
Antihypertensive drugs	119,2	127,6	136,6	148,4	163,8	175,7	186,9	197,1	210,2	215,7	232,9
Antidiabetic drugs	27,0	28,9	32,3	35,6	39,1	43,2	46,0	48,9	51,7	53,3	55,7
Antiplatelet drugs	17,5	19,6	21,7	24,0	26,6	29,9	32,2	35,0	37,6	39,5	42,4

DDD: number of doses (adult average maintenance dose per day) prescribed and sold in the National Health System

Consumption of statins and antihypertensive, antiplatelet and antidiabetic drugs, individually considered, displayed an inverse and statistically significant relationship with incident IHD hospitalisation rates in models adjusted for age, sex and prevalences of smoking, obesity and overweight (Table 2), and this association became progressively greater when growing lags were taken into account. Similarly, the use of drugs

considered jointly was inversely associated (IRR 0.97, 95% CI 0.97-0.98) with IHD incidence. The greater magnitude of the effect of drug use when considered individually rather than jointly should not be construed as a discrepancy: instead, this is attributable both to the difference in scale, and to drug associations and the lack of adjustment among the individual drug usages due to collinearity. In contrast, prevalence of smoking and that of obesity and overweight were both positively associated with incidence of hospitalisation due to IHD. In the models in which adjustment was additionally made for prevalences of arterial hypertension, hypercholesterolaemia and diabetes mellitus, and for the number of physically available beds in intensive and coronary care units, the above associations were not substantially modified, i.e., the effect of frequency of smoking was not modified, the effect of frequency of obesity and overweight was slightly attenuated, and the inverse association with drug use was slightly accentuated, both when the respective types of drugs were considered individually and when they were considered jointly.

Furthermore, these associations displayed a statistically significant dose-response relationship in the models adjusted for sex, age, the variables in the table, and year as a random-effect variable (Table 3): whereas the IRR of smoking prevalence in the fourth versus the first quartile was 1.46 (95%CI 1.42-1.50) and the IRRs for prevalence of obesity and overweight were 1.80 (1.78-1.83) and 1.58 (1.55-1.60) respectively, the IRR for cardiovascular disease prevention drug therapy was 0.57 (0.51-0.63). The linear trend was statistically significant for all four variables. The protective effect of cardiovascular disease prevention drug therapy was slightly attenuated when the growing lags between exposure and effect were taken into account (IRR lag 0= 0.57 (0.51-0.63) / IRR lag 3=0.61 (0.57-0.66)). Similarly, while the association with prevalence of overweight was attenuated over time, the association was not modified when the growing lags between exposure and effect for prevalences of obesity and smoking habit were taken into account.

The interannual variability in hospitalisation rates explained by the models considering the four variables simultaneously (continuous scale) was: 92% for no lag between exposure and effect; 95% for a lag of one year; 97% for a lag of two years; and 94% for a lag of three years (data not shown in tables). The proportion of variability in annual rates explained by prevention variables raised from 92% with respect to the empty model, to 97% when calculated with respect to the model adjusted by age and sex, thus meaning a 5% variability in hospitalisation rates due to changes in age-sex population structure from 1996 to 2006.

Table 2. Effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates on annual incident ischaemic heart disease hospitalisation rates 1996-2006. Models for exposure-effect lags of 0, 1, 2 and 3 years.

	Lag0		Lag1		Lag2		Lag3	
	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
1. Adjustment for age, sex, year (random variable) and specified variables								
% Smokers	1.02	(1.01-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)
% Obesity	1.05	(1.04-1.05)	1.05	(1.05-1.05)	1.05	(1.05-1.05)	1.06	(1.05-1.06)
% Overweight	1.04	(1.04-1.04)	1.04	(1.04-1.04)	1.03	(1.03-1.04)	1.03	(1.03-1.03)
Drug use (x10 DHDs*)¶	0.97	(0.97-0.98)	0.97	(0.97-0.97)	0.97	(0.97-0.97)	0.97	(0.96-0.97)
Statins¶	0.92	(0.91-0.93)	0.91	(0.90-0.92)	0.90	(0.88-0.91)	0.87	(0.85-0.90)
Antihypertensive drugs¶	0.95	(0.94-0.95)	0.94	(0.94-0.95)	0.94	(0.94-0.94)	0.93	(0.93-0.94)
Antidiabetic drugs¶	0.81	(0.79-0.83)	0.81	(0.79-0.83)	0.80	(0.79-0.81)	0.78	(0.77-0.79)
Antiplatelet drugs¶	0.77	(0.76-0.79)	0.77	(0.75-0.79)	0.75	(0.74-0.77)	0.72	(0.70-0.74)
*2. Multivariate adjustment:***								
% Smokers	1.01	(1.01-1.01)	1.02	(1.01-1.02)	1.02	(1.02-1.02)	1.02	(1.02-1.02)
% Obesity	1.03	(1.03-1.03)	1.03	(1.03-1.04)	1.03	(1.03-1.04)	1.03	(1.03-1.04)
% Overweight	1.03	(1.03-1.03)	1.03	(1.03-1.03)	1.03	(1.02-1.03)	1.03	(1.03-1.03)
Drug use (10 DHDs*)¶	0.96	(0.96-0.97)	0.96	(0.96-0.97)	0.96	(0.96-0.96)	0.96	(0.96-0.96)
Statins¶	0.90	(0.89-0.91)	0.89	(0.88-0.90)	0.87	(0.86-0.89)	0.85	(0.83-0.87)
Antihypertensive drugs¶	0.92	(0.91-0.93)	0.92	(0.91-0.93)	0.92	(0.92-0.93)	0.92	(0.92-0.93)
Antidiabetic drugs¶	0.73	(0.68-0.77)	0.74	(0.71-0.77)	0.75	(0.73-0.77)	0.75	(0.74-0.75)
Antiplatelet drugs¶	0.70	(0.66-0.73)	0.70	(0.67-0.73)	0.70	(0.68-0.71)	0.68	(0.67-0.70)

* DHDs: No. of Defined Daily Doses per 1000 inhabitants per day.** Adjusted for variables specified in the table plus age, sex, year of discharge as a random-effect variable, prevalence (%) of arterial hypertension, prevalence (%) of hypercholesterolaemia, prevalence (%) of mellitus diabetes, and number of hospital beds in intensive care and coronary care units.¶ Not adjusted among themselves because collinearity.

