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European cardiovascular mortality over the last three decades: evaluation of time trends, forecasts for 2016

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Key words: Europe, cardiovascular mortality, mortality forecast
Parole chiave: Europa, mortalità cardiovascolare, previsione di mortalità

Abstract

***Background**. The circulatory diseases, in particular ischemic heart diseases and stroke, represent the main causes of death worldwide both in high income and in middle and low income countries.*
Our aim is to provide a comprehensive report to depict the circulatory disease mortality in Europe over the last 30 years and to address the sources of heterogeneity among different countries.
***Methods.** Our study was performed using the WHO statistical information system - mortality database - and was restricted to the 28 countries belonging to the European Union (EU-28). We evaluated gender and age time series of all circulatory disease mortality, ischemic heart diseases, cerebrovascular diseases, pulmonary and other circulatory diseases and than we performed forecast for 2016. Mortality heterogeneity was evaluated by countries using the Cochrane Q statistic and the I-squared index.*
***Results**. Between 1985 and 2011 SDR for deaths attributable to all circulatory system diseases decreased from 440.9 to 212.0 x 100,000 in EU-28 and a clear uniform reduction was observed.*
Heterogeneity among countries was found to be consistent, therefore different analysis were carried out considering geographical area.
***Conclusions.** We forecast a reduction in European cardiovascular mortality. Heterogeneity among countries could only in part be explained by both geographical and health expenditure factors.*

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Note for the reader

Maybe the reader could be surprised that a prediction of death rates for 2016 was reported in an article published in 2017. Let us first reassure readers about the usefulness of such a prediction in the short period. Today, the most up-to-date cardiovascular mortality in Europe regards 2012-2013 with data from east Europe getting validated later[1]. So, a prediction for the 2016 still has some utility. Moreover, long time period prediction may be affected by plateaus or slope changes. In the present paper plateau and slope changes were investigated without success. Because of the reported monotonicity of cardiovascular mortality in Europe a safer approach was chosen since - in the case of a plateau - any prediction based on a linear trend is intended to fail.

[1]European detailed mortality database (DMDB). Copenhagen: WHO Regional Office for Europe [2017].

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Introduction

The circulatory diseases represent the leading cause of mortality worldwide despite country income and geographical area. When looking at high income countries it is possible to notice that ischemic heart disease grossly represents up to fifteen percent of the total deaths. Cerebrovascular disease, on the other hand, represents about ten percent of the total deaths, being the second cause of mortality worldwide. This scenario is maintained when considering low and middle income countries. In particular, when looking at low-income countries, only the ischemic heart disease is still the leading cause of death, while the cerebrovascular diseases represents the third cause, since HIV/AIDS represents the second cause (1). Fortunately, a consistent reduction of the mortality due to circulatory diseases was observed over the last years (2-7).

Here we will provide a comprehensive report intended to depict the circulatory disease mortality in Europe over the last 30 years using the mortality database of the World Health Organization (WHO). We will estimate age and gender cardiovascular mortality forecasts for 2016 using the last available data and the trend resulting from rigorous time series modelling. Finally, we will address the sources of heterogeneity among different countries.

Methods

The following report is based on the data from the WHO Health for All mortality database (HFA-MDB) (8) restricted to the 28 countries belonging to the European Union (EU-28) as geographically defined by the treaty of Lisbon in 2007 (9). Age-standardized death rates (SDRs) were calculated using the direct method and the standard European population structure over the period 1985-2011 was considered. We first reported results about all circulatory disease mortality with the intention of giving a comprehensive picture. Then, we focused on the ischemic heart disease and the cerebrovascular disease because those are the two main causes of mortality among circulatory patients. Finally, for the sake of completeness, we reported results about mortality attributable to pulmonary and other minor circulatory system diseases. The codes used to classify the causes of death that we considered are reported in Table 1. Mortality trends over time were fitted using a join-point regression model (10) aimed to identify up to five segments (up to four join-points) with at least five data points from the last available calendar year. When the join model resulted significant, the segment from the join-point to the last observation was used for the forecast. When no change over the observed time was found, prediction was based on the period ranging from the last observation (2011) to the most recent observation corresponding to the best model fitting according to the corrected Akaike Information Criterion (AICc). Among many valid approaches, the AICc (11) was chosen because considered more adequate to model selection for time series (12). Predicted SDR and 95% confidence limits were computed by means of generalized linear log-Poisson count models. Age specific and age standardized forecasts of SDR in 2016 were computed by gender.

