Association between metabolic risk factors and cardiovascular disease mortality: population-level analysis in high income countries

Mariachiara Di Cesare, James Bennett, Nicky Best, Sylvia Richardson, Majid Ezzati

School of Public Health, Department of Epidemiology and Biostatistics, Imperial College London

Introduction

Starting from the 1970s a consistent decline in the mortality level from cardiovascular diseases (CVD) has been observed among high income countries (Hunink et al. 1997; Havlik and Feinleib 1979). Yet cardiovascular disease mortality (ischemic heart diseases and stroke or other cerebrovascular diseases) is still the leading cause of death worldwide accounting for almost a quarter of the total deaths - more than 13 million of people in 2008 – (WHO 2011).

A vast literature exists on the main risk factors associated with cardiovascular diseases mortality, and the explanation of the mechanisms behind this relationship at individual level. It is widely recognized that high systolic blood pressure (SBP), high serum total cholesterol (TC), and high body mass index (BMI) , represent (together with smoking), the main modifiable risk factors associated, independently and in combination (Asia Pacific Cohort Studies Collaboration 2004; Lowe et al. 1998; Thomas et al. 2002), with cardiovascular disease mortality (Field et al. 2001; Asia Pacific Cohort Studies Collaboration 2004; Roth et al. 2004; Lewington et al. 2007; Wei et al. 2000). These risk factors have been considered among the responsible of health disparities within and between populations, as well as possible determinants of slowing down the increasing trend in life expectancy (Hozawa et al. 2007; Danaei et al. 2010; Kivimaki et al. 2008). Changes in lifestyles, diet, and treatment during the past decades have had important effects on levels of such risk factors. According to recent studies (Finucane et al. 2011; Danaei et al. 2011b; Farzadfar et al. 2011; Danaei et al. 2011a) mean SBP decreased globally by 0.8 mm Hg per decade in men and by 1 mm Hg per decade in women between 1980-2009; very little change was observed in the mean TC (0.1 mmol/L); while mean BMI and mean FPG increased respectively by 0.4 Kg/m^2 per decade in men and 0.5 Kg/m^2 per decade in women, and by 0.07 mmol/L per decade in men and 0.09 mmol/L per decade in women. Nevertheless, the analysis of subregions and countries suggests a high heterogeneity in trends, as well does the comparison between men and women.

If the evidence at individual level is well known it is still matter of debate if the same relation between metabolic risk factors and cardiovascular mortality observed at individual level holds at the population level. Currently, most of the research interest on the association at population level has focused on the contribution of smoking to overall mortality levels (Preston et al. 2010; Peto et al. 2006; McCartney et al. 2011; Preston et al. 2011) while little (Kuulasmaa et al. 2000) attention has been dedicated to the metabolic risk factors.

Following this idea the main goal of this paper is to analyze the relation between metabolic risk factors and cardiovascular mortality among high income countries during the last 30 years with the objective of analyzing the relation between levels of risk factors and levels of CVD mortality and disentangling possible associations.

Data

Data on metabolic risk factors – BMI, TC, and SBP – come from previously reported estimations (Finucane et al. 2011; Danaei et al. 2011b; Farzadfar et al. 2011; Danaei et al. 2011a), in the period 1980-2009. Observed cardiovascular deaths (Chapter IX of ICD-9) by age and sex for the same period come from the WHO mortality database (adjusted for ill-defined deaths and vital registration completeness). High income countries[1] have been included in the analysis if death rates available in at least 20 years within the 30 years period, bringing to a total of 645 country-year observations.

For the analysis age-specific and age standardized (using the WHO world standard population) death rates for cardiovascular diseases and for BMI, TC, and SBP have been calculated.

Preliminary results

The mean age-standardized death rate (SDR) for cardiovascular diseases per 100,000 (population over 25 years old) decreased between 1980-2009 for both men and women with a reduction in the gender gap from 265.7 per 100000 in 1980 to 95.0 in 2009 is observed.

The age-standardized mean BMI increased between 1980 and 2009 for both men - from 25.2 kg/m^2 (95% uncertainty interval 24.0-26.3) in 1980 to 26.6 kg/m^2 (25.6-27.6) in 2009 - and women - from 24.5 kg/m^2 (23.0-26.0) in 1980 to 25.6 kg/m^2 (24.3-27.0) in 2009 letting to a final increase in the gap between men and women equal to 1 kg/m^2 in 2009 (0.7 kg/m^2 in 1980). The age standardized mean SBP shows a decrease during the period of observation - from 136.8 mm Hg (130.6-143.2) to 131.5 mm Hg (125.3-137.6) among men and from 131.7 mm Hg (125.2-138.2) to 123.2 mm Hg (116.9-129.6) among women. The trend shows an increase in the gap between men and women equal to 8.2 mm Hg higher level in the SBP for men than for women in 2009 (5.1 mm Hg at 1980). While the mean age-standardized total cholesterol shows a decrease between 1980-2009, from 5.8 mmol/L (5.3-6.4) to 5.2 mmol/L (4.7-5.7) for men and from 5.8 mmol/L (5.1-6.5) to 5.2 mmol/L (4.6-5.8) for women. No differences in the level and in the gap between men and women are observed.

In Figure 1 the association between the SDR for CVD and each of the age-standardized metabolic risk factors is shown. A *loess* smoothed curve has been fitted to the data for each year (red for 1980, purple for 2009). The chart gives information about how the association between CVD mortality changed in time (slope of the curves) and the level of variation between countries by year (length of the curve). Results for men are shown on the left side of the panel while results for women are shown on the right side.

In general all figures show a clear temporal pattern, with fitted curves moving from higher to lower levels of SDR for cardiovascular diseases.