Table 3. Dose-response analysis of the effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates. Models for exposure-effect lags of 0, 1, 2 and 3 years.

	Lag0		Lag1		Lag2		Lag3	
	IRR**	95%CI	IRR**	95%CI	IRR**	95%CI	IRR**	95%CI
% Smokers								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	0.92	(0.91-0.93)	0.91	(0.90-0.93)	0.92	(0.91-0.94)	0.93	(0.91-0.94)
3rd quartile	1.23	(1.21-1.25)	1.21	(1.19-1.23)	1.20	(1.18-1.22)	1.18	(1.15-1.20)
4th quartile	1.46	(1.42-1.50)	1.48	(1.44-1.52)	1.50	(1.46-1.55)	1.49	(1.45-1.54)
P trend	*<0.001*		*<.0001*		*< 0.001*		*< 0.001*	
% Obesity								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	1.46	(1.44-1.47)	1.45	(1.43-1.46)	1.34	(1.33-1.36)	1.32	(1.30-1.33)
3rd quartile	1.71	(1.69-1.73)	1.65	(1.63-1.67)	1.53	(1.51-1.55)	1.48	(1.46-1.50)
4th quartile	1.80	(1.78-1.83)	1.82	(1.79-1.85)	1.75	(1.73-1.79)	1.86	(1.78-1.90)
P trend	*<0.001*		*<0.001*		*<0.001*		*<0.001*	
% Overweight								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	1.23	(1.22-1.24)	1.21	(1.19-1.22)	1.14	(1.13-1.16)	1.06	(1.05-1.08)
3rd quartile	1.41	(1.39-1.43)	1.35	(1.33-1.37)	1.30	(1.28-1.31)	1.22	(1.20-1.24)
4th quartile	1.58	(1.55-1.60)	1.50	(1.47-1.52)	1.43	(1.41-1.45)	1.33	(1.31-1.36)
P trend	*<0.001*		*<0.001*		*<0.001*		*<0.001*	
Use of drugs (x10 DHDs*)								
1st quartile	1.00		1.00		1.00		1.00	
2nd quartile	0.85	(0.76-0.93)	0.87	(0.80-0.94)	0.83	(0.78-0.88)	0.84	(0.78-0.90)
3rd quartile	0.71	(0.65-0.79)	0.73	(0.68-0.79)	0.71	(0.67-0.75)	0.70	(0.65-0.75)
4th quartile	0.57	(0.51-0.63)	0.59	(0.55-0.64)	0.62	(0.58-0.66)	0.61	(0.57-0.66)
P trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	

* DHDs: No. of Defined Daily Doses per 1000 inhabitants per day. ** IRR adjusted for variables specified in the table plus age, sex and year of discharge as a random-effect variable. Four independent models, each including the variable of interest on a categorical scale adjusted for the others on a continuous scale.

Lastly, figure 2 describes the time series of incidence analysed using Poisson non-parametric generalised additive models. Left plot displays the downward trend in the annual age-and sex-adjusted incidence rates, which shows very narrow confidence interval because the very large size of the study population. This downward trend disappeared after additionally adjusting for the four explanatory variables (Figure 2, right plot), which shows that the decrease was due to the effect of these same variables. From 2004 onwards, however, the declining trend remained in evidence even after adjustment was made for use of preventive drug therapy and prevalence of smoking, obesity and overweight.

DISCUSSION

The results show that, after decades of continuous rises, hospitalisation due to incident IHD in the Spanish adult population fell after 1997, a drop that was associated with the decline in smoking and, in equal measure, with the increase in pharmacological treatment of vascular risk. This decrease in IHD hospitalisation rates could have been even greater, had it not been for the frequency of excessive weight, which not only failed to decline but actually rose. Overall, the factors analysed accounted for over 90% of the decrease in incident IHD hospitalisation rates. The decline occurred despite the increased sensitivity of diagnostic tests and the ensuing change in the IHD-definition criteria.[30]

The accuracy of the results is reinforced because the associations show a strong dose-response relationship and a correct temporality, with the effect being maintained in response to growing lags between exposure and disease. The associations found are biologically plausible, since both the role of smoking in the aetiology of coronary disease and the effect of drugs on vascular risk have been sufficiently proved by *in vitro* studies and clinical trials. Lastly, the results are in line with: what has been published with respect to the decreases in IHD mortality [15-21] and hospital morbidity recorded in other countries;[22-26] the decline in Spain in the incidence of smoking-related diseases such as asthma and lung cancer;[28] the reduction in mean population levels of serum cholesterol and systolic blood pressure;[21] and the increase in the rates of detection, treatment and control of vascular risk as documented by cross-sectional studies on the Spanish population.[31]

The study shows the success of the smoking control strategies implemented in the 1990s,[32] based on legislative measures targeted at restricting the sale, raising the price and placing limitations on the advertising of cigarettes, information programmes about smoking-related risks, and anti-smoking campaigns. These measures were followed by a considerable decline in the frequency of active smoking, principally among light and moderate smokers.[28] The most recent legislative measures, aimed at preventing passive smoking, have not achieved such a marked decrease in active smoking prevalence. Our results suggest,

however, that part of the decline in IHD incidence in the lattermost years of the study is not accounted for by the factors analysed, indicating, in turn, that this may be due to the decline in passive smoking resulting, not only from the cumulative reduction in active smoking itself in the years preceding the entry into force of these measures, but also from the direct impact of the first Anti-smoking Act. Different studies undertaken in Spain [33,34] and other countries [12,13] have shown the effect on IHD mortality and morbidity of a legal ban on smoking in the workplace.