We evaluated SMR trends by comparison of different countries using a random effect analysis of trend slopes over the observational period defined by the best model fitting as quoted above. Results were reported by mean age standardized mortality reduction over the last 10 years. We used a random effect meta-analytic based approach to evaluate differences among countries. Here, the Cochrane Q statistic and the I-squared index were used to assess for the heterogeneity. In a supplementary evaluation aimed to explain

Table 1 - List of codes and definitions used.

Overall cardiovascular diseases	ICD-9 BTL codes: B25-B30; ICD-9 codes: 390-459; ICD-10 codes: I00-I99; ex-USSR 175 list: 84-102; ICD-10 Mortality Condensed list 1: 1064; EUROSTAT list of 65 causes: 33)
Ischemic heart diseases	ICD-9 BTL codes: B27; ICD-9 codes: 410-414; ICD-10 codes: I20-I25 ex-USSR 175 list: 90-95; ICD-10 Mortality Condensed list 1: 1067; EUROSTAT list of 65 causes: 34)
Cerebrovascular diseases	ICD-9 BTL codes: B29; ICD-9 codes: 430-438; ICD-10 codes: I60-I69; ex-USSR 175 list: 98,99; ICD-10 Mortality Condensed list 1: 1069 EUROSTAT list of 65 causes: 36
Pulmonary heart, other heart diseases	ICD-9 BTL codes: B28; ICD-9 codes: 415-429; ICD-10 codes: I26-I51; ex-USSR 175 list: 97; ICD-10 Mortality Condensed list 1: 1068; EUROSTAT list of 65 causes: different codes in E65

the heterogeneity we grouped countries according to geographic criteria. When the heterogeneity was not reduced by geographical grouping we used a single-variable meta-regression approach (13) to perform residual heterogeneity. In this supplementary attempt we included a variable defined as health expenditure country rank within geographical area. Health expenditure was computed using data regarding gross domestic product (GDP) and percentage of GDP reported by country by the WHO Health for All database (8).

Analysis accounting for bias in parameter dispersion and reliability of the forecast were performed. We first accounted for parameter dispersion performing a parallel analysis using the negative binomial based model. We then compared variances from Poisson and negative binomial models by means of Levene test for equality of variances. The negative binomial model was chosen over the Poisson model when parameter dispersion was biased. We checked for the reliability of our forecast shifting backwards the observational time by 5 years across the period 1980-2006 validating our method by performing a new forecast of the most recent SMR in 2011.

Poisson and negative binomial models were applied using the SAS software vers. 9.2 genmode procedure; join-point analysis was performed by the SEER*stat software 4.1.1, a tool specifically developed and furnished by the NIC-NIH to these purposes. Random effect analysis was performed by the STATA software vers.12.

Results

Between 1985 and 2011 SDR for deaths attributable to all circulatory system diseases has been reduced from 440.9 to 212.0 x 100,000 in EU-28. When looking at genders separately this scenario remains unchanged. In men, during the same period, SDR for all cardiovascular causes has been reduced from 549.5 to 262.3 x 100,000. This result is consistent with the one for women where we observed a reduction of mortality from 362.1 to 171.4 x 100,000. The contribution to all circulatory system disease mortality given by the sum of the ischemic heart and cerebrovascular disease represents about 35% of the total cardiovascular mortality burden. For these two major causes of mortality a parallel reduction over the observation period was noticed. In particular, we observed a reduction from 222.2 to 108.4 x 100,000 for ischemic heart disease mortality in

men. Women experienced a similar SMR reduction over the same period (from 106.3 to 54.34 x 100,000). Moreover, the mortality attributable to cerebrovascular disease has been reduced from 128.5 to 55.9 x 100,000 in men and from 105.1 to 44.7 x 100,000 in women.

When looking at the shape of the relation between mortality rate and time we observed a clearly uniform reduction (Figure 1). This relation was particularly strong over the last 10 to 12 years when no joint-points were found. Consequently, model fitting analysis by the AICc identified the period 2000-2011 as the best to perform the most reliable forecast of mortality rate. When considering statistical tests applied to models comparing gender by cause of death we observed a statistically significant faster mortality reduction in men for all circulatory system and ischemic heart diseases. Notably, according to our mortality forecasts for 2016, the mortality in men is expected to be higher than in women for all but pulmonary, heart and other diseases. Cardiovascular mortality trends by gender and age classes are reported in Table 2.

Here it is possible to notice that no mortality reduction is expected for pulmonary and other diseases when considering younger men and women. Not surprisingly, in this analysis we observed a substantial higher mortality reduction for older compared to younger subjects.

