

TITLE:

Contrasting cardiovascular mortality trends in Eastern Mediterranean populations: contributions from risk factor changes and treatments

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Abstract

BACKGROUND

Middle income countries are facing an epidemic of non-communicable diseases, especially coronary heart disease (CHD). We used a validated CHD mortality model (IMPACT) to explain recent trends in Tunisia, Syria, the occupied Palestinian territory (oPt) and Turkey.

METHODS

Data on populations, mortality, patient numbers, treatments and risk factor trends from national and local surveys in each country were collated over two time points (1995-97; 2006-09); integrated and analysed using the IMPACT model.

RESULTS

Risk factor trends: Smoking prevalence was high in men, persisting in Syria but decreasing in Tunisia, oPt and Turkey. BMI rose by 1-2kg/m² and diabetes prevalence increased by 40%-50%. Mean systolic blood pressure and cholesterol levels increased in Tunisia and Syria.

Mortality trends: Age-standardised CHD mortality rates rose by 20% in Tunisia and 62% in Syria. Much of this increase (79% and 72% respectively) was attributed to adverse trends in major risk factors, occurring despite some improvements in treatment uptake.

CHD mortality rates fell by 17% in oPt and by 25% in Turkey, with risk factor changes accounting for around 46% and 30% of this reduction respectively. Increased uptake of community treatments (drug treatments for chronic angina, heart failure, hypertension and secondary prevention after a cardiac event) accounted for most of the remainder.

DISCUSSION

CHD death rates are rising in Tunisia and Syria, whilst oPt and Turkey demonstrate clear falls, reflecting improvements in major risk factors with contributions from medical treatments.

However, smoking prevalence remains very high in men; obesity and diabetes levels are rising dramatically.

Introduction

Coronary heart disease (CHD) is the most common cause of mortality globally, generating more than 7 million deaths each year. CHD is expected to remain a leading cause of death beyond 2030^{1,2}. Different regions are at varying stages in their CHD epidemics. For example, after peaking in the 1960s, CHD mortality in Western countries has subsequently halved. Central European countries have experienced more recent and abrupt declines following socioeconomic transformations in 1989/1990³. The drivers of these CHD mortality trends are increasingly well characterised in affluent countries. Diverse studies generally suggested that risk factor improvements explain half to two thirds of the mortality declines with the remaining one third to half coming from evidence based treatments⁴⁻⁶. CHD and other non-communicable diseases (NCDs) are increasing as a proportion of total mortality in most middle and low income countries^{1,2,7}. However, much less information on the CHD burden (mortality, morbidity and costs) and CHD trends are available from these populations. This is particularly worrisome for countries in the Eastern Mediterranean Region, where predictions suggest substantial increases in the number of NCD deaths by 2020⁸. For countries in this region, there is therefore an urgent need to analyse local and regional CHD trends and quantify the impact of risk factors and treatments.

Risk factor trends across the WHO-EMRO region were recently summarised in GBD Lancet papers⁹⁻¹². However, such analyses risk portraying a relatively “homogenous” view of the region, whereas mortality trends are strikingly heterogeneous. For instance, our analyses show

that CHD mortality is rising rapidly in many countries including Tunisia and Syria, but decreasing in other Mediterranean countries such as the occupied Palestinian territories and Turkey.

It is clearly important to identify trends in CHD mortality in low and middle income settings and appraise their variations between countries, so as to inform effective policies to reduce the future disease burden. Our aim was therefore to analyse recent CHD trends in Tunisia, Syria, **occupied Palestinian territories** (oPT, West Bank), and Turkey (middle income countries in the Eastern Mediterranean region), and assess the recent contribution of risk factor changes and evidence based treatments. These four countries were selected on the basis of a) data availability and quality, b) previous successful collaborations, some of which had resulted in substantial relevant data collection over time, and c) representing a range of economic development, population size, and absolute mortality rates across this region (see Tables 1 and 2).

Methods

The socio-demographic and economic characteristics of the Tunisian, Syrian, oPt (West Bank), and Turkish populations are compared in Table 1.

The IMPACT Model

We used an updated version of the IMPACT CHD mortality model (Appendix 1). This has been employed and validated in a variety of countries from North America through Europe to China⁴¹³. Data on risk factor levels and current uptake levels of evidence-based treatments were identified by extensive searches for published and unpublished data, and complemented where necessary with specifically designed surveys.

Data sources used to populate the model are detailed in Appendix 2 and in previous work¹⁴. In brief, they include:

- a) Population and CHD mortality data (from national statistical agencies).
- b) Patient numbers and uptake of specific medical and surgical treatments in nine CHD patient groups.
- c) Population trends in major cardiovascular risk factors (smoking, total cholesterol, systolic blood pressure, body mass index, diabetes and physical inactivity).