The results support a primary prevention strategy based on pharmacological control of vascular risk. Evidence of the effectiveness of this strategy at a population level, which implies the mass use of medication, is especially important in an adverse economic context, and more so when the use of drugs for cardiovascular disease prevention in healthy persons has been the subject of controversy.[35] Specifically, in the case of the various statins, meta-analyses of clinical trials have yielded contradictory results,[36-40] with some authors being of the opinion that it is preferable to change the lifestyles of these patients. While this study does not purport to assess the clinical effect of these drugs, its results nonetheless show a statistically significant decrease in the age- and sex-adjusted hospitalisation rate associated with the use of both statins and hypertensive, antiplatelet and antidiabetic drugs. Although the presence of strong collinearity ruled out any analysis of the independent effect of each of these drugs with adjustment for remainder, their use considered jointly *did* show a strong protective effect, regardless of the effect of sex, age, smoking prevalence and excessive weight, a finding in line with the consideration that vascular risk is multifactorial and cannot be corrected by controlling the respective risk factors in isolation.[7] The appropriate balance between economic and health objectives by policies aimed at reducing pharmaceutical costs, such as those fostering the use of generic drugs or a gradual reduction in profit margins for producers and distributors,[41] have been decisive factors in this public health success. Even so, recent studies reveal that there is still much room for improvement in the detection, treatment and control of vascular risk.[31]

In contrast with smoking and control of vascular risk, prevalences of overweight and obesity, positively associated with incident IHD hospitalisation rates, increased across the study period, indicating that prevention based on promoting a healthy diet and physical exercise and changing obesogenic lifestyles is proving inadequate or ineffective, probably because the effects of these policies will only be seen in the longer term.[10] Without ignoring smoking prevention or therapeutic control of vascular risk, our results indicate that, from a public health stance, treatment and prevention of excess weight should be made a priority. Community interventions aimed at changing the prevalence of obesity and sedentarism are multidisciplinary, going beyond the strict scope of health care and involving multiple levels, such as education, the food sector, town planning and administration, provision of sports facilities, transport policy, etc.[11] Moreover, with the change of lifestyles many treatments could be avoided -and in this respect our sympathies are with those who advocate this- but, until such a time as a cost-effective means of changing the prevalence of obesity and sedentarism becomes available, the use of vascular prevention drug therapy is an inevitable strategy.

In the correct interpretation of the results of this study, some limitations must be borne in mind. Firstly, this study was based on health indicators and targeted at the assessment of public health; its results should not be extrapolated to the clinical sphere, i.e., to the clinical management of individual patients, and are thus not interpretable as outcomes of clinical or intervention trials, even though they may nuance the latter insofar as they provide an illustration of their external validity. Secondly, the results are exclusively applicable to cases of hospitalised incident IHD; having said this, however, the possibility that the decline in hospitalisations might be due to increases in pre-admission mortality can be conclusively ruled out because mortality rates due to sudden death or poorly defined causes not only decreased across the study period but they actually decreased to a greater extent.[2] Errors of measurement that are inherent in the ecological design and limit causal inference are of little relevance in this study, in view of the fact that, in all the factors considered, causality was clearly shown. Identification of incident cases was based on an estimate but the method used was validated, with high sensitivity and specificity values being obtained. What is more, the proportion of cases of acute infarction with previous clinical history in our series (26.6%) agrees with the results of the PRIAMHO II Registry,[42] in which 24% of cases were shown to have a history of previous infarction or revascularisation.

The remaining potential study limitations stem from the nature of the available data and, were they to have some impact, would in all cases bias the results towards the null hypothesis and so tend to underestimate the effect. With respect to the exposure data studied, these were drawn from a self-report questionnaire without any objective measures of smoking, weight and height; and, while self-reported smoking data are regarded as valid, those on obesity and overweight may be underestimated. The data relating to drug use refer to total use: these drugs are prescribed, not only for primary prevention, but also for secondary prevention and treatment of other conditions, such as arrhythmias and heart failure. Nevertheless the frequency of these diseases is infinitely lower than the prevalence of vascular risk in the general adult population, and is indeed almost negligible in comparison. At all events, the error would, yet again, tend more towards overestimating exposure and, by extension, underestimating the effect. Lastly, specific dietary factors (i.e., fish, vegetables or alcoholic beverages), nutritional factors (i.e. fats) and physical activity factors were not analysed for reasons of parsimony; instead, the frequency of obesity and overweight was used as an indicator of quality of diet and physical activity as a whole.

In conclusion, after decades of continuous rises, incidence of IHD hospitalisation fell from 1997 onwards, a decline that was associated with the decrease in smoking and, in equal measure, with the increase in vascular risk drug therapy. The cumulative decline of 52% over 13 years might have been even greater if there had not been a concomitant increase in the prevalence of excessive weight, also associated with incidence. These results indicate that current IHD primary prevention strategies have been effective at a population level, thanks to an appropriate balance between financial and health goals, something that should

be left intact despite the current economic crisis. Future strategies should lay special stress on the prevention and treatment of excessive weight.

