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Morbidity and Mortality Trends of Ischemic Heart Disease and Medical Interventions in Mediterranean Countries—Pre-COVID Analysis: Croatia, Slovenia, France, Italy, and Spain

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Featured Application: This comprehensive epidemiological analysis provides detailed insight into epidemiological trends of ischemic heart disease and cardiac interventions in Mediterranean countries. Variations among countries are mainly attributable to different levels of preventive care, disease patterns, and distinctive characteristics of their healthcare system. Based on the results of this study, future analyses should be focused on exploring sex differences and the appropriateness of cardiac interventions in clinical settings. There is a need to implement country-tailored and effective primary prevention strategies.

Abstract: Ischemic heart disease (IHD) morbidity and mortality indices, along with medical intervention rates, were analyzed among Mediterranean countries, Croatia, Slovenia, Spain, Italy, and France, in the pre-COVID period. Standardized IHD incidence and prevalence rates from 1990 and mortality rates from 1985 were obtained from the Global Burden of Disease Study 2017 and Health for All databases. Coronary artery bypass graft (CABG) and transluminal coronary angioplasty (TCA) rates in the 2011–2019 period were obtained from Eurostat. Trends were estimated with Joinpoint regression analysis. IHD mortality rates range from 13.6 to 74.3 for females and from 37.8 to 126.03 for males. IHD mortality rates in Croatia were 5.6-fold higher among females and 3.3-fold higher among males compared to France. All countries decreased standardized IHD prevalence and incidence rates, although the magnitude varied. The high-to-low ratio, Croatia vs. Spain, was 3.5-fold for CABG and 3.2-fold for TCA. Slovenia, as opposed to Croatia, reduced the gap for all medical indicators except for relatively high prevalence rates. Despite a significant rise in medical interventions in Croatia, ineffective clinical and public health initiatives have led to only modest declines in IHD mortality rates over the past decade.

Keywords: ischemic heart disease; mortality rates; Mediterranean countries; medical interventions rates; coronary artery bypass graft; transluminal coronary angioplasty

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1. Introduction

Cardiovascular diseases (CVD) represent a major public health problem and are the leading cause of mortality, morbidity, and disability in the European Union (EU). Mortality

of ischemic heart disease (IHD), the most common form of CVD, declined in developed countries: in 2000, it comprised about one-third of IHD mortality rates recorded in the 1960s [1]. Nevertheless, the burden and magnitude of IHD mortality varies across EU country members. Western, Northern, and Southern European countries experienced a steady decline compared to Central–Eastern European (CEE) countries. Although gaps in healthcare indicators are narrowing between new EU country members and the EU average, the total life expectancies in Croatia and neighboring Slovenia are still below the EU average (81.3 years), at 78.6 years, and 81.6 years, respectively [2]. Croatia, the last country member to join the EU in 2013, is still undergoing a multifaceted transformation process of socioeconomic and cultural convergence towards Western Europe. Still, health issues remain undervalued and insufficiently researched. The burden of disease is generally higher, and a large proportion of all deaths is attributable to behavioral risk factors [3,4]. More than half of the IHD mortality reduction is estimated to be attributable to the risk factors and the rest to medical and surgical interventions [5]. However, EU country members have different CVD prevention strategies and rates of medical interventions. Thus, Croatia has not conducted comprehensive epidemiological research, and an efficient CVD control and prevention strategy is still under development [6,7]. The CVD burden in Croatia, regardless of its Mediterranean lifestyle heritage and negative IHD mortality trend over the past two decades, remains higher compared to the EU average and other Mediterranean countries. Although these countries have been historically considered as low-risk cardiovascular regions, they have different burdens and dynamics of IHD mortality [8–10].

The aim of the study is to assess the differences in trends of SDR, standardized incidence rate (SIR), and standardized prevalence rate (SPR) of IHD as well as rate of interventions for coronary artery bypass graft (CABG) and transluminal coronary angioplasty (TCA) between new (Slovenia and Croatia) and old EU country members and Mediterranean countries (Spain, Italy, and France).

2. Materials and Methods

2.1. Data Sources and Study Design

In this observational comparative study, SDRs of IHD for all ages per 100,000 from 1985 to the latest available year before the COVID-19 pandemic for France (2017), Spain (2019), Italy (2019), Slovenia (2019), and Croatia (2019) were obtained from the Health for All database [11]. SDR for IHD (ICD-10 codes: I20–I25) was directly standardized to the European Standard Population.

Standardized incidence and prevalence rates of IHD from 1990 to 2017 were obtained from the Global Burden of Disease Study 2017 (GBD 2017) [12].

The crude rates of CABG and TCA per 100,000 population from 2011 to 2019 were obtained from the Eurostat database—Cardiovascular Disease Statistics 2019, Statistics Explained [13]. We calculated the annual TCA:CABG rates ratio by dividing crude rates of TCA with crude rates of CABG. To quantify the magnitude of differences, we compared high-to-low rates and expressed them as high-to-low ratios.

2.2. Statistical Analyses

To estimate the changes in IHD morbidity and mortality trends as well as the trend of medical interventions, we used the Joinpoint Regression Program, Version 5.0.2, from the National Cancer Institute, Bethesda, MD, USA) (http://surveillance.cancer.gov/joinpoint/, accessed on 29th February 2024) [14]. Joinpoint analysis identified points at which a significant change of direction in the trend occurred. To determine the number of joinpoints or for the Model Selection Method, joinpoint uses the Weighted Bayesian Information Criterion (WBIC), which combines the BIC and a version of BIC with a harsher penalty term (BIC3). This new default method is less conservative, and joinpoints are more easily detected than in the previous default choice of permutation tests. The model also computes an estimated annual percentage change (APC) and average APC (AAPC) over the entire

study period [15]. All estimates are presented with 95% confidence intervals (CIs) calculated using the empirical quantile method [16]. Additionally, for Slovenia and Croatia, the percentage change in IHD mortality rates was estimated for the most recent data, with 1991 as the baseline.

We compared average incidence, prevalence, mortality standardized rates, and average CABG and TCA rates among countries for the last ten years with the ANOVA or Kruskal–Wallis test, depending on the normality of data distribution.

Data were statistically analysed using the JASP program (JASP Team (2020) (Version 0.14.1) [Computer software]. A p-value of 0.05 was used for the level of statistical significance.

3. Results

For the 1985–2019 period, the SDR of IHD was available each year for Spain, Slovenia, and Italy. Data were missing for France for the following years: 2015, 2016, 2018, and 2019, and for Croatia for 2018.

According to the latest year, the SDRs were lowest in France (2017) and highest in Croatia (2019); for females, they ranged from 13.16 to 74.28, and for males, from 37.84 to 126.03. The high-to-low ratio for Croatia vs. France was 5.6-fold for females and 3.3-fold for males. Male mortality rates exceeded those of females, and the ratios were as follows: France 2.88, Spain 2.78, Slovenia 2.51, Italy 2.10, and Croatia 1.70.

3.1. Trends in Standardized Death Rates of IHD from 1985 to 2019 According to Sex

3.1.1. Standardized Death Rates of IHD among Females

IHD mortality trends (1985–2019), expressed as AAPC, among females significantly decreased in Spain −3.05 (95% CI −3.20, −2.90), France −4.01 (95% CI −4.16, −3.87) Italy −2.76, (95% CI −2.89, −2.63), and Slovenia −3.42, (95% CI −3.83, −2.84). Conversely, Croatia only significantly increased IHD mortality rates by 1.85% (95% CI 1.27, 2.47)

Slovenia significantly increased by +21.55 from 1987 to 1991 and Croatia by +46.08 from 1990 to 1993. In the latest time period, all countries had a significant and negative APC; Croatia had the lowest at −1.91%, and Slovenia had the highest decrease at −5.06% (Figure 1, Table 1).