In the first row of the panel the age-standardized BMI is plotted against the SDR for CVD (men and women). In the first years of observation the association (slope of the curve) between BMI and CVD mortality suggests higher level of mortality among those countries with higher levels of BMI

[1] Australia, Austria, Belgium, Canada, Denmark, Finland, France, Greece, Ireland, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Norway, Portugal, South Korea, Spain, Sweden, Switzerland, UK, United States. Germany has been omitted given that death rates were available for less than 20 years observations.

(red/yellows curves). This association has weakened in time especially in correspondence of higher levels of BMI flattening the curve towards the end of the period of analysis.

The association between age-standardized SBP and SDR for CVD (second pair of figures) tends to decrease in time among men, but with different effect according to the level of SBP. For both men and women the association between SBP and SDR for CVD is weak for levels of SBP respectively under 130 mm Hg 125 mm Hg, while a positive association is observed higher SBP values.

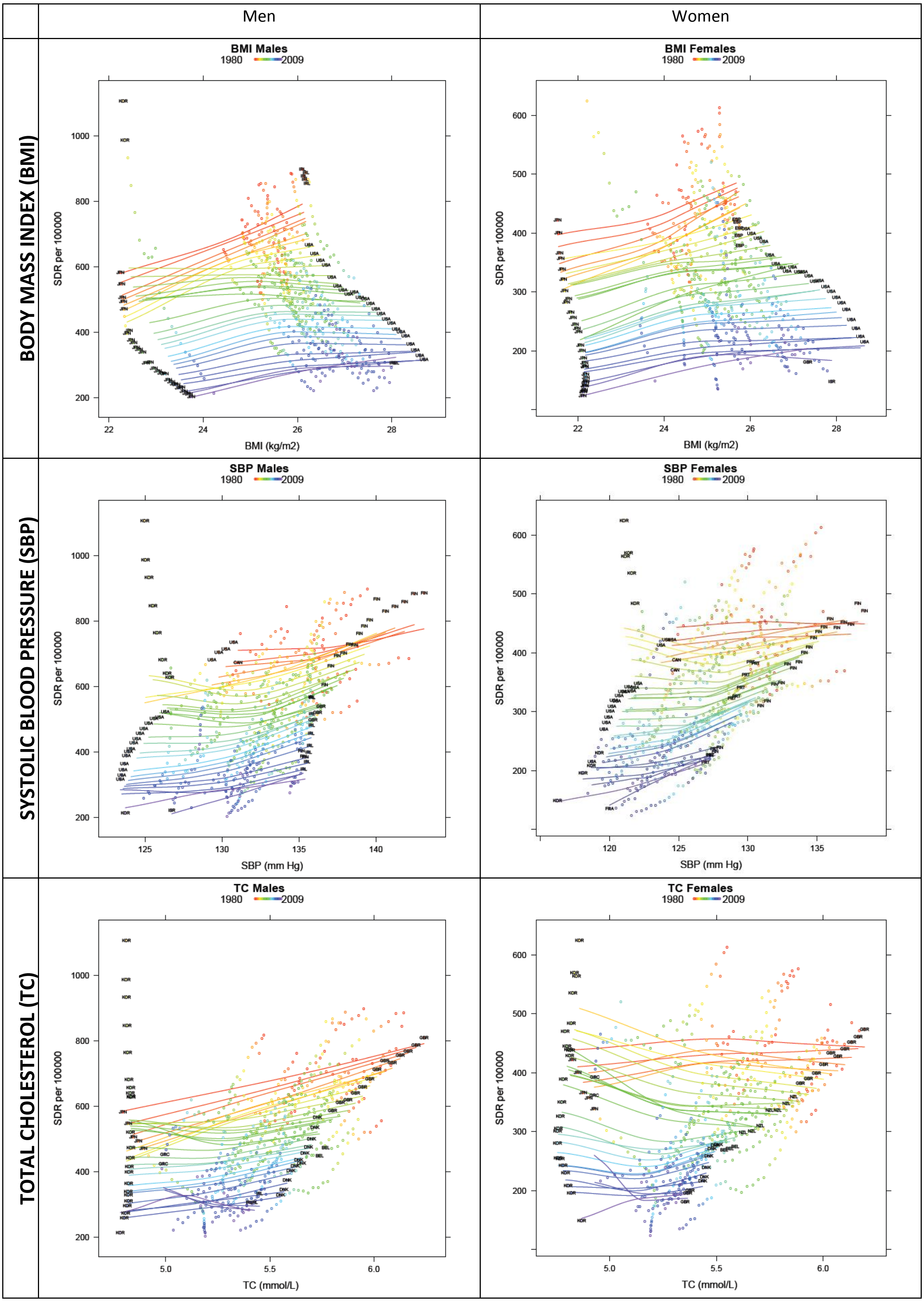
The last pair of curves shows the association between SDR for CVD and TC suggesting that the positive relationship observed at the beginning of the period 1980-2009 is replaced by a weaker association in the recent years for men. For women a U-shaped association is observed through all the period of observation. For both men and women a reduction in variability is observed between countries across years.

A negative binomial regression, to account for over-dispersion, will be used to model the impact of each of the three metabolic risk factors on the level of cardiovascular disease mortality, separately for each sex.

$Deaths_{c,a,y} \sim NegBin(\mu_{c,a,y})$

Where $Deaths_{c,a,y}$ are the number of cardiovascular diseases deaths observed in country *c*, age *a*, and year *y*. Then the ln of the death rate $\mu_{c,a,y}$, offset by $\ln(population_{c,a,y})$, will be modelled as a function of country, age, year, and metabolic risk factor. Interactions and random effects will be considered.

Figure 2 – SDR for cardiovascular diseases and age-standardized BMI, SBP, TC by sex. 1980-2009



Note: labels for countries included for max and min in each year

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