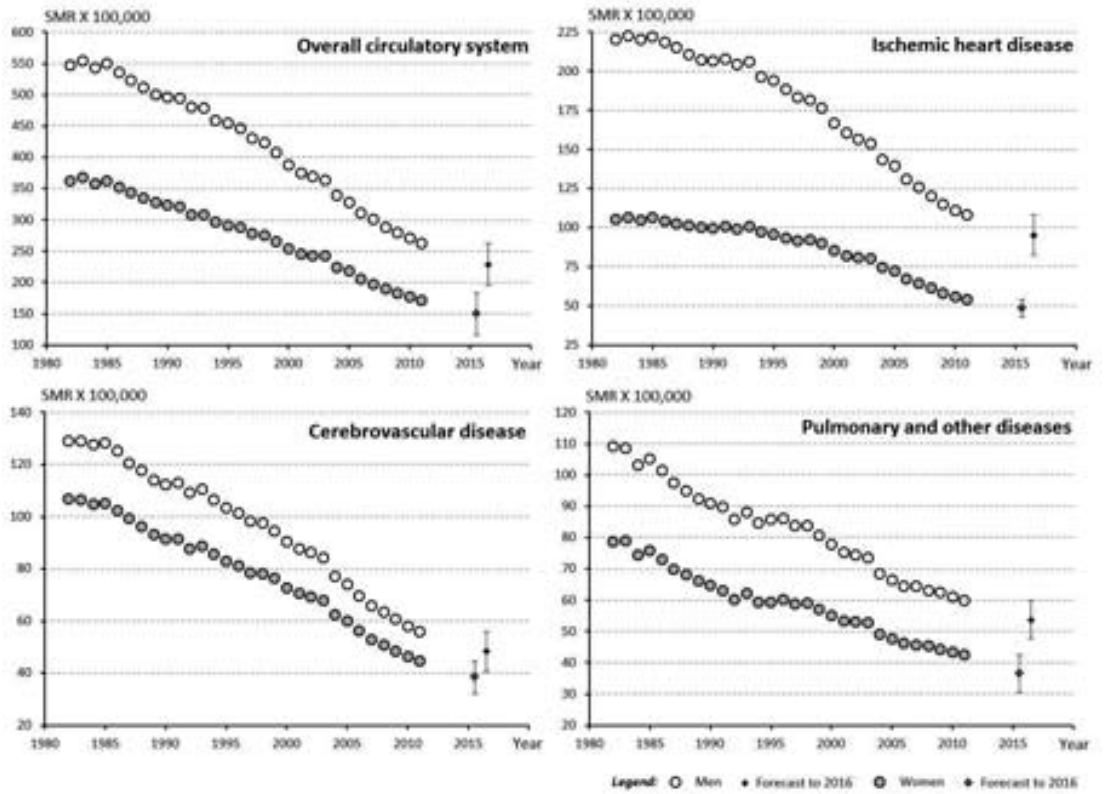


Figure 1 - Cardiovascular Standardized Mortality Rates (SMRs) trends over the period 1980-2011 and forecasts to 2016 by gender.

Table 2 - Cardiovascular Standardized Mortality Rates (SMRs) by gender and age classes. Values are given as deaths x 100,000.

Death cause (age class)	Men		Women	
	Observed 2011	Predicted 2016	Observed 2011	Predicted 2016
Overall Circulatory System (30-44)	24.57	21.20 (20.41; 22.00)	9.06	7.86 (7.36; 8.35)
Overall Circulatory System (45-59)	154.12	134.24 (132.12; 136.35)	48.2	41.11 (39.98; 42.25)
Overall Circulatory System (60-74)	608.11	512.94 (509.37; 516.52)	276.86	227.86 (225.41; 230.30)
Overall Circulatory System (≥75)	3576.56	3161.68 (3151.16; 3172.19)	3060.92	2733.40 (2643.41; 2823.39)
Overall Circulatory System (all-ages)	262.27	228.83 (203.13; 254.53)	171.39	149.54 (147.35; 151.72)
Ischemic Heart Disease (30-44)	9.5	7.75 (7.29; 8.20)	2.15	1.89 (1.65; 2.13)
Ischemic Heart Disease (45-59)	74.99	63.18 (61.78; 64.58)	15.76	13.42 (12.80; 14.04)
Ischemic Heart Disease (60-74)	277.55	230.78 (228.33; 233.23)	97.44	79.90 (78.47; 81.33)
Ischemic Heart Disease (≥75)	1342.71	1226.57 (1219.99; 1233.14)	933.57	859.35 (853.86; 864.84)
Ischemic Heart Disease (all-ages)	108.4	95.34 (93.64; 97.04)	54.34	48.63 (47.41; 49.86)
Cerebrovascular Disease (30-44)	4.22	3.65 (3.32; 3.98)	2.64	2.27 (2.02; 2.52)
Cerebrovascular Disease (45-59)	25.02	21.91 (21.10; 22.71)	13.14	11.25 (10.68; 11.81)
Cerebrovascular Disease (60-74)	124.13	104.33 (102.63; 106.03)	74.66	61.03 (59.79; 62.28)
Cerebrovascular Disease (≥75)	821.86	709.27 (704.43; 714.10)	783.8	682.30 (677.69; 686.91)
Cerebrovascular Disease (all-ages)	55.92	48.29 (47.08; 49.49)	44.73	38.40 (37.35; 39.45)
Pulmonary Heart Disease (30-44)	8.39	8.09[I] (7.55; 8.63)	3.14	2.91[I] (2.59; 3.24)
Pulmonary Heart Disease (45-59)	36.68	35.03 (33.88; 36.18)	12.57	11.48 (10.84; 12.12)
Pulmonary Heart Disease (60-74)	123.68	107.29 (105.35; 109.23)	61.14	52.61 (51.29; 53.93)
Pulmonary Heart Disease (≥75)	862.82	771.79 (766.72; 776.87)	793.54	723.31 (717.87; 728.76)
Pulmonary Heart Disease (all-ages)	59.87	53.76 (52.41; 55.11)	42.47	38.05 (36.89; 39.22)