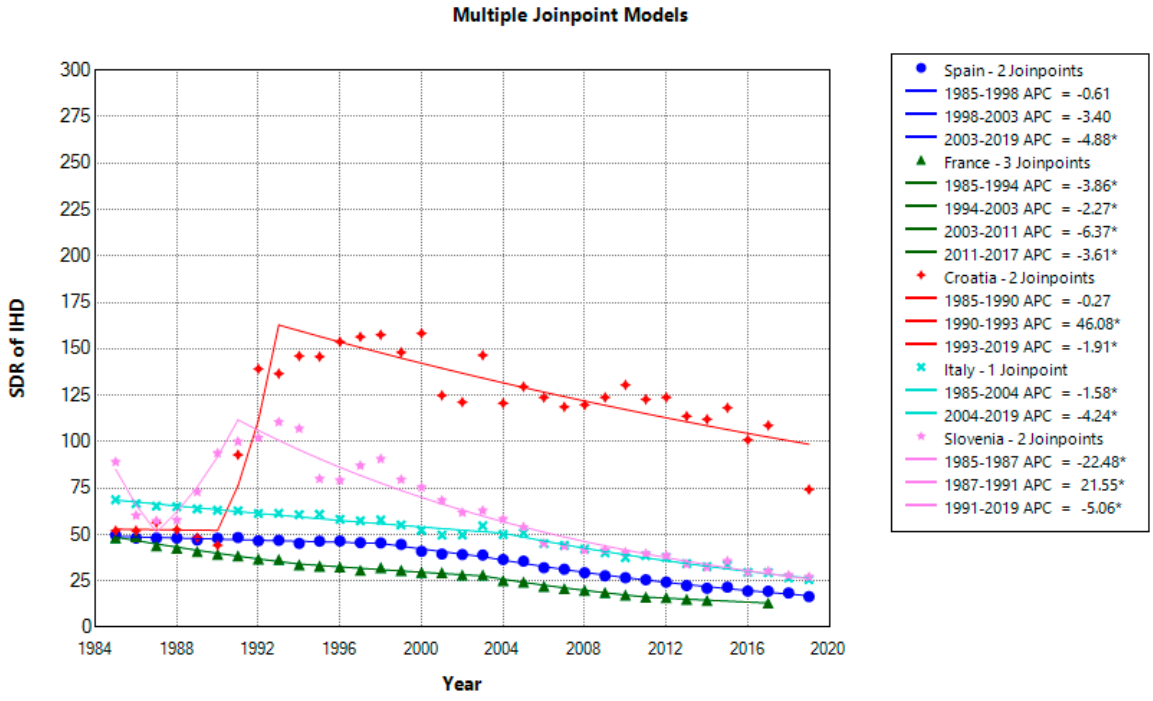

Figure 1. Standardized death rates of ischemic heart disease—females. * $p < 0.05$.

Table 1. Joinpoints and annual percentage changes of IHD mortality among females.

Country	Period	APC	Period	APC	Period	APC	Period	APC
Spain	1985–1998	−0.61	1998–2003	−3.40	2003–2019	−4.88 *		
France	1985–1994	−3.86 *	1994–2003	−2.27 *	2003–2011	−6.37 *	2011–2017	−3.61 *
Croatia	1985–1990	−0.27	1990–1993	+46.08 *	1993–2019	−1.91 *		
Italy	1985–2004	−1.58 *	2004–2019	−4.24 *				
Slovenia	1985–1987	−22.48 *	1987–1991	+21.55 *	1991–2019	−5.06 *		

APC = annual percentage changes; * $p < 0.05$.

When we compared 2019 vs. 1991 data, the percentage change was −72.85% in Slovenia and −20.10% in Croatia. The mean SDRs among females during the last ten years differed significantly ($p = 0.003$). Croatia (112.92) had substantially higher mortality than Slovenia (33.66), Italy (32.63), Spain (21.65), and France (17.49) ($p < 0.001$). France had significantly lower rates than Slovenia and Italy ($p < 0.001$) and similar rates to Spain ($p = 0.77$). Italy had significantly higher rates than Spain ($p = 0.029$), similar to Slovenia ($p = 0.99$). Spain had significantly lower rates than Slovenia ($p = 0.01$).

3.1.2. Standardized Death Rates of IHD among Males

During 1985–2019 IHD mortality trends among males, expressed as AAPC, significantly decreased in France −3.43%, 95% CI [−3.60, −3.30], Italy −2.92%, 95% CI [−3.05, −2.80], Slovenia −2.85%, 95% CI [−3.20, −2.42] and Spain −2.55%, 95% CI [−2.64, −2.46]. Croatia also decreased mortality by −0.18%, 95% CI [−0.78%, 0.38%], but without significance.

Spain, Italy, and France experienced a decline in male mortality, while Slovenia increased in 1988–1992 and Croatia in 1990–1993. All countries significantly decreased in the latest time periods, from −2.12% in France to −10.62% in Croatia (Figure 2, Table 2).

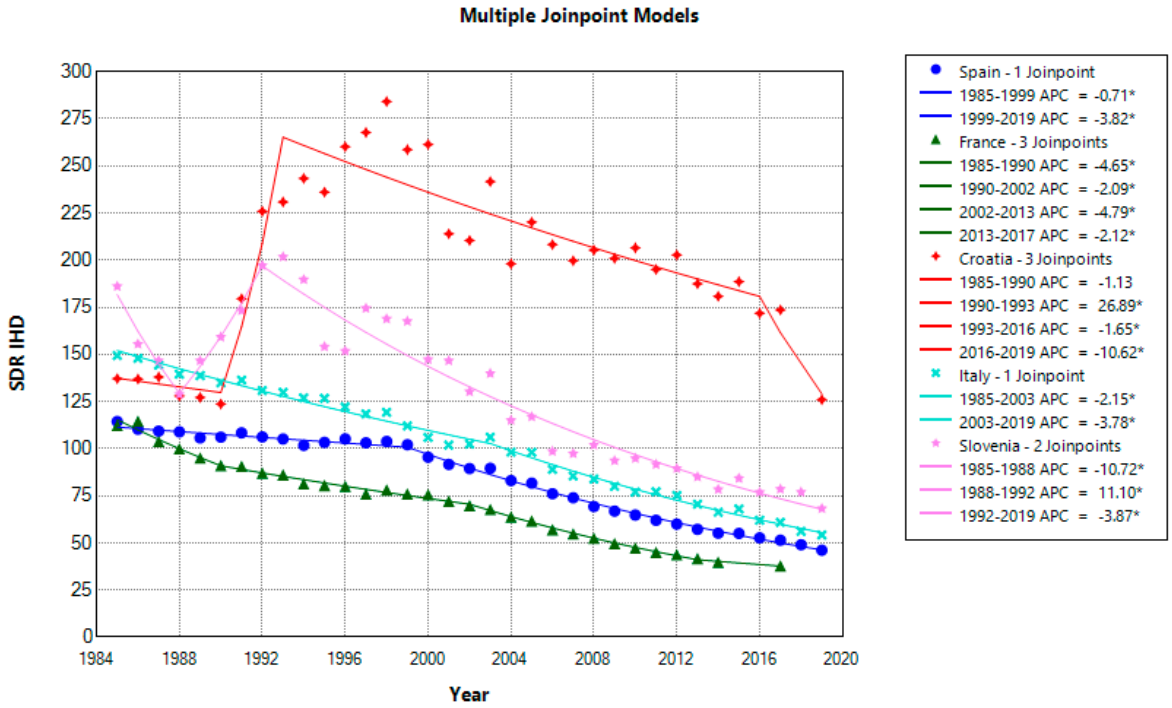

Figure 2. Standardized death rates of ischemic heart disease—males. * $p < 0.05$.