In order to estimate trends, these data items were acquired for two time points (referred to as the **initial** and **final** years respectively). These were the most recent year with data available (final), and one 10-15 years previously (initial); 1997-2009 for Tunisia, 1996-2006 for Syria, 1998-2009 for oPt and 1995 – 2008 for Turkey). Data were stratified by 10-year age groups and sex. Due to variations in data availability, there were some minor differences in the age groups included for each population (25+ in Tunisia and Syria; 25-74 in West Bank, oPt; 35-84 in Turkey).

Change in CHD deaths between the initial and final years

The number of CHD deaths expected in the final year was calculated by applying the age and sex specific death rates in the initial year to the population age and sex structure in the final year. The observed CHD deaths in the final year were then subtracted to estimate the difference between the initial and final years. This was described as the **number of deaths prevented or postponed** (DPPs) if negative, or **increased mortality** if positive (the number the model attempts to explain in each country).

Data on patient numbers and treatment uptakes during the initial and final years were obtained for nine mutually exclusive CHD subgroups: patients hospitalized during that year for an acute myocardial infarction (AMI) or unstable angina pectoris (UAP) or heart failure due to CHD, community-dwelling patients who were post-AMI survivors, patients with chronic angina, patients receiving revascularisation (CABG or PCI), patients in the community with heart failure due to CHD (i.e. those treated outside of hospital), and individuals eligible for primary prevention being hypertensive (eligible for blood pressure lowering treatments) or having hypercholesterolaemia (eligible for lipid lowering therapy). These data, along with information on **uptake levels of evidence based treatments** were obtained from a combination of national statistics, local surveys, grey literature, hospital records and specifically designed surveys as appropriate (Appendix 2). These were used for estimating treatment coverage in the initial and final years.

Data on trends in *population risk factors* (smoking prevalence, total cholesterol, systolic blood pressure, body mass index, diabetes) were obtained mainly from national and local surveys complemented by published and grey literature (Appendix 2).

The mortality changes attributed to risk factor trends

The deaths attributable to population changes in risk factor levels were estimated using one of two approaches.

The regression β coefficient approach was used to quantify the population mortality impact of change in continuous risk factors (systolic blood pressure, total cholesterol and BMI). The mortality change was then estimated as the product of the CHD deaths observed in the initial year, the subsequent change in the risk factor, and the β regression coefficient quantifying the change in CHD mortality expected per unit of absolute change in the risk factor (Appendix 1). These regression coefficients were derived from international studies after controlling for all other coefficients included in the model (see Appendix 1, eTable3). For example, the coefficient for BMI is independent of that for BP, cholesterol and Diabetes. They also control for the effects of increased treatment uptake (for lowering blood pressure and cholesterol levels) over time (see Appendix 1, page 7).

A second approach, ***population attributable risk fraction***, was used for categorical variables- smoking, diabetes, and physical inactivity by applying Levin's formula (Appendix 1). Lag times between the change in cardiovascular risk factor levels and change in CHD mortality rates were assumed to be relatively rapid¹⁵⁻¹⁸ and were therefore not specifically modelled.

CHD deaths are caused by multiple risk factors acting simultaneously. Enumerating mortality changes from risk factor trends should ideally therefore not use a simple additive approach. Instead, the effects of risk factor changes were jointly estimated using the cumulative risk-reduction approach (a multiplicative approach). This can be stated in the equation:

$$\text{Cumulative effect} = 1 - ((1 - a) * (1 - b) * (1 - c) * \dots * (1 - n))$$

Where n is the total number of additional risk factors (in this case 5 as in total we modelled 6)

This cumulative effect of change in all risk factors over the study period was calculated by age and sex for each country (see Appendix 1, page 8-10). The ratio of the cumulative effect to the corresponding additive effect was then calculated, yielding 70 adjustment factors. These adjustment factors were used to scale down the additive DPPs for each risk factor. These adjusted DPPs, summed over all seven risk factors, then equalled the estimated total combined DPPs, capturing the multiplicative net impact of positive and adverse changes in risk factors. All risk factor DPPs quoted in the results tables refer to the adjusted DPPs.

Estimating the mortality reduction attributable to medical and surgical treatments

The model included all medical and surgical treatments for the nine mutually exclusive patient groups in both the initial and final years.

Case-fatality data were obtained from large, unselected, population-based patient cohorts. Survival benefit over a one-year time interval was used for all treatments, as we are only interested in quantifying deaths prevented or postponed for at least one year. (**Appendix 1**)

The **mortality reduction for each treatment** was then calculated as the number of patients in each group, multiplied by the group age-sex-specific case fatality, the treatment uptake and the relative mortality reduction (efficacy). **The efficacy of each therapeutic intervention** was based on recent meta-analyses and randomised controlled trials. (**Appendix 1, eTable 1**)

The potential effect of multiple treatments in an individual patient was calculated conventionally using the Mant and Hicks **cumulative relative benefit** approach³.