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Competing Interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Annual trends in explanatory variables and incident ischaemic heart disease hospitalisation rates.

Figure 2. Time series of incidence analysed using non-parametric generalised additive models. Left plot: smoothed series adjusted for age and sex. Right plot: smoothed series adjusted for age, sex, prevalence of smoking, obesity and overweight, and use of cardiovascular disease prevention drug therapy. Solid lines represent the incidence rate ratios (IRRs) and dashed lines are the upper and lower limits of its 95% confidence interval.

Author Contributions

MJM conceived of the study, its design and coordinated the research team. MJM, EA-C, CO, and IG performed the statistical analysis and interpretation of data and prepared the draft manuscript. All authors participated in the design of the study and in critical review of the manuscript. All authors read and approved the final manuscript.

Data sharing

Technical appendix and supplementary material available online. Individual patient datasets are protected by Spanish regulations; these may be obtained from the Spanish Ministry of Health and the National Institute of Statistics under specific data loan agreements.

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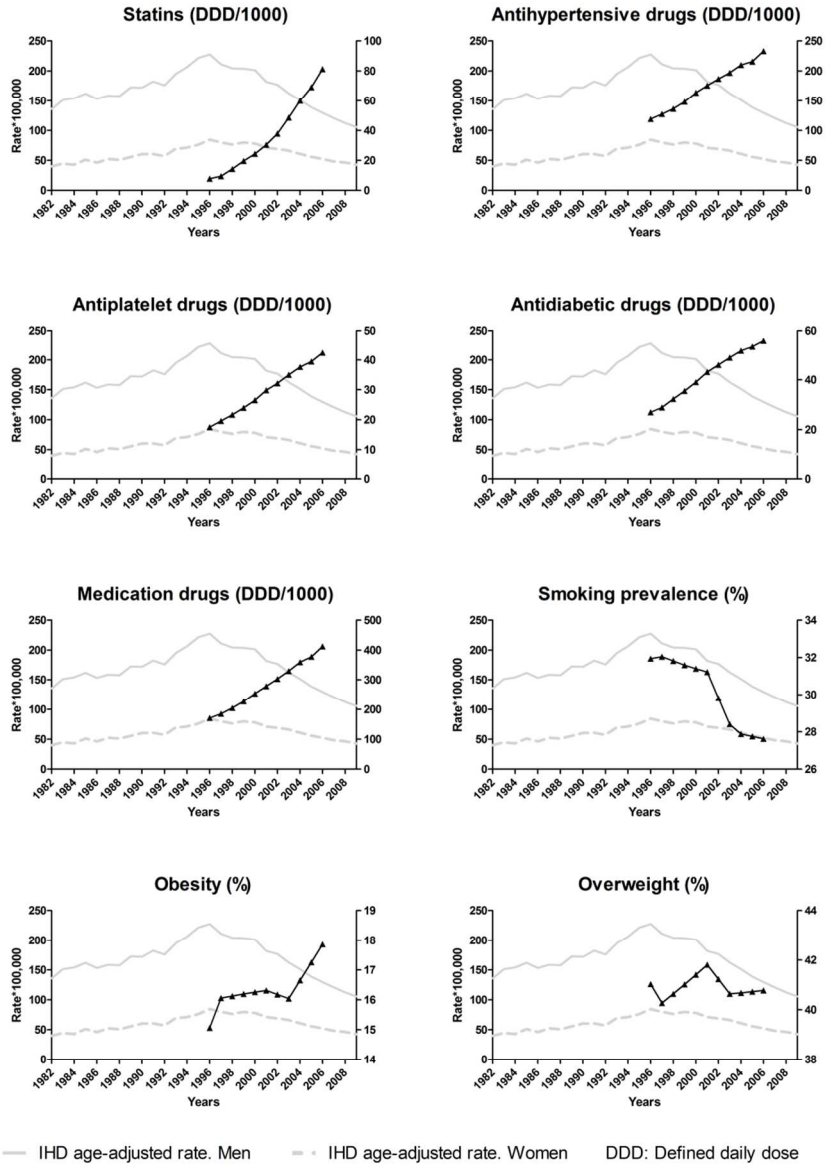

Figure 1. Annual trends in explanatory variables and incident ischaemic heart disease hospitalisation rates.
90x124mm (300 x 300 DPI)

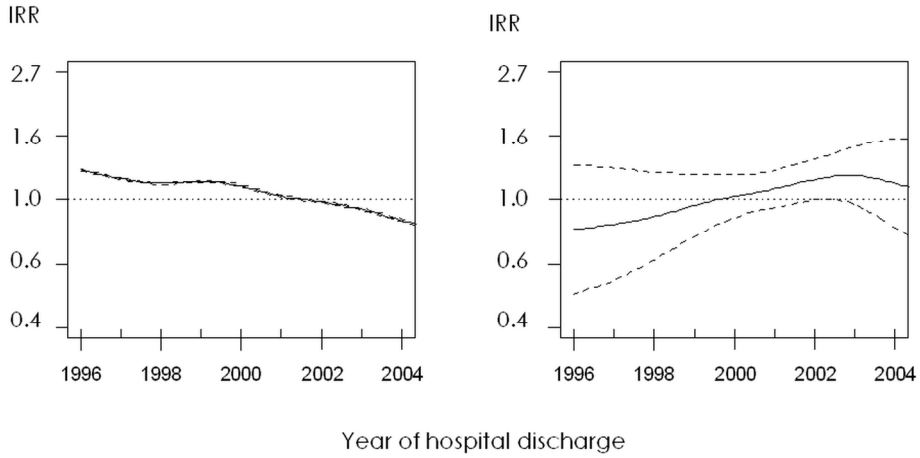

Figure 2. Time series of incidence analysed using non-parametric generalised additive models. Left plot: smoothed series adjusted for age and sex. Right plot: smoothed series adjusted for age, sex, prevalence of smoking, obesity and overweight, and use of cardiovascular disease prevention drug therapy.
167x90mm (300 x 300 DPI)

TECHNICAL APPENDIX

1. THEORETICAL BASIS OF THE MATEMATICAL MODELS USED IN THE ANALYSES. Poisson regression. Mixed effects Poisson models. Generalized additive models. Recommended bibliography.