When SDR in 2019 vs. 1991 were compared, the percentage change of IHD mortality in Slovenia was −60.60% and in Croatia −29.80%.

There were significant differences among mean SDR during the last ten years; Croatia had the highest values (183.38), followed by Slovenia (82.46), Italy (66.78), Spain (55.38), and France (46.97) ($p < 0.001$). Croatia had significantly higher rates compared with the other four countries ($p < 0.001$). France had significantly lower rates than Slovenia and Italy ($p < 0.001$) and similar to Spain ($p = 0.55$). Italy had rates similar to Spain's ($p = 0.25$) and significantly lower than Slovenia's ($p = 0.05$). Spain had significantly lower rates than Slovenia ($p < 0.001$).

Table 2. Joinpoints and annual percentage for male IHD mortality (1985–2019).

Country	Period	APC	Period	APC	Period	APC	Period	APC
Spain	1985–1999	−0.71 *	1999–2019	−3.82 *				
France	1985–1990	−4.65 *	1990–2002	−2.09 *	2002–2013	−4.79 *	2013–2017	−2.12 *
Croatia	1985–1990	−1.13	1990–1993	+26.89 *	1993–2016	−1.65 *	2016–2019	−10.62 *
Italy	1985–2003	−2.15 *	2003–2019	−3.78 *				
Slovenia	1985–1988	−10.72 *	1988–1992	+11.10 *	1992–2019	−3.87 *		

APC = annual percentage changes * $p < 0.05$.

3.2. Trends in Standardized Incidence Rates of IHD from 1990 to 2017 According to Sex

3.2.1. SIR of IHD among Females

All countries significantly decreased SIR of IHD for females from 1990 to 2017, however with different AAPC; Spain by −1.71, 95% CI [−1.73, −1.70], Croatia by −1.69%, 95% CI [−1.71, −1.67], Slovenia by −1.38%, 95% CI [−1.39, −1.37], Italy by −1.07% 95% CI [−1.10, −1.04], and France by −0.98%, 95% CI [−0.99, −0.97]. Trends per time periods are presented in Figure 3 and Table 3.

Percentage changes in SIR between 2017 vs. 1990 were as follows: Spain −37%, Croatia −37%, Slovenia −31%, Italy −26%, and France −23%. The high-to-low ratio for 2017 was 1.85 (Croatia 122.89 vs. Spain 66.18).

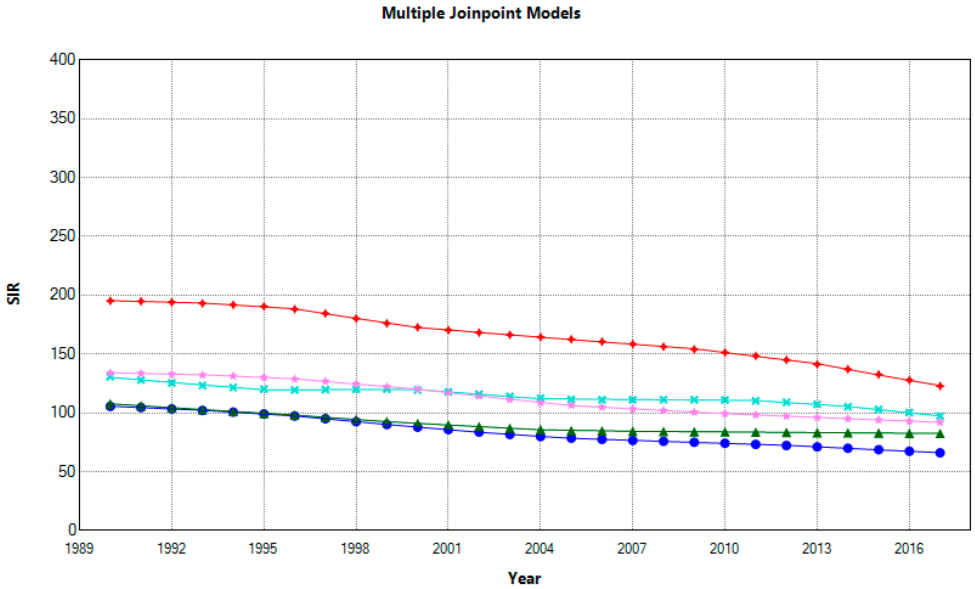

Figure 3. Trends in SIR of IHD for females. Spain = blue, France = dark green, Croatia = red, Italy = turquoise, Slovenia = violet.

Table 3. Joinpoint analysis for standardized incidence rates of IHD among females (1990 to 2017).

Country	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC
Spain	1990–1993	−1.08 *	1993–1996	−1.61 *	1996–2004	−2.48 *	2004–2012	−1.17 *	2012–2017	−1.77 *		
France	1990–1996	−1.54 *	1996–1999	−1.92 *	1999–2004	−1.54 *	2004–2007	−0.50 *	2007–2017	−0.22 *		
Croatia	1990–1993	−0.34 *	1993–1996	−0.86 *	1996–2000	−2.17 *	2000–2009	−1.22 *	2009–2013	−2.10 *	2013–2017	−3.47 *
Italy	1990–1995	−1.68 *	1995–2000	+0.04	2000–2004	−1.68 *	2004–2011	−0.19 *	2011–2014	−1.51 *	2014–2017	−2.63 *
Slovenia	1990–1993	−0.43 *	1993–1996	−0.86 *	1996–2000	−1.75 *	2000–2005	−2.43 *	2005–2010	−1.33 *	2010–2017	−1.10 *

APC = annual percentage changes * $p < 0.05$.

The mean SIR for females in the last ten years were Spain 71.97, France 83.56, Slovenia 97.45, Italy 107.05, and Croatia 143.27. Croatia had significantly higher mean rates, while Spain had a significantly lower rate than the other countries ($p < 0.001$). France had a significantly lower mean rate than Slovenia and Italy ($p < 0.001$). Italy had a significantly higher rate than Slovenia ($p < 0.001$).

3.2.2. SIR of IHD among Males

From 1990 to 2017, AAPC of SIR of IHD for males significantly decreased in all countries: Croatia by −1.79%, 95% CI [−1.80, −1.77], Slovenia by −1.25%, 95% CI [−1.25, −1.24], Spain by −1.22, 95% CI [−1.23, −1.21%], France by −1.04%, 95% CI [−1.06, −1.03], and Italy by −0.88% 95% CI [−0.89, −0.86].

The percentage changes of SIR from 1990 to 2017 were as follows: Croatia −39%, Slovenia −29%, Spain −28%, France −25%, and Italy −21%. Trends per time periods are presented in Figure 4 and Table 4. The high-to-low ratio for 2017 was 1.3, Croatia 210.62 vs. Spain 161.01.