Treatment adherence and overlaps (*Appendix 1, page 7*)

To avoid double counting, **potential overlaps** between different groups of patients were identified and adjusted. **Adherence** (the proportion of treated patients actually taking therapeutically effective levels of medication) was assumed to be 100% in hospital patients, 70% in symptomatic community patients, and 50% in asymptomatic community patients¹⁹⁻²¹.

Sensitivity Analyses (*Appendix 1, page 7*)

Similar to economic evaluation studies in health²², 95% uncertainty intervals around the model output (i.e., DPPs) were calculated using Monte Carlo simulation. This calculation involved replacing all fixed input parameters used in the model by appropriate probability distributions, and repeatedly recalculating the model output with values sampled from the defined input distributions (see Appendix 1 Page 10 eTable 1). We used the EXCEL add-in Ersatz software (www.epigear.com) to perform 10,000 runs to determine the 95% uncertainty intervals of the DPPs (2.5th and 97.5th percentile values corresponding to the lower and upper limits). For clarity, the “best” estimates only are reported in the text and the “maximum” and “minimums” in Tables 3 and 4.

Model validation: comparison with observed mortality falls

The model estimates for the total number of deaths prevented or increased by each risk factor change and each treatment were summed. These estimates were then compared with the observed changes in mortality in each age group for men and women.

Results

Mortality trends

Age adjusted CHD mortality rates rose by 20% in Tunisia and by 62% in Syria during the observation period for each country. In contrast, age adjusted CHD mortality rates fell by 17% in oPt and by 29% in Turkey (Table 2, Figure 1).

These mortality trends resulted in approximately 680 additional deaths in Tunisia and some 6,370 additional deaths in Syria, in the final year compared with the initial year. The declines in mortality rates resulted in approximately 120 fewer deaths in oPt and 35,720 fewer deaths in Turkey (see Table 2; minimum and maximum estimates are detailed in Tables 3 and 4).

Large variations in CHD mortality trends were seen for men and women, with the relative changes generally favouring men, except in Tunisia (Table 2, Figures 2-3).

Risk factor trends and associated mortality changes (Figure 2 and Table 3)

SMOKING: Smoking prevalence decreased in all countries apart from Syria. Major changes were seen in Turkey; a fall of -11% (41% relative reduction) followed by oPt -10% (31% relative reduction). However smoking generally remained common among men (45% to 59% prevalence across the four countries). In Tunisian women, smoking prevalence doubled from 2% to 4%, resulting in some 30 additional deaths in the final model year. In Syria, smoking increased in women from 10% to 15% generating approximately 100 additional deaths in the final year. In oPt smoking prevalence decreased by 14% among men and by 7% in women. In Turkey, there was a major reduction in smoking prevalence of 20% in men and 2% in women, accounting for over 7200 fewer CHD deaths in men and nearly 1200 fewer deaths in women (Table 3 and Appendix 3).

SYSTOLIC BLOOD PRESSURE: Population mean systolic blood pressure (SBP) levels increased slightly in Tunisia (+0.6 mmHg) and rose substantially in Syria (+8.7 mmHg) but were broadly static in oPt and decreased in Turkey (-2.6 mmHg).

Important differences were seen between men and women. In Tunisia, SBP increased on average by 4 mmHg for men (129 mmHg to 133 mmHg), whereas in women it fell by 2 mmHg (131 mmHg to 129 mmHg) – see Figures and Appendix 3. Similarly in oPt, average SBP decreased by 0.7 mmHg in men while among women it increased by 0.7 mmHg.

The increase in SBP in Tunisia and Syria resulted in over 2,200 additional deaths according to our model estimates. The decrease in Turkey and oPt resulted in nearly 9,000 CHD fewer deaths in the two countries.

CHOLESTEROL: Cholesterol levels increased in both Syria (+0.3 mmol/l) and Tunisia (+0.14 mmol/l). In Turkey levels remained broadly constant (+0.01 mmol/l), and in oPt decreased by 0.06 mmol/l.

There were different trends for men and women. In Tunisia, cholesterol increased by 0.73mmol/l in men but decreased by 0.42mmol/l in women. In Syria, cholesterol levels increased in both men and women (0.22 and 0.38 mmol/l respectively), and rose modestly in Turkey (by 0.01 mmol/l in men and women). In oPt, cholesterol levels decreased in men (-0.07 mmol/l) and women (-0.11mmol/l). Over 270 additional CHD deaths in Tunisia, 310 in Turkey and 1350 in Syria were attributable to the rises in cholesterol. The reduction in oPt resulted in approximately 40 fewer CHD deaths.

BMI: BMI rose substantially in all four countries, increases ranging from 1.4 kg/m² in Tunisia to 3kg/m² in oPt. Absolute levels were much higher in women over the whole time period. BMI generally rose more among men than women (except in Syria where the increase was similar in

men and women). More than 80 deaths in Tunisia, nearly 400 deaths in Syria, and over 3000 deaths in Turkey were attributed to this obesity rise (Table 3).