[I] Not statistically significant mortality reduction respect to 2011

The faster mortality reduction observed in men is here confirmed when considering older subjects and all circulatory system and ischemic heart disease mortality as outcomes. When it comes to look at countries separately, the results become more challenging. Looking at absolute values of mortality (Figures 2-3) by country and gender makes it clear that a dramatical heterogeneity among countries exists. We found a higher cardiovascular mortality in East European countries such as Bulgaria, Poland and Romania and in Latvia and Lithuania in the Baltic area. This

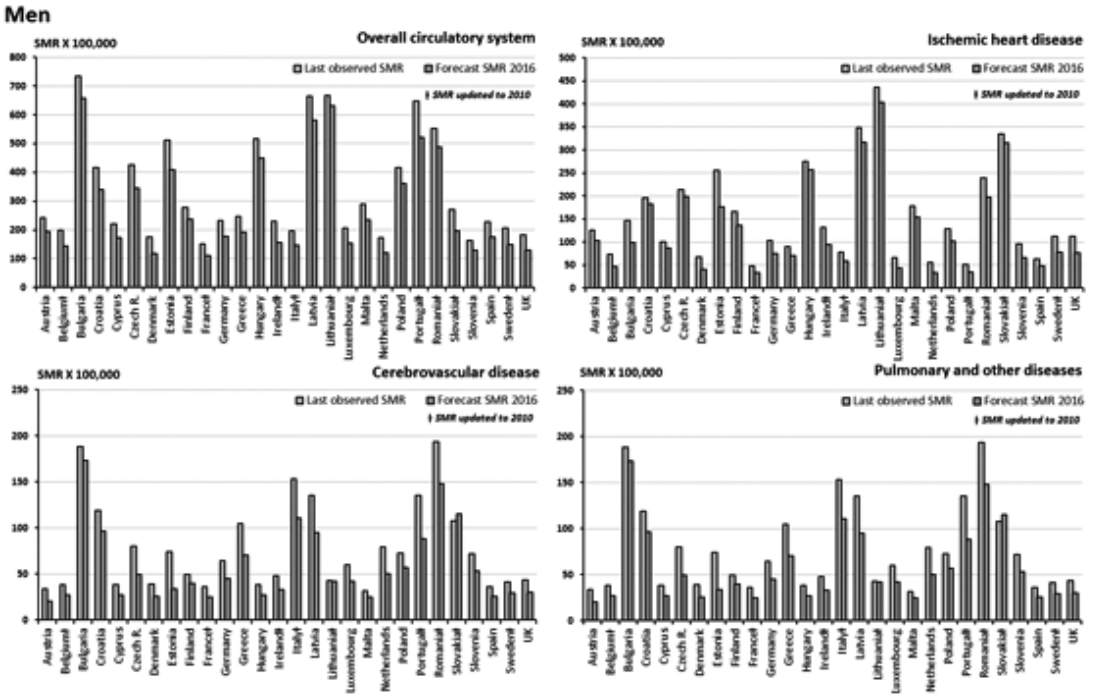


Figure 2 - Cardiovascular Standardized Mortality Rates (SMRs) in 2011 and forecast to 2016 by EU-28 countries in men.