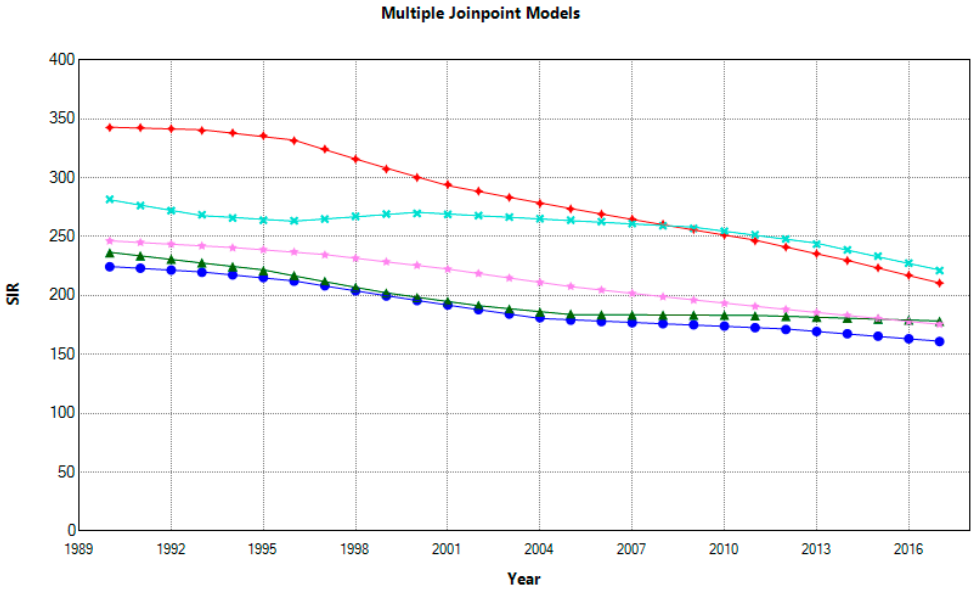

Figure 4. Trends in SIR of IHD for males. Spain = blue, France = dark green, Croatia = red, Italy = turquoise, Slovenia = violet.

The mean values of SIR for males over the last ten years were as follows: Spain 170.31, France 181.76, Slovenia 188.41, Italy 245.10, and Croatia 239.73. Croatia had a significantly higher mean rate than France, Slovenia, and Spain ($p < 0.001$) and non-significantly lower rate than Italy ($p = 0.93$). France had a significantly higher rate than Spain ($p < 0.001$) and a significantly lower rate than Italy ($p < 0.001$) but non-significantly lower than Slovenia ($p = 0.16$). Italy had a significantly higher rate than Slovenia and Spain ($p < 0.001$). Spain had a significantly lower rate than Slovenia ($p < 0.001$).

Table 4. Joinpoint analysis for male IHD age standardized incidence rates (1990–2017).

Country	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC
Spain	1990–1993	−0.69 *	1993–1996	−1.16 *	1996–2004	−2.01 *	2004–2012	−0.63 *	2012–2017	−1.24 *		
France	1990–1995	−1.30 *	1995–1999	−2.27 *	1999–2002	−1.83 *	2002–2005	−1.32 *	2005–2011	−0.07 *	2011–2017	−0.43 *
Croatia	1990–1993	−0.20 *	1993–1996	−0.87 *	1996–2001	−2.44 *	2001–2011	−1.70 *	2011–2014	−2.37 *	2014–2017	−2.85 *
Italy	1990–1993	−1.62 *	1993–1996	−0.59 *	1996–2000	+0.71 *	2000–2009	−0.53 *	2009–2013	−1.34 *	2013–2017	−2.63 *
Slovenia	1990–1994	−0.58 *	1994–1997	−0.83 *	1997–2001	−1.33 *	2001–2004	−1.74 *	2004–2007	−1.51 *	2007–2017	−1.38 *

APC = annual percentage changes * $p < 0.05$.

3.3. Trends in Standardized Prevalence Rates of IHD from 1990 to 2017 According to Sex

3.3.1. SPR of IHD among Females

From 1990 to 2017, the AAPC of SPR of IHD among females significantly decreased in Italy by −1.13%, 95% CI [−1.14, −1.13], Slovenia by −0.93%, 95% CI [−0.93, −0.93], Croatia by −0.80%, 95% CI [−0.80, −0.80], France by −0.79%, 95% CI [−0.79, −0.78], and Spain by −0.59%, 95% CI [−0.60, −0.58].

Percentage changes of SPR from 1990 to 2017 were as follows: Spain −15%, France −19%, Croatia −20%, Slovenia −22%, and Italy −27%. The high-to-low ratio for 2017 was 2.11, Croatia 2046.21 vs. France 968.69. Trends per time periods are presented in Figure 5 and Table 5.

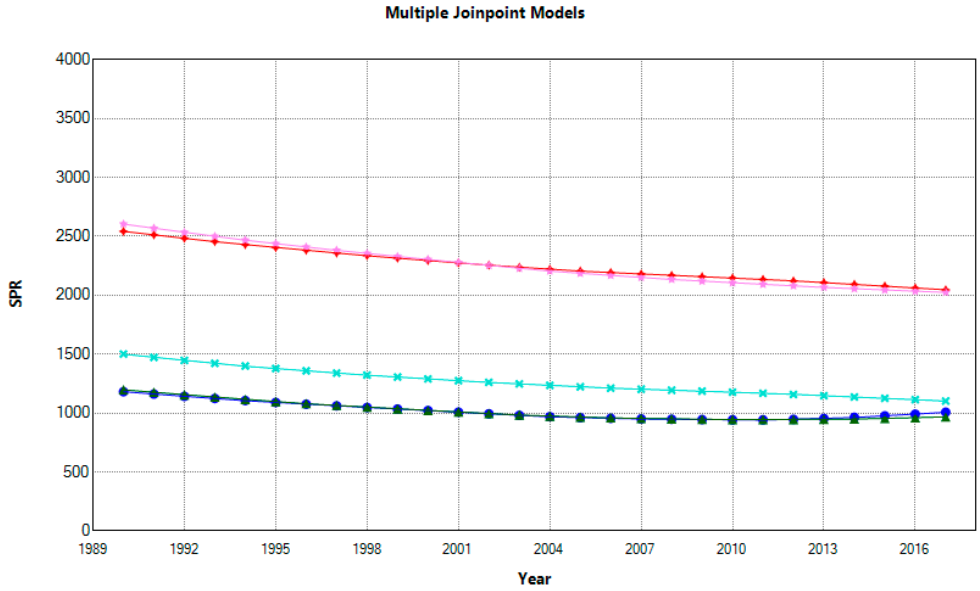

Figure 5. Trends in SPR of IHD from 1990 to 2017 for females. Spain = blue, France = dark green, Croatia = red, Italy = turquoise, Slovenia = violet.

Table 5. Joinpoint analysis for female IHD age standardized prevalence rates from 1990 to 2017.

Country	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC
Spain	1990–1994	−1.64 *	1994–2004	−1.31 *	2004–2007	−0.64 *	2007–2011	−0.23 *	2011–2014	+0.74 *	2014–2017	+1.52 *
France	1990–1996	−1.71 *	1996–2003	−1.32 *	2003–2006	−0.83 *	2006–2010	−0.37 *	2010–2014	+0.14 *	2014–2017	+0.61 *
Croatia	1990–1993	−1.16 *	1993–1998	−0.99 *	1998–2002	−0.87 *	2002–2005	−0.75 *	2005–2012	−0.54 *	2012–2017	−0.72 *
Italy	1990–1994	−1.75 *	1994–1998	−1.39 *	1998–2002	−1.18 *	2002–2006	−0.97 *	2006–2012	−0.73 *	2012–2017	−1.01 *
Slovenia	1990–1994	−1.34 *	1994–1997	−1.18 *	1997–2004	−1.09 *	2004–2008	−0.82 *	2008–2013	−0.64 *	2013–2017	−0.52 *

APC = annual percentage changes * $p < 0.05$.