DIABETES: Diabetes prevalence also increased substantially in all four countries. Overall, a 43% relative increase was observed in Tunisia, 52% in Syria, 44% in oPt and 21% in Turkey. In general bigger increases were seen in men than in women. In Tunisia, diabetes prevalence increased more among men (12% to 19%) compared with women (12% to 16%). In Syria there was a similar relative increase in diabetes in men and women of +52%, but overall prevalence was higher in women (15% versus 11% in men). In oPt, the relative increases in diabetes were also around 2.5 times as much in men (+64%) as in women (+26%), In Turkey diabetes increased similar in men and women (+21%).

Our model estimated that over 5,000 additional CHD deaths could be attributed statistically to the rising diabetes prevalence in the region (approximately 30 in oPt, 60 in Tunisia, 600 in Syria, and around 4,500 additional deaths in Turkey – Table 3).

PHYSICAL INACTIVITY: Trends in physical inactivity are particularly difficult to interpret and could not be estimated at all in Syria. The contribution of physical inactivity trends was in general small because available data suggested that physical activity levels were low and remained low over the time period of the study.

Effect of adjusting for cumulative risk factor trends

Adjusting for multiple risk factor trends occurring simultaneously reduced the proportion of the total mortality change that could be explained by risk factors significantly. In absolute terms, this was reduced by between 6 percentage points in Turkey (from 36% to 30%); 10 in oPt (from

56% to 46%) to 18 in Syria (from 90% to 72%) and 19 percentage points in Tunisia (from 98% to 79%) to and age group, compared with a simpler additive model.

Estimating the contribution of medical and surgical treatments

The impact of other primary preventive therapies (mainly statins) was low except in Tunisia (Table 4a, Figure 3).

Overall contribution of evidence based treatments and risk factors

Overall treatment uptakes increased in all countries.

a) in countries with *increasing* mortality rates (Tables 3 & 4a)

Adverse trends in risk factors explained approximately 79% of the observed mortality rise in Tunisia and over 72% of the increase in Syria, after adjusting for the effects of cumulative risk factor changes. In effect, this means that between 21% of the rise in Tunisia and 28% in Syrian cannot be explained.

These mortality rises occurred in spite of improved treatment uptakes, resulting in approximately 450 fewer CHD deaths in Tunisia and some 2140 fewer deaths in Syria (Table 4a).

b) in countries with *declining* mortality rates (Tables 3 & 4b)

In the occupied Palestinian territories (oPt) risk factor changes explained more than 46% of the overall mortality fall with treatments accounting for approximately 32% and in Turkey the relative contribution was approximately 30% for risk factor reduction and 47% for increased

treatment uptake (Table 3). This means that 22% of the decline was not explained in Turkey and 23% in oPt.

The largest medical contributions generally came from the community based treatments (treatment outside of hospital settings), particularly prescribing of aspirin and other secondary preventive medical therapies such as statins and anti-hypertensives after AMI, and community treatments for heart failure. In oPt and Turkey, hypertensive therapies also made important contributions.

Model validation

The IMPACT model has been replicated in over 15 countries worldwide, though most of these are high income countries. The model has also recently been validated for forward prediction in European populations²³. The agreement for future projection was generally high (varying from 90% of 106% of expected deaths prevented or postponed, albeit over short periods of time^{23 24}. We assessed agreement between model estimates of the number of deaths prevented or postponed with official mortality statistics in these countries. The IMPACT Model estimates were apparently able to explain approximately 75% of the observed mortality changes in Turkey, and oPt, but less in Syria, and Tunisia respectively, although the fit depends on whether adjusted or unadjusted risk factor DPPs are combined, and whether risk factor and treatment trends are also summed (Tables 3 and 4, Appendix 4 Table 2). This may reflect that the model was originally developed for populations where CHD mortality is declining, or possibly reflect issues with data quality. However the model does not include trends in all CHD risk factors and hence 100% agreement would not be expected.