effect is maintained regardless of gender and age class considered. In the random effect analysis, when evaluating mortality reduction, this plainness is maintained and enhanced. Heterogeneity among countries was found to be consistent when all countries are considered in the same analysis where we found an I^2 index largely higher than 80% for all of the mortality causes, despite gender. Stratifying by gender and mortality cause did not result in a relevant reduction of heterogeneity among countries. Heterogeneity was found to be mild to relevant when considering cardiovascular mortality due to all causes (I^2=78.4% men and I^2=45.8% in women). The heterogeneity of 83.1% and 77.8% was found for ischemic heart disease for men and women respectively. Cerebrovascular disease was also affected by a relevant degree of heterogeneity among countries, being 87.2% and 79.0% for men and women respectively. Finally, the scenario did not change when we considered pulmonary and other causes of cardiovascular death, where a high degree of heterogeneity among countries was also found (men I^2=78.1%; women I^2=74.0%). Grouping countries by geographical area resulted in a dramatically reduction of heterogeneity. We observed a not significant heterogeneity after grouping southern/Mediterranean countries and middle/western countries for almost all of mortality causes despite gender. On the other hand, residual heterogeneity was observed among Middle/Eastern and North/Baltic countries, despite gender. Notably a supplementary heterogeneity reduction could be observed in Baltic countries if Latvia and Lithuania or Denmark and Sweden are considered

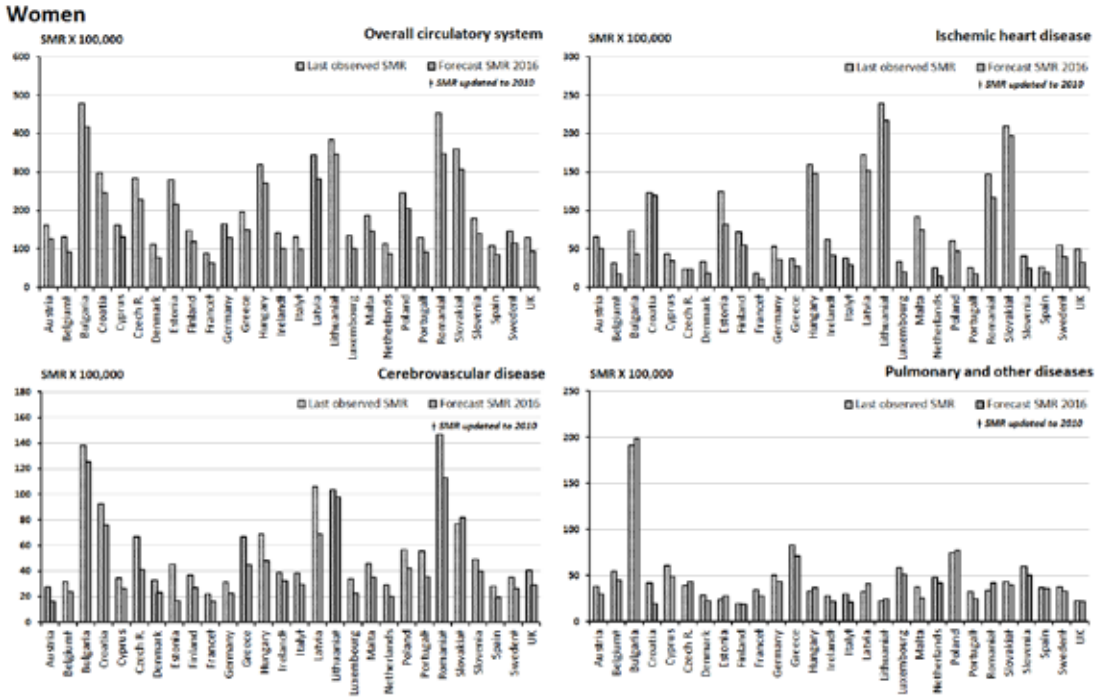
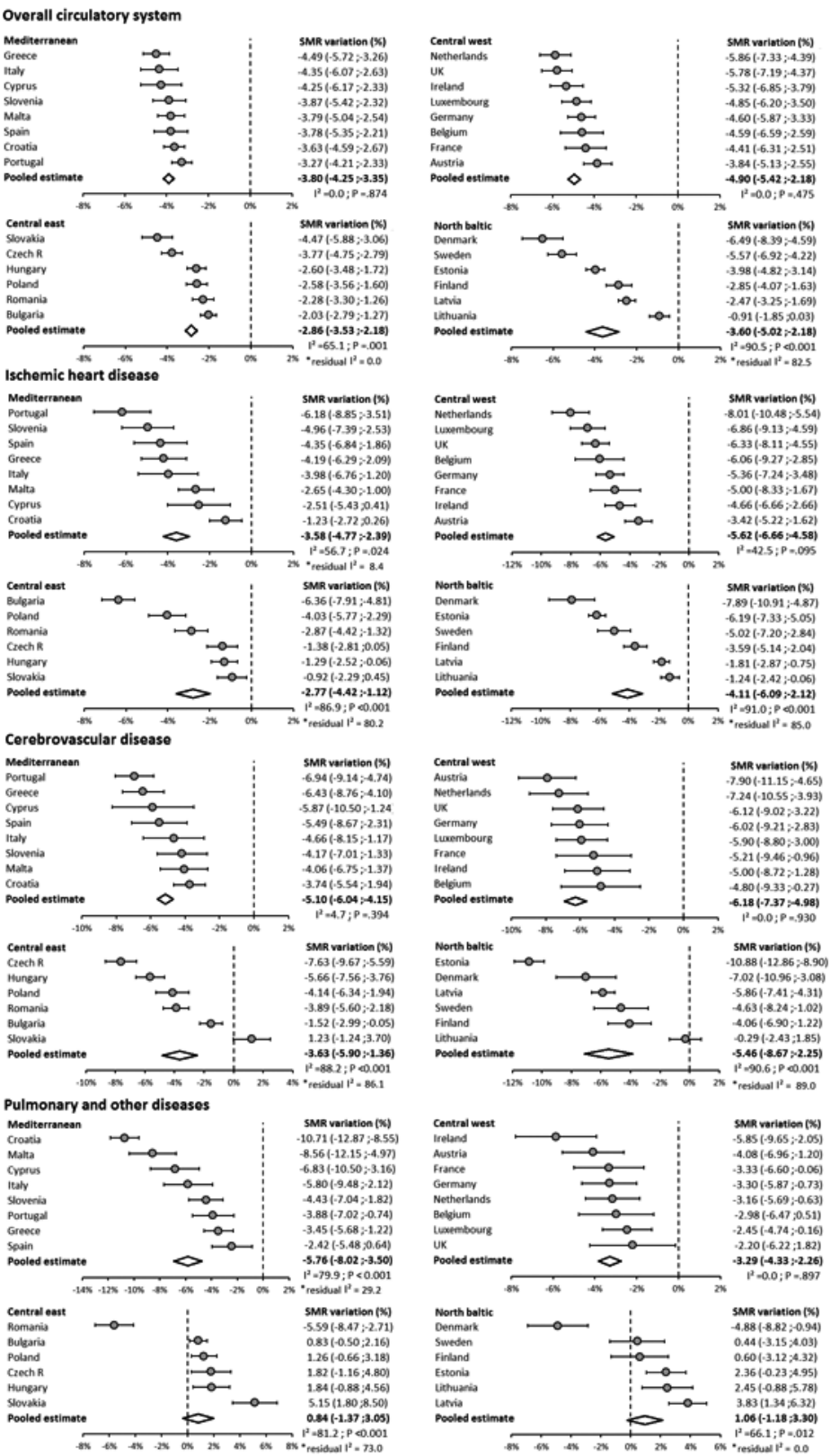