The mean values of SPR for females over the last ten years were as follows: France 953.08, Spain 961.79, Italy 1156.28, Slovenia 2083.21, and Croatia 2118.03. Croatia had a significantly higher mean rate than France, Italy, and Spain ($p < 0.001$) and was similar

to Slovenia ($p = 0.36$). France had a significantly lower mean rate than Italy and Slovenia ($p < 0.001$) and a non-significantly lower rate than Spain ($p = 0.72$). Italy had a significantly higher mean rate than Spain and lower rate than Slovenia ($p < 0.001$). Spain had a significantly lower mean rate than Slovenia ($p < 0.001$).

3.3.2. SPR of IHD for Males

From 1990 to 2017, the AAPC of SPR of IHD for males significantly decreased: Slovenia by −0.87% 95% CI [−0.87, −0.87], Croatia by −0.72% 95% CI [−0.72, −0.72], Italy by −0.59% 95% CI [−0.60, −0.57], France by −0.39%, 95% CI [−0.40, −0.38], and Spain by −0.35%, 95% CI [−0.36, −0.35]. Trends per time periods are presented in Figure 6 and Table 6.

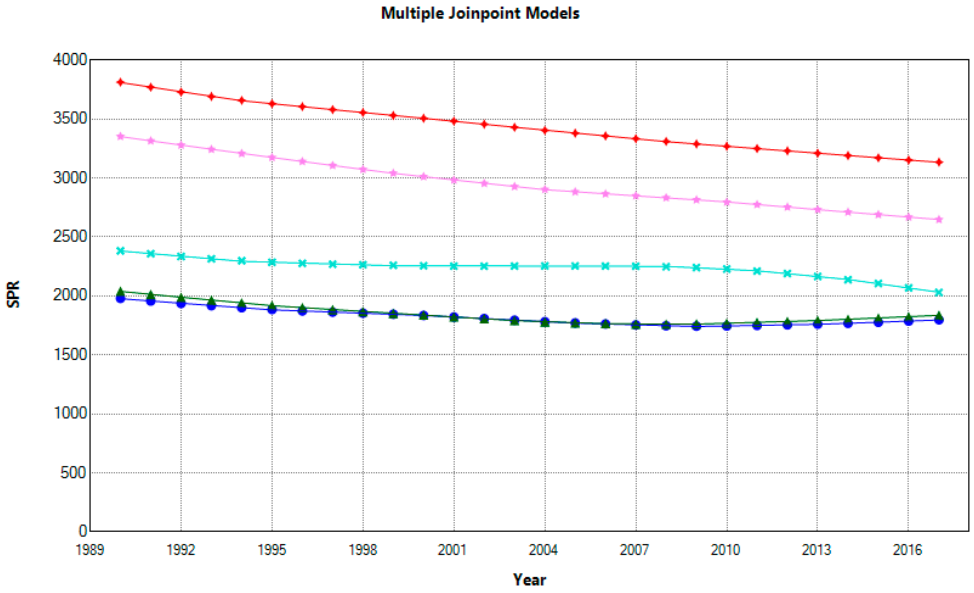

Figure 6. Trends in SPR of IHD from 1990 to 2017 for males. Spain = blue, France = dark green, Croatia = red, Italy = turquoise, Slovenia = violet.

Table 6. Joinpoint analysis for male IHD age standardized prevalence rates from 1990 to 2017.

Country	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC
Spain	1990–1995	−0.98 *	1995–2000	−0.51 *	2000–2005	−0.72 *	2005–2009	−0.40 *	2009–2013	+0.25 *	2013–2017	+0.53 *
France	1990–1995	−1.22 *	1995–2003	−0.85 *	2003–2006	−0.50 *	2006–2009	−0.06	2009–2013	+0.43 *	2013–2017	+0.61 *
Croatia	1990–1994	−1.03 *	1994–2001	−0.69 *	2001–2005	−0.75 *	2005–2009	−0.68 *	2009–2017	−0.60 *		
Italy	1990–1994	−0.93 *	1994–1999	−0.33 *	1999–2008	−0.03 *	2008–2011	−0.56 *	2011–2014	−1.12 *	2014–2017	−1.71 *
Slovenia	1990–1999	−1.08 *	1999–2004	−0.93 *	2004–2010	−0.61 *	2010–2017	−0.78 *				

APC = annual percentage changes * $p < 0.05$.

Percentage changes in SPR from 1990 to 2017 were as follows: Spain −9%, France −10%, Italy −15%, Croatia −18%, and Slovenia −21%. The high-to-low ratio for 2017 was 1.74, Croatia 3134.45 vs. Spain 1798.03.

The mean values of SPR for males in the ten last available years were as follows: Spain 1762.60, France 1789.96, Italy 2170.73, Slovenia 2751.98, and Croatia 3230.72. Croatia had a significantly higher mean rate than the other four countries ($p < 0.001$). France had a significantly lower mean rate than Italy and Slovenia ($p < 0.001$) and a non-significantly lower rate than Spain ($p = 0.07$). Italy had a significantly higher mean rate than Spain and significantly lower rate than Slovenia ($p < 0.001$). Spain had a significantly lower mean rate than Slovenia ($p < 0.001$).

3.4. Trends in the Coronary Artery Bypass Graft and Transluminal Coronary Angioplasty Rates in the 2011–2019 Period

The CABG and TCA rates are presented in Figures 7 and 8, Tables 7 and 8. The TCA:CABG ratio is presented in Figure 9 and Table 9.

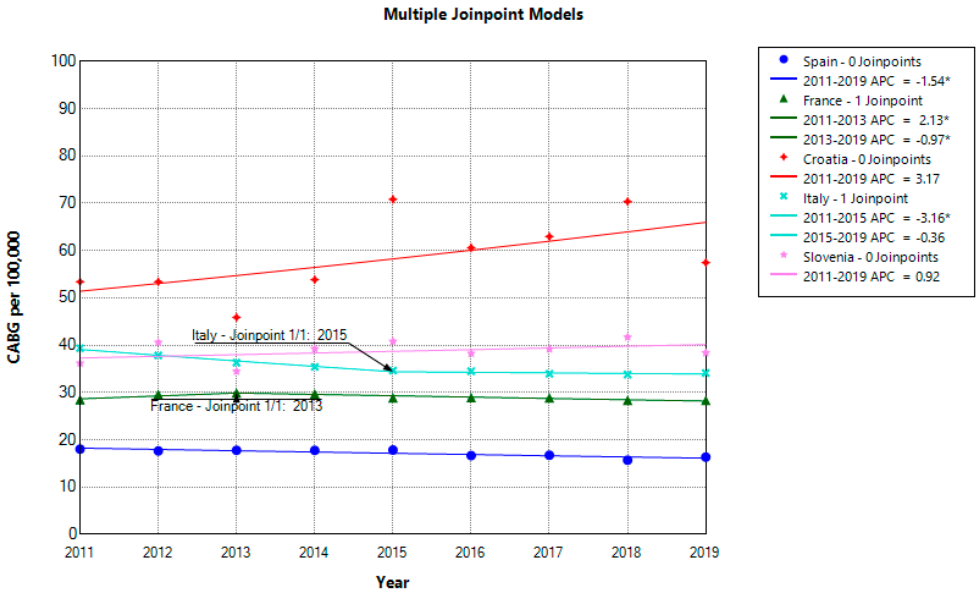

Figure 7. CABG per 100,000 population from 2011 to 2019. * $p < 0.05$.