Discussion

Summary of main findings

CHD mortality rates have dramatically risen in Tunisia and Syria, but have thankfully fallen in the occupied Palestinian territory (oPt) and Turkey. These mortality trends mainly reflect changes in major cardiovascular risk factors, moderately alleviated by treatment contributions. These treatment contributions appeared slightly greater in Tunisia and Turkey; this may reflect a stronger primary health care system in the latter case²⁵, and higher uptake of effective medical therapies for secondary prevention after AMI or CABG/PCI surgery. In Tunisia, uptake of initial treatments for AMI was also proportionately higher. Treatment contributions appeared weakest in Syria, probably reflecting a limited and deteriorating primary health care system (even before 2011)²⁵, though there was some prescribing of effective drug treatments for chronic angina and heart failure. In all four countries, BMI and hence diabetes was rising, and these adverse trends would have resulted in increases in CHD mortality of about 2-10% and 10-20% respectively. However, trends in other risk factors were more heterogeneous. In Syria, smoking prevalence increased slightly (explaining 3% of the upward trend) but in Turkey and oPt smoking prevalence fell substantially (explaining almost 25% of the reduction in mortality). Systolic blood pressure also fell in Turkey (explaining almost another 25% of the downward trend), possibly reflecting both increased prescribing of anti-hypertensives and falls in salt consumption^{26 27}. Cholesterol levels declined slightly in oPt and were relatively flat in Turkey, but around 40% of the small increase in CHD mortality in Tunisia could be attributed statistically to rising cholesterol levels, and just over 20% in Syria. Overall, in the two countries with increases in CHD mortality, (Tunisia and Syria), the adverse risk factor trends explained most (70-80% roughly) of the increase. In populations with falling CHD mortality rates, about one-third to half the decline was attributed to declines in major risk factors (smoking

cholesterol and blood pressure), with another one-third to half attributed to increased uptake of effective medical and surgical treatments for CHD (see Appendix 4, Table 2). In some Western countries, the IMPACT model has been able to explain more of the mortality trends, but this may not be surprising given imperfect data. The data on risk factor changes generally came from high quality nationally representative studies using good valid measurement methods such as repeated BP measurements, fasting plasma glucose for diabetes, particularly in Tunisia. However in Syria and oPt some data was based on sub-regional studies which we had to assume were nationally representative, particularly at the earlier time point. Risk factor data and quality are addressed in more detail in another publication¹⁴ and appendix 3. Routine data on treatment uptakes and trends was of more variable quality but we supplemented this by carrying out our own surveys and audits specifically for this project (see appendix 2). It is possible that our analyses may slightly over-estimate the treatment contributions, since hospitals that take part in such studies are more likely to be tertiary referral centres, and may hence be performing better than other secondary centres, although we adjust for this factor in probabilistic sensitivity analyses. We would also acknowledge that treatment data from the first time point (in the mid-1990s) were more uncertain and limited. However, this does not greatly influence model estimates since very little in the way of effective medical or surgical treatments were available in any of the 4 populations at the beginning of the model period. Death certification data is more variable in quality in low and middle income countries. Reassuringly, there has been no change in completeness of Tunisian death certification over this time period which could bias our results²⁸, and death certification data from oPt was classed as “medium” quality according to WHO criteria²⁹. In Turkey, analyses of causes of death from a previous national burden of disease study were used to adjust death certification estimates³⁰. Whilst there are concerns about national death registry deaths in Syria, we used alternative sources (the Aleppo Household survey)³¹, which we considered more valid albeit at

the possible cost of generalisability. The diverging trends powerfully emphasise that regions should not be treated homogeneously³². Previous Global Burden of Disease analyses³³ projected specific risk factor trends against the levels and changes in wealth and urbanisation in around 100 developing countries. For example, with increasing affluence both obesity and cholesterol levels tend to increase. Our study shows that CHD death rates are rising in Tunisia and even more substantially in Syria (prior to the current conflict), the poorest of the four countries (Gross National Income in International Dollars (Purchasing Power Parity) GNI I\$ 4,010 in 2005, and compared with Tunisia (GNI 6,820). By contrast, Turkey, with a far higher GNI of 11,330 demonstrated clear mortality falls. Furthermore, all four populations experienced substantial increases in BMI, with Syria showing the greatest increase, and Turkey the least.

The occupied Palestinian territory (oPt) appears an interesting outlier, with slight cholesterol falls (and generally favourable risk factor trends) despite apparently very modest levels of wealth and the lowest GNI of the four (GNI I\$2,710). However, there are known difficulties in estimating GNI for the oPt³⁴. The mortality falls may reflect substantial international donations, high levels of education and literacy and a relatively well developed public health system^{35 36}, partly facilitated by a small population size. Furthermore, it suggests that CHD mortality trends cannot simply be predicted by levels of economic development.

Perhaps most critical in explaining differences across the region are the smoking levels and trends. Smoking prevalence remained very high in men in Syria and Tunisia but declined in Turkey and oPt. Although smoking is relatively uncommon among women in Tunisia and Syria, both may be underreported (particularly as most national sources are self-reported) and there are also worrying signs that it may be increasing, particularly in younger people³⁷.

Different trends were seen for obesity between men and women. Although greater increases in BMI were observed in men, mean BMI remains much higher in women, particularly in Syria and

Tunisia. The high levels of female obesity presumably reflect traditional gender roles, gender inequality, and limited opportunities for women to leave the home environment (and partake in any physical activity). Data on physical activity are seriously limited across the region; however a recent Tunisian survey³⁸ demonstrated very low levels of female participation in regular exercise of any kind. Trends in other risk factors were broadly similar by gender.