2. TECHNICAL DETAILS. Data file structure. Model sintax and otputs. Percentage of annual IHD rates variability explained by independent variables.

3. OTHER SUPPLEMENTARY MATERIALS. Identification of incident cases. Formula for the calculation of Number of Defined Daily Doses per 1000 population and per day.

1. THEORETICAL BASIS OF THE MATEMATICAL MODELS USED IN THE ANALYSES

POISSON REGRESSION

Poisson regression models are a particular class of generalized lineal models that are commonly used for count data, that is, when the response variable is discrete taking non-negative integer values. Distribution of count data is typically a Poisson distribution. In our study the response variable is the count of cases discharged from hospitals with the diagnoses of incident IHD each year from 1996 to 2006.

It can be modelled that the response variable is a function of some explanatory variables. In our models, the count of IHD cases discharged each year from hospitals in Spain is modelled as varying in function of the age, sex, the proportion of smokers, obese and overweighted in the Spanish population in such year (and also 1, 2, and 3 years before to test the associations taking into account the possible latency between exposure and its effect), and of the prescription of drugs for vascular risk factors.

Regression coefficients and their confidence intervals for each of the explanatory variables reflect its effect on the response variable. It measures the change in the response variable for each unit change in the explanatory variables, given that the rest of explanatory variables remain constant. Exponentiation of regression coefficients gives the incident rate ratio (IRR) for each explanatory variable.

The number of incident IHD cases discharged from hospitals depends also on the size of the population, which is thus entered in the model and considered not as an explanatory variable (so it is not given a regression coefficient) but as the size of exposure. Due to the log link in Poisson regression, this is equivalent to having rates as the dependent variable (see below) and therefore, regression coefficients in the explanatory variables reflect their effect on incidence rates. As age and sex are included in the model, effect is measured as age and sex adjusted IRRs.

$$\log(\text{n cases}) = \log(\text{p population}) + \sum\beta(x);$$

$$\log(\text{n cases}) - \log(\text{p population} = \sum\beta(x);$$

$$\log(\text{n cases/p population}) = \sum\beta(x).$$

In many occasions the dependent variable is not strictly Poisson, and in these situations there is variability in data that is not adequately captured by the model, which is called overdispersion of data. This has implications, among them that confidence intervals are erroneously narrow, and significance values are wrong. Also, when data are time series, there is autocorrelation and assumptions in the model are not fulfilled. There are several forms of correcting one or another of such errors; including the time variable (in our case year) as a random-effect variable in the model effectively corrects for both at the same time. This implies using a mixed fixed and random effects Poisson model. The command in Stata for these kind of models is 'xtmepoisson'.

MIXED EFFECTS POISSON MODELS

Mixed models are very valuable tools that have many applications in statistics and in epidemiology, such as analysis of repeated measures, meta-analysis, multicenter trials, matched case-control studies, geographical analysis, or multilevel/hierarchical analysis. The basic idea in these models is that the data are grouped in some way (same patient, same study, same centre, same case-control couple, same geographical unit, same level) that make the individual observations in each group sharing specific circumstances. In depth statistical characteristics and applications of these models are too extensive and lay out of the scope of this journal and its readers. However we include some bibliographical references in case someone is interested in their study.

GENERALIZED ADDITIVE MODELS

The primary restriction of a glm is the fact that it is a lineal model. The Generalized Additive Model (GAM) is an adaptation of generalized lineal model that allows nonlinear transformation of the input variables to be fit by the data. It extends the generalized lineal model by fitting nonparametric functions to estimate the relationship between the explanatory and the response variables. The nonparametric functions are estimated from the data using smoothing operations. GAM models further allows to graphically depict the relationship including both smoothing and also a non-parametric fit, with no a priori assumptions on the actual shape of the relationship between response and predictor. As time is used as the predictor, the result is a smoothed time series of the response.

GAM have been extensively used for dose-response relationship analysis, especially when this relationship is or may be non-linear, i.e, presence of cut-off values, saturation values or any kind of non-monotonous shape. In our study we have used GAM models to represent the change in the shape of the smoothed time series with and without including the explanatory variables.

We have used the command *gam* implemented in the mgcv library of the R statistical package.

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2. TECHNICAL DETAILS.

DATA FILE STRUCTURE

Derived from the pertinent medical records, data on every individual, anonymised hospital discharge due to this cause were drawn from official microfiches. From these, incident cases were selected. For modelling purposes, the count of incident cases was computed for each year, sex and age group. Parallel year, sex and age group data were obtained from official sources for population data and for the explanatory variables, resulting in a file with the structure shown in Table sup. 1.

An incident event was defined as that in which the following two conditions were fulfilled: a) diagnosis at discharge of acute IHD, acute myocardial infarction, intermediate coronary syndrome (unstable angina) or angina pectoris (ICD 410, 411 or 413); and, b) first admission due to IHD, as shown by a check for duplicate entries based on the fields, "sex", "date of birth" and "province of residence". Events for which control for duplicates could not be performed for lack of any record of the patient's complete date of birth (n= 91,176, 3.1%), were excluded.