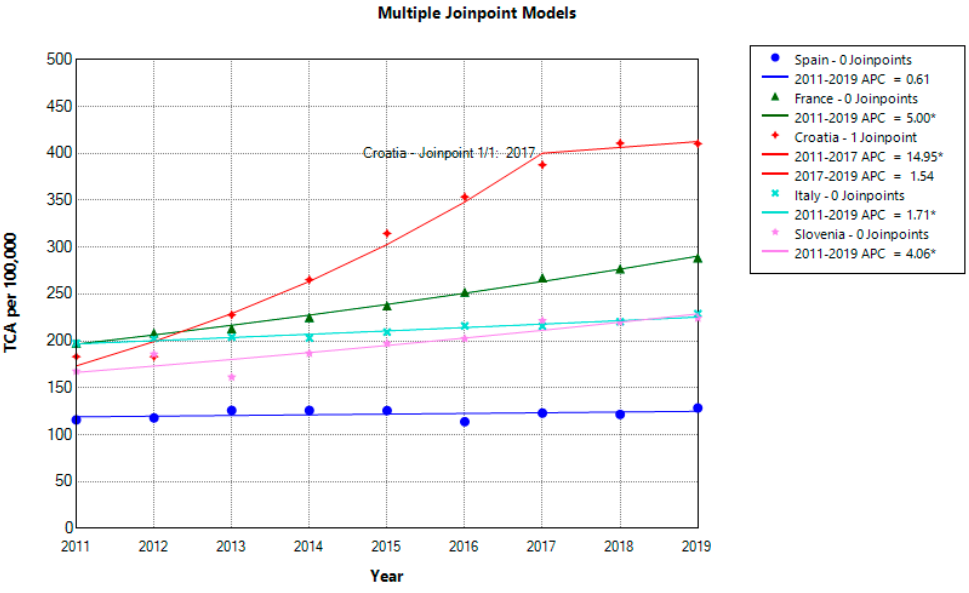

Figure 8. TCA per 100,000 population from 2011 to 2019. * $p < 0.05$.

Table 7. Joinpoint analysis for CABG per 100,000 population (2011–2019).

Country	Period	APC	Period	APC
Spain	2011–2019	−1.54 *		
France	2011–2013	+2.13	2013–2019	−0.97 *
Croatia	2011–2019	+3.17		
Italy	2011–2015	−3.16 *	2015–2019	−0.36
Slovenia	2011–2019	+0.92		

APC = annual percentage changes; CABG = coronary artery bypass graft; * $p < 0.05$.

Table 8. Joinpoint analysis for TCA per 100,000 population (2011–2019).

Country	Period	APC	Period	APC
Spain	2011–2019	+0.61		
France	2011–2019	+5.00 *		
Croatia	2011–2017	+14.95 *	2017–2019	+1.54
Italy	2011–2019	+1.71 *		
Slovenia	2011–2019	+4.06 *		

APC = annual percentage changes; TCA = transluminal coronary angioplasty; * $p < 0.05$.

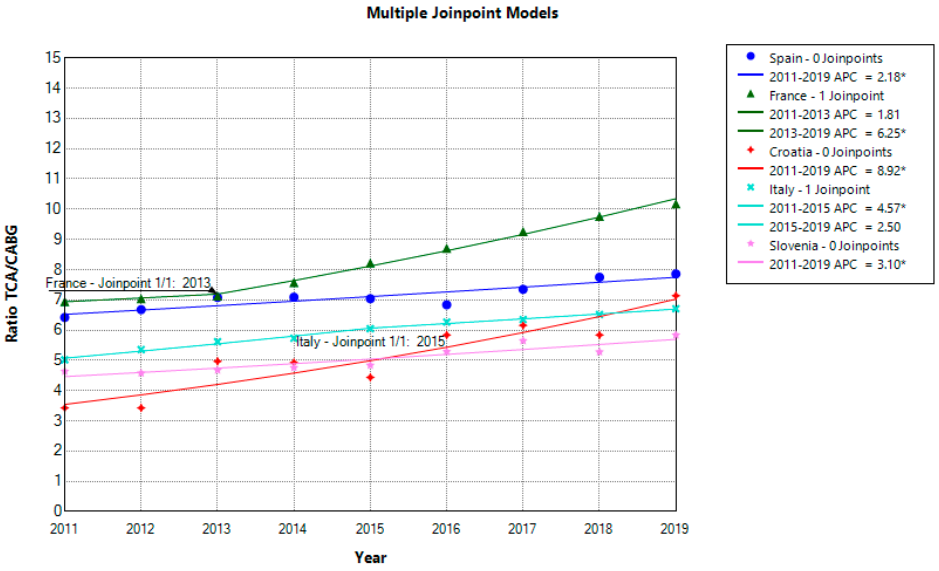

Figure 9. TCA:CABG ratio (2011–2019). * $p < 0.05$.

Table 9. Joinpoint analysis for the TCA:CABG ratio from 2011 to 2019.

Country	Period	APC	Period	APC
Spain	2011–2019	+2.18 *		
France	2011–2013	+1.81	2013–2019	+6.25 *
Croatia	2011–2019	+8.92 *		
Italy	2011–2015	+4.57 *	2015–2019	+2.50 *
Slovenia	2011–2019	+3.10 *		

APC = annual percentage changes; CABG = coronary artery bypass graft; TCA = transluminal coronary angioplasty; * $p < 0.05$.

From 2011 to 2019, the AAPC of CABG rate per 100,000 population significantly decreased in Spain and Italy: −1.54%, 95% CI [−2.45, −0.62] and −1.77%, 95% CI [−2.25, −1.29]. In France, the rate decreased by −0.21%, 95% CI [−0.49, 0.06]. Slovenia and Croatia had an increase of +0.92%, 95% CI [−1.39, 3.20], by +3.17%, with a 95% CI [−0.28, 6.78] (Figure 7, Table 7). For Croatia (57.46) vs. Spain (16.35), the high-to-low ratio for 2019 was 3.51.

The mean values of CABG rates in the 2011–2019 period were as follows: Spain 17.18, France 29.02, Italy 35.55, Slovenia 38.76, and Croatia 58.75. Croatia had a significantly higher mean rate than the other four countries ($p < 0.001$). France had a significantly lower mean rate than Italy and Slovenia ($p < 0.001$) and a significantly higher rate than Spain ($p < 0.001$). Italy had a significantly lower mean rate than Slovenia ($p = 0.04$) and a significantly higher rate than Spain ($p < 0.001$). Spain had a significantly lower mean rate than Slovenia ($p < 0.001$).

From 2011 to 2019, the AAPC of the TCA rate per 100,000 population significantly increased in Italy by +1.71%, 95% CI [1.26, 2.15], in Slovenia by +4.06%, 95% CI [2.38, 5.76],

in France by +5.00%, 95% CI [4.57, 5.43], and in Croatia by +11.44%, 95% CI [9.97, 13.10]. Spain had the lowest rate and non-significant increase of +0.61%, 95% CI [−1.19, 2.46] (Figure 8, Table 8). The high-to-low ratio for Croatia (410.26) vs. Spain (128.59) for 2019 was 3.19.

The mean values of TCA rates were as follows: Spain 122.12, Slovenia 196.46, Italy 210.93, France 240.85, and Croatia 304.09. Croatia had a significantly higher mean rate than Slovenia ($p = 0.05$) and Spain ($p < 0.001$), and a similar rate to France ($p = 0.36$) and Italy ($p = 0.09$). France had a significantly higher mean rate than Spain ($p < 0.001$) and Slovenia ($p = 0.03$) and a non-significantly higher rate than Italy ($p = 0.14$). Italy had a significantly higher mean rate than Spain ($p < 0.001$) and was similar to Slovenia ($p = 0.46$). Spain had a significantly lower mean rate than Slovenia ($p < 0.001$).