Dietary trends

Rapid risk factor and mortality changes observed in this study clearly reflect substantial economic and nutritional transitions in the Middle East. A dramatic rise in per capita energy and fat supplies in most countries has occurred over the past four decades. For example, between 1971 and 1997, calorie intakes rose by over 40% in Syria and Tunisia, (from 2,340 to 3,350 calories in Syria and from 2,280 to 3,280 calories in Tunisia)³⁹. Fat intakes similarly increased by over 60% over the same time period³⁹. Sugar consumption may also have risen³⁹⁻⁴¹, whilst intakes of fruit, vegetables and fibre have all fallen³⁹. The high calorie intakes, and limited physical activity have resulted in particularly high obesity rates, and hence escalating diabetes prevalence in this region. Sodium intake is also high, thereby increasing blood pressure²⁶. Rapidly increasing urbanisation probably underlies some of the dietary trends, with increased availability of processed foods, and possibly compounded by lower requirements for routine physical activity. In Turkey for example, between 1988 and 2008 the proportion of the population dwelling in urban areas increased from 25% to 75%.

Methodological adjustment for cumulative risk factor trends

The methodological refinement in this paper, accounting for multiple risk factor trends occurring simultaneously, significantly affected the proportion of the mortality trend that could be attributed to individual risk factor changes, reducing it by up to nearly 20% compared with

previous analyses. This contrasts with a previous study which did not demonstrate significant differences between these two approaches in a UK setting³⁴. This difference may reflect the rapid risk factor trends that have been observed in the middle income countries in this study, and suggests that this refinement is most critical in countries in transition, undergoing rapid epidemiological changes. However, most current global modeling studies that attribute mortality trends to specific risk factor trends do not generally use a cumulative approach. Our study thus provides evidence of the importance of specific modeling approaches in this context, as well as original data for this under-researched region.

Increasing uptake of evidence-based treatments

Some favourable trends in the uptake of effective treatments have occurred, particularly in oPt and Turkey. The major contributors were improved uptake of aspirin and other secondary prevention medications, plus community heart failure treatments. Although the patterns were broadly similar there were some important differences between countries. For instance Tunisia had a much higher uptake of statins for primary prevention, but in other populations these uptakes remained low at the end of our period of analysis (approximately 2008), suggesting significantly greater potential with increasing use in the future⁴². Simple, accepted drug regimens or combinations (generally including aspirin, a calcium channel blocker, ACE inhibitor and statin) may be cost-effective for CHD patients even in low income settings and merit further study^{43 44}. However, treatment uptakes are still generally very low⁴⁵ emphasising the remaining potential for cheap, effective medical therapies to help reduce CHD mortality rates.

Strengths and limitations of the data and IMPACT model methodology

Modelling studies have a number of potential strengths, providing integration and simultaneous consideration of large amounts of data. The IMPACT Model has been widely used to explain CHD mortality trends, and has now been validated in over 15 high income populations³⁴. However, this is the first analysis of middle income populations in the Middle East.

We acknowledge many limitations. All models are dependent on the quality and extent of data available, and the outcome data (CHD mortality) is particularly important. Mortality trends by cause of death remain uncertain in many low and middle income countries due to incomplete or inaccurate coding, and a lack of trend data. Global Burden of disease analyses highlight the significant declines in adult mortality seen in many low and middle income countries in recent decades⁴⁶. Life expectancy has risen in all 4 populations, but this is driven mainly by substantial declines in infant mortality⁴⁷. As CHD is a major component of total mortality, this might lead us to expect that age-specific CHD mortality is also falling globally. However, our data from Syria and Tunisia demonstrated increasing age-specific CHD mortality in recent years. In support of our findings, major CHD risk factors (smoking, blood pressure, and blood cholesterol) which together account for about 85% of variation in CHD mortality⁴⁸ were either stagnant or increased in Syria and Tunisia over this time period; no substantial decreases were observed. Reassuringly, there has been no change in completeness of Tunisian death certification over this time period which could bias our results²⁸, and whilst there are concerns about national death registry deaths in Syria, we used alternative sources (WHO and the Aleppo Household survey). A picture of continued adult mortality decline is by no means clear cut since other authors using the Demographic and Health surveys suggest that mortality decline has recently flattened in some MENA countries (Jordan, Yemen and Morocco)⁴⁹. Further, an increase in age-specific CHD mortality has also recently been reported in the largest country in this region (Egypt⁴⁶). Hence our detailed analyses by country highlight the heterogeneity in cause of death trends among middle income countries. The Middle East

suffers particularly high male smoking rates and very low levels of physical activity; BMI and diabetes have been increasing faster than elsewhere in the world.

Overall, the IMPACT model apparently explained up to 77% of the mortality trend observed in each country. This appears acceptable, particularly considering the variable death certification and imperfect risk factor measurement across the region.