Figure 3 - Cardiovascular Standardized Mortality Rates (SMRs) in 2011 and forecast to 2016 by EU-28 countries in women.

apart. Among Middle-East countries it was not possible to uniquely identify countries causing heterogeneity. When performing random effect regression using health expenditure rank within geographical area as explanatory covariate, a supplementary heterogeneity reduction is obtained. Briefly, we obtained a relevant heterogeneity reduction for all-diseases male deaths within the east European area (residual I^2 reduced to 0% from 65.1%). In men a supplementary heterogeneity reduction was obtained for ischemic heart disease deaths in the Mediterranean area (residual I^2 reduced to 8.4% from 56.7%) and for pulmonary disease deaths in both Mediterranean and Baltic areas where heterogeneity was reduced to 29.2% and 0% from 79.9% and 66.1%, respectively (Figure 4). In women such approach resulted in heterogeneity reduction when ischemic heart and pulmonary heart disease deaths in Mediterranean (residual I^2 reduced to 20.8% from 55.9%) and Baltic (residual I^2 reduced to 0% from 57.2%) countries are considered (Figure 5).

Discussion and conclusions

The present work reports cardiovascular mortality trends in Europe over the last 30 years, pointing out that a consistent reduction of mortality due to circulatory diseases has been observed. Cardiovascular mortality was reduced consistently over the observational period despite age classes and genders. It is well known that cardiovascular death rates went down because of the specific cardiovascular disease prevention programs carried out in Europe during the last decades.