The method used to control for duplicates was validated by comparing the results against data on 30,205 hospitalisations in eight cities for which patient identification codes were available, yielding a sensitivity of 97.88% and specificity of 88.73. The distribution by age, sex and diagnostic category of this validation sample did not differ from that of the study population. The results of these analyses are shown in tables sup. 2, 3 and 4.

Table sup. 1. File structure

Sex	Year	Age	Pop	Cases	Smoking
Men	1996	30-34 y	1586299	351	57.67
Men	1996	35-39 y	1450668	915	58.27
Men	1996	40-44 y	1274861	2015	58.27
Men	1996	45-49 y	1205540	3247	49.76
Men	1996	50-54 y	1090239	4056	49.76
Men	1996	55-59 y	935055	4785	40.03
Men	1996	60-64 y	1025528	6431	40.03
Men	1996	65-69 y	924165	8097	28.71
Men	1996	70-74 y	731542	6876	28.71
Men	1996	75-79 y	462032	4906	16.42
Men	1996	80-84 y	279073	3015	16.42
Men	1996	85 + y	184300	1519	16.42
Men	1997	30-34 y	1606873	275	55.86
Men	1997	35-39 y	1484122	828	60.19
Men	1997	40-44 y	1306110	1570	60.19
⋮	⋮	⋮	⋮		
Men	2006	60-64 y	1061310	3647	31.34
Men	2006	65-69 y	869044	3574	20.56
Men	2006	70-74 y	869815	4170	20.56
Men	2006	75-79 y	680368	3776	9.3
Men	2006	80-84 y	428671	2977	9.3
Men	2006	85 + y	265248	1982	9.3
Women	1996	30-34 y	1561500	121	53.38
53.38	1996	35-39 y	1448200	217	36.54
36.54	1996	40-44 y	1277497	350	36.54
36.54	1996	45-49 y	1218406	682	17.64
17.64	1996	50-54 y	1116991	983	17.64
17.64	1996	55-59 y	989781	1455	7.01
Women	1996	60-64 y	1124800	2616	7.01
Women	1996	65-69 y	1068123	3461	2.00
Women	1996	70-74 y	925186	4239	2.00
Women	1996	75-79 y	695034	4222	.92
Women	1996	80-84 y	501698	2931	.92
Women	1996	85 + y	406709	2368	.92
Women	1997	30-34 y	1580205	67	54.85
Women	1997	35-39 y	1480723	111	37.48
Women	1997	40-44 y	1310445	276	37.48
⋮	⋮	⋮	⋮		
Women	2006	85 + y	587440	3205	1.49

MODELS SINTAX AND OUTPUTS

MODELS IN TABLE 2 OF THE ARTICLE.

Effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates on annual incident ischaemic heart disease hospitalisation rates 1996-2006. Models for exposure-effect lags of 0, 1, 2 and 3 years.

Section 1. Adjustment for age, sex, year (random variable) and specified variables

Sintax:

```
xtmepoisson incidentes grupoedad sexo fuma obes sobrepeso medicomb10, exposure(pob) ||
año:, covariance(independent) irr
```

LAG0

incidentes	IRR	Std. Err.	z	P>|z|	[95% Conf.	Interval]
grupoedad	1.392495	.0016029	287.63	0.000	1.389357	1.39564
sexo	.6927362	.006319	-40.25	0.000	.6804613	.7052325
fuma	1.014939	.0002595	57.99	0.000	1.01443	1.015448
obes	1.044838	.0005036	91.00	0.000	1.043851	1.045825
sobrepeso	1.041036	.0004449	94.10	0.000	1.040165	1.041909
medicomb10	.9737405	.0011353	-22.82	0.000	.9715179	.9759681
_cons	6.33e-06	3.41e-07	-222.21	0.000	5.70e-06	7.04e-06
ln(pob)	1	(exposure)				

LAG1

incidentes	IRR	Std. Err.	z	P>|z|	[95% Conf.	Interval]
grupoedad	1.399234	.0017278	272.05	0.000	1.395852	1.402624
sexo	.6640241	.0066417	-40.93	0.000	.6511333	.67717
fumalag1	1.015785	.0002767	57.50	0.000	1.015243	1.016327

```
      obeslag1 |   1.049157   .0005648    89.14   0.000     1.048051    1.050265
 sobrepesolag1 |   1.037582   .0004643    82.44   0.000     1.036673    1.038493
medicomb10lag1 |   .9722693    .001042   -26.24   0.000     .9702293    .9743137
         _cons |   6.60e-06   3.54e-07  -222.11   0.000     5.94e-06    7.33e-06
       ln(pob) |          1  (exposure)
------------------------------------------------------------------------------
```

LAG2

```
------------------------------------------------------------------------------
    incidentes |        IRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
     grupoedad |   1.401669    .001869   253.23   0.000      1.39801    1.405337
          sexo |   .6287316   .0070053   -41.65   0.000     .6151503    .6426126
      fumalag2 |    1.01591   .0002953    54.31   0.000     1.015332    1.016489
      obeslag2 |   1.052288   .0006391    83.92   0.000     1.051036    1.053542
 sobrepesolag2 |   1.034201   .0004911    70.82   0.000     1.033239    1.035164
medicomb10lag2 |   .9701146   .0009521   -30.91   0.000     .9682502    .9719826
         _cons |   7.69e-06   4.21e-07  -215.03   0.000     6.91e-06    8.56e-06
       ln(pob) |          1  (exposure)
------------------------------------------------------------------------------
```