The model itself makes many simplifying assumptions. First it ignores potential lag times between changes in a risk factor and change in mortality, however, evidence suggests that lag times can be very short in practice¹⁵⁻¹⁸. It assumes a log-linear association between risk factors and CHD mortality; and the regression approach implicitly assumes that other, unmeasured risk factors have not changed over the model time period. This is not likely to be the case in practice. It assumes that trial estimates (efficacy) of medical and surgical treatments can be realised in practice; however, it does account for variable uptake and compliance of treatments. Estimates of one-year case-fatality had to be obtained from international rather than national sources and are thus uncertain (see eTable 3). We did not explicitly consider competing risks. However, reductions in smoking prevalence (in Turkey and oPt) should also reduce death rates from common cancers and respiratory diseases. Increases in BMI and diabetes however might also increase risk of deaths from diabetes or cancers. The model does account for changes in age structure over time, which are small over this relatively short time period. The data itself are only available at the population level. The model itself is thus essentially ecological in nature. However, we only include treatments and risk factors where there is strong evidence of a causal relationship with CHD mortality.

Naturally, data availability was variable across the countries involved. We populated the models with “national level” data or data from surveys covering a range of representative areas (such as in Turkey). Most of the major risk factors were measured rather than self-reported e.g.

BMI was measured as height and weight, SBP and total cholesterol and diabetes were also measured using appropriate blood pressure monitors and blood tests. Smoking status is usually self-reported in surveys. While generally considered valid, this could result in an underestimate of smoking status, particularly among women in countries like Tunisia, where female smoking is still culturally frowned upon⁵⁰. Physical inactivity is also self-reported, and could be less reliable. Using national level or regional data may also conceal important heterogeneity within countries e.g. by urban / rural location or socio-economic status^{30 31 51-53}. It is possible that the relative contribution to CHD mortality trends from increased treatment uptake could be lower in some poorer, rural regions where health insurance coverage is lower and services weaker. For example, situational analyses of NCD clinics, a separate part of this EC funded project, found that both patient record keeping and staff skills were weaker in poorer rural areas, and along with inadequate referral arrangements, could potentially lead to poorer treatment outcomes²⁵.

Our model explains change in mortality over time, rather than the absolute levels. Whilst trends within the four countries are considered reliable (Appendix 2), comparisons between them should be made cautiously, due to potential differences in coding practices and quality of death certification. The model probably captures all major contributions to mortality change, but the contributions of each component have substantial uncertainty. However, probabilistic sensitivity analysis demonstrated that the relative contributions of risk factor changes and treatments to the overall mortality trends were reasonably consistent.

The current model only reports on mortality. Other outcomes (incidence, life years gained or lost, and cost-effectiveness) though potentially valuable⁵⁴ would require further data which is not readily available in the region. However this merits attention in future work.

Policy Implications

Our results may be cautiously generalisable to other low and middle income populations, especially in the Eastern Mediterranean region (recognising the many potential similarities in social, cultural and economic attributes of these societies). It also highlights both the challenges (missing data) and benefits (identifying potential heterogeneity and effects of individual treatments) of grounding analysis in country-specific data, compared with other approaches. Clearly, the political catastrophe that has engulfed Syria since 2011 inevitably reduces the immediate relevance of the lessons that may be drawn from our Syrian findings; however, in the longer term these may provide a baseline for subsequent policy analysis and future policy development in a post-conflict era.

Our findings highlight the consistently powerful effects of even small changes in the major cardiovascular risk factors, smoking, blood pressure and cholesterol. Furthermore, dramatic rises in diabetes have occurred across the region, mainly reflecting marked increases in BMI and adverse trends in diet (particularly salt, sugar, saturated fat and calorie intakes). These dietary and obesity trends also underlie most of the observed increases in blood pressure and cholesterol levels.

These current adverse risk factor trends are very worrying and represent a clear wake-up call. They justify stronger regional and global policy responses targeting smoking, unhealthy diet, and physical inactivity. Effective interventions exist^{55 56 57-59}; but their implementation may be politically challenging across diverse cultures. However, our analysis clearly demonstrates different trends across the countries, suggesting that national policies should perhaps be tailored to local priorities. Countries such as oPt and Turkey have performed relatively well on reducing SBP, cholesterol and smoking (despite on-going political difficulties). Neighbouring countries might therefore perhaps consider similar policies. Mortality trends broadly reflect

changes in risk factors more than improved treatment uptake. In countries with well-established primary health care systems, medications may provide a useful strategy in addition to population-based interventions. Yet, whilst appropriately targeted medical interventions can be cost-effective, they may be difficult to implement, especially in countries without comprehensive primary health care. Population based policy interventions to reduce risk factors can also be challenging to implement and enforce, and the evidence base for reducing obesity and diabetes in low and middle income countries is sparse. However, evidence from other countries suggests that tobacco control and dietary policies can be powerful, rapid and cost saving.^{55 56 60, 61 62} These evidence-based policy interventions should therefore be strongly recommended for the prevention of both CHD and other non-communicable diseases.