* Residual heterogeneity was performed taking into account country health expenditure income rank within geographical area

Figure 4 - Random effect analysis of cardiovascular Standardized Mortality Rates (SMRs) reduction (%) in men over the last 10 years.

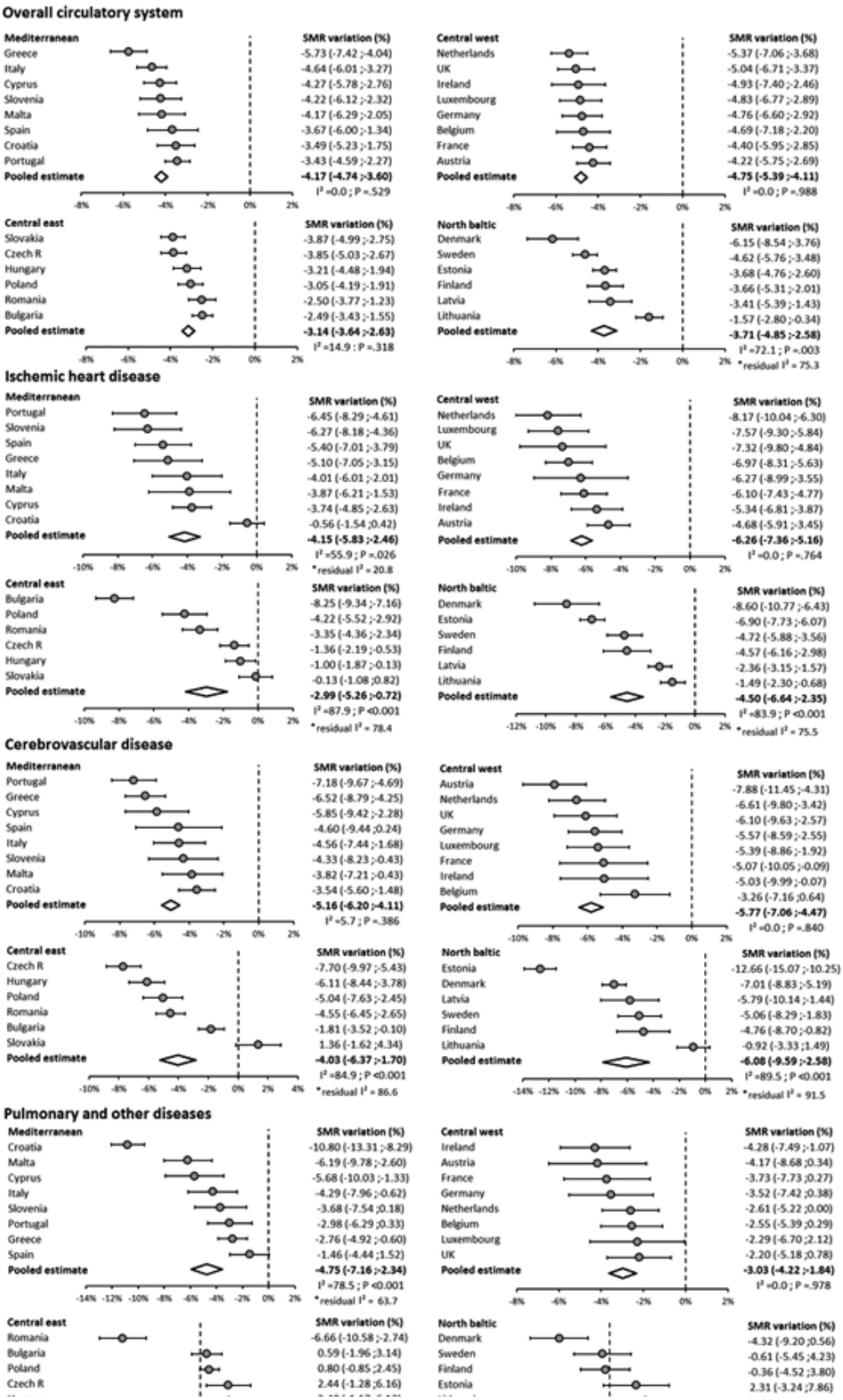


Figure 5 - Random effect analysis of cardiovascular Standardized Mortality Rates (SMRs) reduction (%) in women over the last 10 years.