The TCA:CABG ratio has continuously and significantly increased, and AAPCs from 2011 to 2019 were as follows: Croatia with +8.9%, 95% CI [5.37, 12.65], France with +5.1, 95% CI [4.68, 5.85], Italy +3.5%, 95% CI [2.75, 4.31], Slovenia +3.1%, 95% CI [1.24, 5.00], and Spain +2.2%, 95% CI [1.18, 3.21] (Figure 9 and Table 9). The high-to-low ratio for France (10.18) vs. Slovenia (5.84) for 2019 was 1.74.

4. Discussion

This study of IHD mortality, prevalence, incidence, and rates of medical interventions over three decades revealed pronounced differences between new and old Mediterranean EU country members.

Female IHD mortality has significantly decreased from 1985 to 2019 in all countries except Croatia (+1.85%). The extent and patterns differ. France had the highest average reduction (AAPC) at −4.01%, while Italy had the lowest at −2.76%. Croatia and Slovenia had irregular patterns and upward IHD trends that could have been attributable to massive political, social, and healthcare changes accompanied by war. Nonetheless, potential changes in coding practice also cannot be excluded (Figures 1 and 2). The comparison of mean mortality rates among females over the last ten years showed a significantly higher rate in Croatia (112.92) than in Slovenia (33.66), Italy (32.63), Spain (21.65), and France (17.49). France and Spain had similar rates, as well as Italy and Slovenia, which, as opposed to Croatia, narrowed the gap with old EU country members in female IHD mortality.

Male mortality has also significantly decreased in all countries except Croatia, with a negligible and non-significant reduction of −0.18%. As in the case of female IHD mortality, France had the highest average decrease over the 1985–2019 period of −3.43%. Within the last decade, Croatian males had a significantly higher mortality (183.38) compared to males in Slovenia (82.46), Italy (66.78), Spain (55.38), and France (46.97). Still, Slovenia managed to reduce the gap but less successfully compared with the reduction in female IHD mortality.

Moreover, comparing the IHD mortality data for new country members, Slovenia and Croatia, for 2019 vs. 1991, showed significant between-country differences. While Slovenia considerably reduced mortality for females and males by −72.85% and −60.60%, this reduction in Croatia was much lower, at −29.80% for males and −20.10% for females. These differences can be explained by unsuccessful Croatian healthcare reforms, which systematically neglected politically sensitive aims. Health efficiency still represents a significant healthcare system problem [17]. Although the EU makes considerable effort to equalize health care across country members, distinctions deep-rooted in their historical, political, socioeconomic, and health traditions remain prominent. Cardioprotective Mediterranean heritage in the form of diet and lifestyle seems lost in transition, and the East–West health gap is still visible. Croatia has 5.6-fold higher IHD mortality for females and 3.3-fold higher IHD mortality for males compared to France. Despite the short coastline, the French paradox most likely contributed to the lowest mortality among all analyzed countries. Yet, the term Croatian paradox was also coined to address high CVD mortality, which is more similar to that in CEE than in Mediterranean countries [18,19] (Figures 1 and 2).

The excess of male IHD mortality is expected, and male-to-female ratios ranged from 2.88 in France to 1.70 in Croatia. Male disadvantages can partly explain such variations, but smoking might have a crucial role. More harmful effects of smoking on females narrowed the ratio and often are overlooked. In many European countries, male smoking is declining and/or has reached a plateau, whereas female smoking is increasing [20]. Besides smoking, sex-specific mortality differences also cannot exclude potential health disparities regarding prevention, diagnosis, treatment strategies, and cardiovascular outcomes [21,22].

Countries with a decline in IHD mortality efficiently control major risk factors and provide better medical care but also address relevant political, economic, and social determinants [23]. Various models consistently indicate that risk factor reduction explains a more significant proportion of mortality decline than medical treatments [24]. In general, prevention confirmed its effectiveness, and modelling studies suggested that 50–60% of the decrease in IHD mortality in Europe is attributable to prevention strategies at both population and individual levels [25,26]. Primordial prevention seems incredibly demanding since social determinants extend outside the health sector. Studies suggest that social factors are equally important as traditional risk factors such as smoking, dyslipidemia, and hypertension [27,28]. In high-income countries, a steady decline in IHD mortality since the 1980s has been attributed to primary and secondary prevention. However, the effects of prevention may hardly be distinguishable within the CV risk continuum [1,29]. Cardiac rehabilitation, pivotal in secondary prevention, is often neglected, with a fragmented uptake across Europe [30]. Secondary prevention is focused on mortality reduction among cardiac patients as opposed to primary prevention, which largely reduces the incidence of IHD.

Hypertension, increased cholesterol levels, BMI, and high fasting glucose remain the most important metabolic risk factors for the reduction in IHD mortality [29,31]. High systolic blood pressure mostly contributed to CVD mortality in both genders, more in Central than in Western Europe, at 62% vs. 51% in males and 60% vs. 50% in females, respectively. High total cholesterol levels, positioned second for both genders, contributed 20% to 30%. High BMI and high fasting glucose plasma, each responsible for around 20% or less of the CVD mortality burden, were ranked last [32]. Still, their relative contribution is complex, and significant between-country variations indicate an urgent need for further country-specific studies. Croatia's highest IHD mortality among analyzed countries is most likely also mainly attributable to hypertension. Insufficient awareness and lack of a formal public health policy, inadequate health promotion, failure to invest in prevention, underdiagnosed and undertreated patients made hypertension one of the most urgent public health problems [33]. According to the hypertension prevalence, Croatia is among the top-ranked countries in the world [34,35].

Morbidity measures such as incidence and prevalence also describe the dynamic of disease in the population. All countries decreased incidence, and AAPCs ranged for females from −23% in France to −37% in Croatia and Spain and males from −21% in Italy to −39% in Croatia. In 2017, for females and males in Croatia vs. Spain, high-to-low ratios were 1.85 and 1.3, respectively. Nonetheless, a dynamic pattern of decreasing trends for females narrowed the gap between first-ranked Croatia and second-ranked Italy. Furthermore, over two decades, the incidence rate reduction for males changed, where Croatia lost the disadvantageous first place, subsequently replaced by Italy (Figure 3). However, despite the SIR reduction, between-country differences for females remained significant. At the same time, males in Croatia and Italy, as well as France and Slovenia, had similar rates. (Figure 4)

The negative trend in prevalence, as opposed to incidence, is relatively uniform for both genders. As indicated, AAPCs for females ranged from −0.59% in Spain to −1.13% in Italy, and males from −0.35% in Spain to −0.87% in Slovenia (Figures 5 and 6).

Compared with 1990, the SPR percentage change for females ranged from −15% in Spain to −27% in Italy and for males from −9% in Spain to −21% in Slovenia. There are considerable differences in disease burden among countries, and in 2017, Croatia had the highest SPR with a high-to-low ratio for females of 2.11 compared to France, and a

ratio of 1.74 for males compared to Spain. During the last decade, Croatian and Slovenian females had significantly higher SPRs than females in other analysed countries. Still, Slovenian males had significantly lower rates than Croatian males. As a measure of disease burden, the prevalence is not the most appropriate way to measure the effect of risk factors. Nonetheless, it can help assess healthcare needs and assist with the future planning of healthcare services and interventions [36].