LAG3

```
------------------------------------------------------------------------------
    incidentes |        IRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
     grupoedad |   1.402652   .0020482   231.72   0.000     1.398644    1.406672
          sexo |   .5972099   .0076339   -40.33   0.000     .5824336    .6123611
      fumalag3 |   1.015794   .0003173    50.17   0.000     1.015172    1.016416
      obeslag3 |   1.055649   .0007405    77.21   0.000     1.054199    1.057101
 sobrepesolag3 |   1.031841   .0005373    60.20   0.000     1.030789    1.032895
medicomb10lag3 |   .9654728   .0016614   -20.42   0.000     .9622219    .9687347
         _cons |   9.13e-06   6.23e-07  -170.13   0.000     7.99e-06    .0000104
       ln(pob) |          1  (exposure)
```

Section 1. Separate analysis for each type of drug. Adjustment for age, sex, year (random variable) and specified variables.

For briefness reasons, only models for statins and antihypertensive drugs and no exposure-effect lag are presented.

Syntax:

```
xtmepoisson incidentes grupoedad sexo fuma obes sobrepeso estatinas10, exposure(pob) ||
año:, covariance(independent) irr
```

incidentes	IRR	Std. Err.	z	P>|z|	[95% Conf.	Interval]
grupoedad	1.392497	.001603	287.62	0.000	1.389359	1.395642
sexo	.692355	.0063155	-40.31	0.000	.6800869	.7048444
fuma	1.014943	.0002595	58.01	0.000	1.014434	1.015452
obes	1.044875	.0005034	91.11	0.000	1.043889	1.045862
sobrepeso	1.040998	.0004448	94.04	0.000	1.040126	1.04187
estatinas10	.9178191	.00416	-18.92	0.000	.9097017	.9260089
_cons	4.10e-06	1.88e-07	-271.02	0.000	3.75e-06	4.48e-06
ln(pob)	1	(exposure)				

```
xtmepoisson incidentes grupoedad sexo fuma obes sobrepeso hipotensores10, exposure(pob)
|| año:, covariance(independent) irr
```

incidentes	IRR	Std. Err.	z	P>|z|	[95% Conf.	Interval]
grupoedad	1.392514	.0016029	287.66	0.000	1.389376	1.39566
sexo	.692778	.0063204	-40.23	0.000	.6805003	.7052772
fuma	1.014943	.0002595	58.01	0.000	1.014434	1.015451
obes	1.044842	.0005036	91.00	0.000	1.043855	1.04583
sobrepeso	1.041037	.000445	94.08	0.000	1.040165	1.04191
hipotensores10	.9450681	.0027863	-19.16	0.000	.9396227	.9505451
_cons	7.98e-06	5.36e-07	-174.96	0.000	7.00e-06	9.11e-06
ln(pob)	1	(exposure)				

MODELS IN TABLE 3 OF THE ARTICLE.

Dose-response analysis of the effect of prevalence of smoking habit, obesity, overweight and use of cardiovascular disease prevention drug therapy on incident ischaemic heart disease hospitalisation rates.

In these models the explanatory variables were categorised in quartiles and entered in the models as factor variables. P-value for linear trend was calculated by entering categories in the continuous scale.

For briefness reasons, only models for drug use (combined) and no exposure-effect lag are presented.

Sintax:

```
xtmepoisson incidentes grupoedad sexo fuma obes sobrepeso i.qmedicomb10, exposure(pob)
|| año:, covariance(independent) irr
```

incidentes	IRR	Std. Err.	z	P>|z|	[95% Conf.	Interval]
grupoedad	1.39253	.0016032	287.62	0.000	1.389391	1.395675
sexo	.6924933	.0063185	-40.27	0.000	.6802195	.7049887
fuma	1.014948	.0002596	58.02	0.000	1.01444	1.015457
obes	1.044876	.0005036	91.08	0.000	1.043889	1.045863
sobrepeso	1.041006	.000445	94.01	0.000	1.040134	1.041879
qmedicomb10						
2	.8451142	.0432436	-3.29	0.001	.7644698	.9342658
3	.7149764	.0365935	-6.56	0.000	.6467344	.7904191
4	.5650465	.0323431	-9.97	0.000	.5050818	.6321305
_cons	3.81e-06	2.08e-07	-228.19	0.000	3.42e-06	4.24e-06
ln(pob)	1	(exposure)				

CORRELATION ANALYSIS BETWEEN DRUG TYPES

Syntax:

```
. pwcorr estatinas hipotensores antiagreg antidiab, sig
```

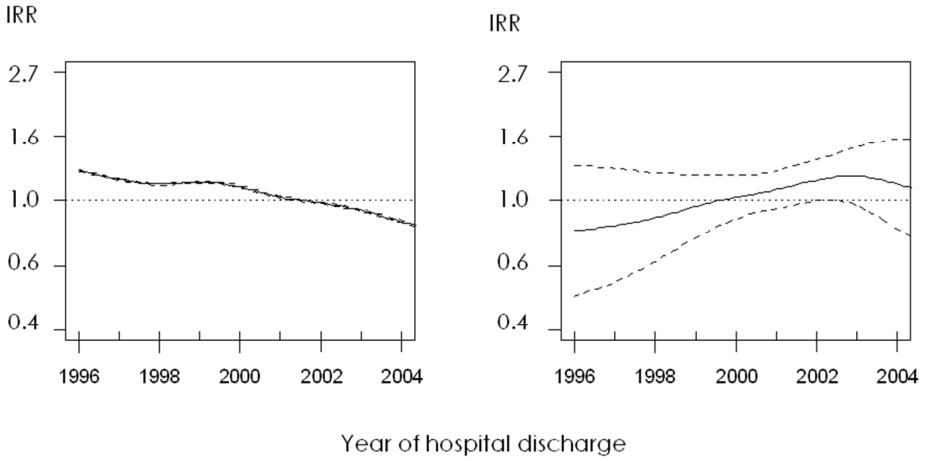
	estati~s	hipote~s	antiag~g	antidiab
estatinas	1.0000			
hipotensores	0.9782	1.0000		
	0.0000			
antiagreg	0.9820	0.9990	1.0000	
	0.0000	0.0000		
antidiab	0.9647	0.9968	0.9966	1.0000
	0.0000	0.0000	0.0000	