Since the mid Eighties, it was supposed that, among others, a major role in cardiovascular mortality was played by smoking, physical inactivity and a rich diet with consequent high cholesterol level and raised blood pressure (14-16). More recently, cardiovascular diseases and related mortality were also associated with social determinants like literacy rate or, more generally, economic income (17-18). Among all those factors, the ones more directly correlated with health status such as smoking, diet and physical inactivity were contrasted in the last decades by programs specifically dedicated to this purpose (12-21). Here we noticed that, despite a clear policy and the efforts made, contradictory trends in Europe were observed: namely, a generalized reduction of blood cholesterol (22) and systolic blood pressure (23) on one side and a slight increase of BMI (24) and diabetes rate on the other (25). To be noticed that, since the mid Eighties, the income and literacy rates also improved (18), likely giving a contribution (15). A supplementary contribution to the reduction of cardiovascular mortality may also be due to the improvements of diagnosis techniques for early detection of cardiovascular impairment. The reduction in cardiovascular mortality was not only due to the success of prevention programs and to the social improvements, and we should not forget the several therapeutic achievements that dramatically contributed to bring down mortality. Over the last years the medical community recognized the importance of thrombolysis, percutaneous angioplasty, coronary stenting and surgical revascularization just to cite the most popular interventions among all (26-33). This positive scenario is not equally distributed across EU-28. In our analysis we highlighted an existing heterogeneity among countries. This heterogeneity regards not only the absolute mortality but also the cardiovascular mortality reduction over time. Grouping countries by a geographic criterion was not sufficient to improve consistency, and other explanatory factors should be introduced. The hypothesis for which this heterogeneity could be simply explained by a misclassification bias due a different coding for former USSR countries - as for the eastern European countries formerly under the Soviet influence - should be rejected because our evaluation was mainly focused on the last 10 years. Instead, it is much more likely that those differences are related to a common factor defined by a less efficient grasp of healthy lifestyle policies, secondary prevention and technical improvements of medical care during the last decade. More recent economic and social improvements in these countries are therefore encouraging for the future and we wish that also an improvement in cardiovascular mortality could follow after an unavoidable delay.

Our work is not free from some weakness. Describing time series for such a long period and having time as the only covariate into the model could lead to an underdispersion of the slope. We accounted for this fitting negative binomial regression. According to the methodology used, our forecasts was based on a limited number of observational years resulting in a major spread and a more conservative estimate of the slope. This technical solution was intended to enhance parameter spread. Moreover, since we detected a lower mortality decrease for some countries our forecast could be negatively biased when applied to high income countries. For those countries a much more precise estimate could be obtained using specific rate reductions that we reported in our random effect analysis. The strength of our work is given by a rigorous method aimed to give the most

reliable and robust mortality prediction. One more strength point is represented by a novel random effect analysis approach evaluating heterogeneity among countries. When considering differences by country, another possible merit of us was using a meta-regression approach aimed to identify a possible source of heterogeneity given by health expenditure within geographical areas.

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Riassunto

La mortalità cardiovascolare in Europa negli ultimi 30 anni: analisi dell'andamento temporale e previsioni per l'anno 2016

Introduzione. Le malattie del Sistema circolatorio, in particolare la cardiopatia ischemica e l'ictus, rappresentano le principali cause di morte nel mondo, sia nei Paesi ad alto reddito che in quelli a medio e basso reddito.

Il nostro obiettivo è quello di fornire un'esaustiva descrizione della mortalità per malattie del sistema circolatorio in Europa negli ultimi 30 anni e di analizzare le fonti di eterogeneità tra i diversi Paesi.

Metodi. Lo studio, realizzato utilizzando gli indicatori presenti nel database dell'Organizzazione Mondiale della Sanità (OMS), riguarda i 28 Paesi appartenenti all'Unione Europea (EU-28). Sono state valutate le serie temporali della mortalità per età e per genere per tutte le patologie circolatorie, per la cardiopatia ischemica, per le patologie cerebrovascolari, per le patologie vascolari polmonari e altre patologie circolatorie e successivamente è stata effettuata una previsione per l'anno 2016. L'eterogeneità per la mortalità è stata valutata utilizzando il test Q di Cochrane e l'indice I-squared.

Risultati. Tra il 1985 e il 2011 i tassi standardizzati di mortalità per tutte le patologie del sistema circolatorio si sono ridotti da 440.9 per 100.000 a 212.0 per 100.000 nei 28 Paesi e si osserva un chiaro andamento uniforme. Considerando tutti i Paesi nella stessa analisi, l'eterogeneità è risultata importante e quindi sono state effettuate sottoanalisi raggruppando per area geografica.

Conclusioni. Dalle analisi effettuate è possibile prevedere una riduzione della mortalità per patologia cardiovascolare in Europa. Inoltre, l'eterogeneità tra i Paesi potrebbe essere parzialmente spiegata sia da fattori geografici che da differenze nella spesa sanitaria.

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