CABG and TCA rates also substantially varied between countries over the 2011–2019 period. Old EU country members, namely Italy, Spain, and France, had negative AAPC of CABG rates by −1.8%, −1.5%, and −0.2% in contrast to an increase in Slovenia (+0.9%) and Croatia (+3.2%) (Figure 7). Differences in average CABG rate were significant, and the high-to-low ratio for Croatia vs. Spain was 3.5-fold. The Croatian CABG rate, previously reported as one of the highest in the EU, exceeded those of OECD countries [37]. Croatia increased the CABG rate from 1994 to 2002 by as much as 6-fold and reached the Slovenian level in 2002 [38]. Although the number of cardiac surgery centers improved, this cannot solely explain such an increase. Fragmentation of hospital care and lack of mandatory data collection enable the precise evaluation of appropriate indications.

All countries had increased TCA rates, and the AAPC ranged from +0.6% (Spain) to +11.4 (Croatia), with a high-to-low ratio 3.19 (Figure 8). Such increased TCA utilization in Europe has been previously described [39]. It is partly attributable to the higher disease burden and worldwide growth of interventional cardiology, as well as broader indications and benefits of TCA, such as less invasiveness and improvements in stent technology. Individual clinical data could explain the contributions of severity of disease per country, but they are not available at the national level. The striking increase in Croatia can partly be explained by the higher availability of technological and human resources, patient preferences, the extent and application of specific non-invasive diagnostic procedures that enhance downstream testing, and the implementation of evidence-based guidelines [40]. In the 1990s and early 2000s, Croatia faced a shortage of invasive cardiologists and equipment, but nowadays, interventional cardiology services are widely employed in public and private settings [41]. Still, evaluation of treatment effectiveness and clinical outcomes, especially those from medium to long-term post-TCA periods and hospital mortality rates, are not routinely available. Nevertheless, the appropriateness of TCA indications and the extent of potential overutilization in clinical practice is the first to be addressed. There is a worldwide trend of overuse, but similar studies in Croatia have not been conducted [42]. In Italy, the rate of inappropriate TCA and coronary angiography is estimated at 22% and 30%, respectively, as in Spain [43,44]. There is a lack of agreement regarding the fundamental definition of this scientifically understudied problem in interventional cardiology. However, some clinical, financial, cultural, and legal drivers of overuse have been previously recognized [45]. Financial interest does not need further clarification since more interventions mean more direct and indirect financial benefits. Regarding clinical issues, TCA is questioned in patients with stable IHD since they can have more benefits from medications or even CABG. Also, secondary prevention with optimal medical therapy has proved its worth compared with TCA [46,47]. Recommendations to reduce overuse require guidelines, a country-specific approach with comprehensive data extraction from hospital databases, and a willingness to conduct economic and cost-effectiveness analyses of invasive cardiology treatments to avoid insufficient cardiovascular care. Also, exposure to unnecessary risk could result in unwanted clinical outcomes and the additional financial burden that continuously strains healthcare budgets.

The TCA:CABG ratio represents an effort to quantify the utilization of cardiological interventions. This indicator was previously used as a parameter of potential overutilization of TCA and as a predictor of in-hospital mortality of patients with acute coronary syndrome [48]. All countries continuously and significantly increased the TCA:CABG ratio in the 2011–2019 period: Croatia at +8.9%, followed by France at +5.1%, Italy at +3.5%, Slovenia at +3.1%, and Spain at +2.2% (Figure 9). The high-to-low ratio for France vs. Slovenia was 1.74. Still, a detailed TCA:CABG ratio analysis requires evaluating the

numerator and denominator. For example, the highest ratio for France can be explained by the augmentation of the TCA rate and reduction in CABG procedures. On the other hand, Croatia simultaneously increased both rates, TCA and CABG, and had lower ratio values. Although the TCA:CABG ratio alone cannot provide accurate conclusions about the overuse of TCA or CABG, it can be indicative and used to quantify the intercountry differences.

IHD causes the most deaths in all analyzed countries [49–53]. This study showed significant health gaps among Mediterranean old and new EU country members, especially in standardized mortality and medical intervention rates. These differences are most likely associated with differences in prevention, constantly facing obstacles such as the lack of political will, competing financial and commercial interests, and missing the focus on social determinants [54]. Unlike prevention, medical interventions can be easily pharmacy-driven, especially in countries without cost-effective preventive strategies and mandatory monitoring of health outcomes, such as Croatia. Cardioprotective Mediterranean diets are rapidly disappearing, especially in transitional countries. Mediterranean heritage has beneficial physical, social, and environmental determinants incorporated not only in a diet but also in a lifestyle. Dietary issues are ranked at fifth place among risk factors that, when combined, are the causes of most deaths and disability in France, Spain, and Italy, while in Croatia and Slovenia, they are ranked at third and fourth place. Mediterranean cuisine represents a fusion of Roman and Greek culture with numerous dishes based on three core ingredients, regardless of region: olives, wheat, and grapes. Socializing around the dining table with Mediterranean dishes followed by a siesta might be as equally relevant in mortality reduction as interventions on surgical tables [55]. Still, to reduce IHD mortality, preventive cardiovascular healthcare strategies should be adjusted to retain Mediterranean heritage at the country level.

Limitations

This study has several limitations. First, the study is based on secondary data. Cross-country comparison of country-specific aggregated data does not allow conclusions about causality. Second, data have different levels of accuracy. Incidence and prevalence data are obtained from survey-based data and cannot be considered as accurate as mandatory collected mortality data drawn from vital statistics. Usually, they are more vulnerable to bias because only a sample is taken instead of a collection of mortality data across the whole population. Third, although they are less inconsistent, retrospective data collection and death certification are marked with a certain robustness, which should be considered during the interpretation of data. Also, methodologies for deciding on causes of death might differ among countries regardless of the existence of the WHO ICD coding system and efforts to standardize coding. The problem of adequate reporting and filling in the reports on death certificates can never be excluded. This could lead to over or under-reporting of death since in the elderly population, mostly affected with IHD, there may be more than a few possible causes of death. Fourth, the comparisons between countries during certain periods are complex because there are differences in definitions of metrics used, quality of data, and methods of acquisition. Still, changes within a country should be more consistent as each country will likely preserve a generally consistent methodology over time. Fifth, the period before the COVID-19 pandemic was purposefully chosen because the pandemic affected health systems and medical procedures and their outcomes in different ways across countries.

Despite the abovementioned limitations and potential methodological difficulties, this study provides new insights into cardiovascular epidemiology among Mediterranean countries. Standardized rates allow comparisons both over time and between countries. Although aggregated data are challenging to interpret regarding causality, their quantification provides indicative leads for future country-specific research with more complex study designs.

5. Conclusions

Europe represents a unique epidemiological niche and offers insights into varied patterns of IHD burden. The health gap between old and new EU country members is particularly evident in the still-existing differences in mortality, prevalence, and medical intervention rates. IHD mortality decreased across all countries except Croatia, which exhibits the highest rate. Mediterranean heritage, incorporated into diet and lifestyle, holds the potential for reducing the IHD burden, but practical implementation requires a country-specific approach. Focusing on promoting cardioprotective lifestyles at the population level and addressing significant environmental and individual behavioral changes demands sustained, long-term commitment compared to easily implemented medical interventions. The role of prevention, often underemphasized, is crucial. Evaluating clinical practices, including the treatment and control of traditional IHD risk factors, holds equal importance, especially in transitional countries. Sex differences in morbidity and mortality patterns emphasize the need for tailored approaches to prevention and interventions.

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