GAM MODELS USED IN FIGURE 2. Syntax and output in R statistical package

Syntax:

```
isquemia.data<- read.table("C:este.dat ", header=TRUE, sep="\t", fill=TRUE)

library(mgcv)
par(mfrow=c(2,2))


gamincidentes<-gam(incidentes~offset(log(pob)) + sexo + grupoedad + s(año), family=poisson, data=isquemia.data)
plot(gamincidentes, ylim=c(-1,1))
abline(h=0, lty=3)

gamincidentes<-gam(incidentes~offset(log(pob)) + sexo + grupoedad + s(año)+ sobrepeso+obes+ fuma+estatinas+hipotensores+antiagreg+antidiab, family=poisson, data=isquemia.data)

plot(gamincidentes, ylim=c(-1,1))
abline(h=0, lty=3)
```

Output:



MODELS USED TO MEASURE THE INTERANNUAL VARIABILITY EXPLAINED BY THE INDEPENDENT VARIABLES

- Model 1: variance of the random term in the complete model.

```
xtmepoisson incidentes grupoedad sexo fuma obes sobrepeso medicomb10, exposure(pob) ||
año:, covariance(independent) irr variance


------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
año: Identity                |
                  var(_cons) |   .0008784   .0003821      .0003745    .0020605
------------------------------------------------------------------------------
```

- Model 2: variance of the random term in the model adjusted for age and sex.

```
xtmepoisson incidentes grupoedad sexo, exposure(pob) || año:, covariance(independent)
irr variance


------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
año: Identity                |
                  var(_cons) |   .0291142   .0124213      .0126168    .0671833
------------------------------------------------------------------------------
```

- Calculation of interannual variability explained by the independent variables

1-(var model 1/var model 2) = 1- (.0008784/ .0291142) = 0.97

OTHER SUPPLEMENTARY MATERIALS.

IDENTIFICATION OF INCIDENT CASES. VALIDATION ANALYSIS

Table supl. 2. Sensitivity and especificity compared with detection by personal code.

		Identification by personal code				
		Duplicated case	Primary case	Total	SE	ES
Identification by sex, birth date and residence						
City 1	Duplicated case	698	135	833		
	Primary case	13	2,612	2,625		
	Total	711	2,747	3,458	98.17	95.08
City 2	Duplicated case	816	242	1,058		
	Primary case	21	2,890	2,911		
	Total	837	3,132	3,969	97.50	92.96
City 3	Duplicated case	2,923	1,752	4,675		
	Primary case	87	7,672	7,759		
	Total	3,010	9,424	12,434	97.10	81.40
City 4	Duplicated case	1,031	311	1,342		
	Primary case	0	3,730	3,730		
	Total	1,031	4,041	5,072	100.00	92.30
City 5	Duplicated case	682	211	893		
	Primary case	5	2,907	2,912		
	Total	687	3,118	3,805	99.56	93.23
City 6	Duplicated case	58	7	65		
	Primary case	1	379	380		
		59	386	445	98.30	98.19
City 7	Duplicated case	45	21	66		
	Primary case	9	573	582		
	Total	54	594	648	83.33	96.46
City 8	Duplicated case	35	2	37		
	Primary case	0	337	337		
	Total	35	339	374	100.00	99.41
TOTAL	Duplicated case	6,288	2,681	8,969		
	Primary case	136	21,100	21,236		
	Total	6,424	23,781	30,205	97.88	88.73

Table supl. 3. Age and sex distribution in validation sample

		Men	Women	Total
		18,622 (65.8%)	*9,663 (34%)*	*28,285 (100.0)*
		n (%)	n (%)	n (%)
Age group	30-44	971 (5.2)	156 (1.6)	1,127 (4.0)
	45-59	4,967 (26.7)	1,139 (11.8)	6,106 (21.6)
	60-74	7,878 (42.3)	3,491 (36.1)	11,369 (40.2)
	75 +	4,806 (25.8)	4,877 (50.5)	9,683 (34.2)

Table supl. 4. Sex and diagnostic group (CIE9-MC) distribution in validation simple.

	Men	Women	Total
	n (%)	n (%)	N (%)
Diagnostic code			
410	9,244 (49.6)	4,711 (48.8)	13,955 (49.3)
411	2,584 (13.9)	1,815 (18.8)	4,399 (15.6)
413	1,607 (8.6)	1,433 (14.8)	3,040 (10.7)
414	5,186 (27.9)	1,704 (17.6)	6,890 (24.4)

FORMULA FOR THE CALCULATION OF NUMBER OF DEFINED DAILY DOSES PER 1000 POPULATION AND PER DAY

$$DHD = \frac{NP \times PP \times Q \times 1000}{DDD \times N \text{ inhabitants} \times 365 \text{ days}}$$

Where

- NP= Number of packs sold
- PP= Number of pills per pack
- Q= Quantity of drug per pill

DDD= Daily Defined Dose