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JC and SC conceived the idea of the study, and JC obtained the funding. MOF led the project supervised by SC and JC. SR, OS, NAR, KS, NBM, AS, RAA, BU, HA, GG, DUA, HS, SD, YD, OA assembled the datasets; extracted the data and populated the models with input from FF, WM, HBR, BU, AH, SC, MoF, JC, KB, PP, and NU. SC, MDh and JC wrote the first draft of the paper, and JC finalised the manuscript. All authors contributed to the analysis, intellectual content, critical revisions to the drafts of the paper and approved the final version. SC is the guarantor.

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Data sharing:

Supplementary appendices (attached) available with open access from the corresponding author.

Abbreviations

AMI: Acute Myocardial Infarction; BMI: Body mass index; CABG: Coronary Artery Bypass Graft; CHD: Coronary heart disease; DPP: deaths prevented or postponed; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; SBP: Systolic blood pressure.

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Tables

Table 1. Socio-demographic and economic comparisons of the four Eastern Mediterranean countries.

Table 2. Crude CHD mortality rates and trends in the four Eastern Mediterranean countries

Table 3. Risk factor trends and consequent mortality changes in the four countries

Table 4a: Treatment contributions: numbers of patients in specific groups and CHD deaths prevented or postponed in Tunisia and Syria where CHD mortality was rising (men and women combined)

Table 4b: Treatment contributions: numbers of patients in specific groups and CHD deaths prevented or postponed in the oPt and Turkey where CHD mortality was falling (*men and women combined*)

Figures

Figure 1. Age-standardised CHD mortality rates and trends in the four Eastern Mediterranean countries (*initial year and final year*)*

Figure 2. Proportion of deaths (increasing or decreasing) attributed to changes in major risk factors, (*by country and sex*)

Figure 3. Proportion of deaths prevented or postponed attributable to increased uptake of specific treatments (*by country and sex*).

Table 1:
Socio-demographic and economic comparison of the four Eastern Mediterranean countries

Country	Population (millions)	Life expectancy (at birth)	% of total mortality attributed to CHD	Per capita GNI PPP\$
Tunisia	10.1	74	27.14%	6,820
Syria	18.9	75	34.25%	4,010
Palestine (oPt)	3.8	72	21.98%	2,710*
Turkey	70	74	18.66%	11,330

Footnotes: GNI per capita PPP\$ is Gross National Income in PPP US \$

Sources: Arab Human Development Report 2009. UNDP, HDR 2007/2008 for Tunisia, Syria and oPt (data for 2005).

Turkey Statistical Institute for Turkish data (2007).

Per capita GNI from World Bank Development Indicators (UN data, 2005).

Life expectancy from World Bank

<http://www.indexmundi.com/facts/indicators/SP.DYN.LE00.IN/compare?country=sy>.

Proportion of all deaths from CHD <http://vizhub.healthdata.org/gbd-compare/> (year 2010)

Table 2:Crude CHD mortality rates and trends in the four Eastern Mediterranean countries

Country (years)	Sex	Population (,000)		Number of deaths	Rate/ 10 ⁵	Number of deaths	Rate/ 10 ⁵	% change in rate	% change in directly age-standardised rate ⁵ [annual change %]	Observed increase or decrease in deaths*
		Initial Year	Final year	Initial year		Final year				
Tunisia (1997-2009)	Total	4301	5700	2106	49	3633	64	+ 30	+20 [+1.7% p.a.]	+682
	Men	2126	2789	1492	70	2429	87	+ 24		+332
	Women	2176	2911	614	28	1205	41	+ 47		+350
Syria (1996 - 2006)	Total	5013	7410	5429	108	12503	169	+ 56	+62 [+6.2% p.a.]	+6372
	Men	2538	3735	3608	142	8119	217	+ 53		+3772
	Women	2475	3675	1821	73	4384	119	+ 62		+2660
oPt (1998 - 2009)	Total	610	913	520	85	586	64	-25	-17 [-1.5% p.a.]	-122
	Men	302	461	318	105	394	86	- 19		-60
	Women	308	452	202	66	192	43	- 35		-62
Turkey (1995 – 2008)	Total	18932	27958	79066	418	96366	345	-17	-29 [-2.2% p.a.]	-35,718
	Men	9418	13655	42938	456	49910	366	-20		-17,162
	Women	9514	14303	36128	379	46457	324	-14		-18,556

Footnotes:

§CHD mortality rates for ages 35-74 (this age range chosen to be consistently available from all 4 populations), standardised to the World Standard Population.

*This figure represents the observed change in mortality using indirect standardisation i.e. after accounting for changes in the age-sex structure of the population over time. This is the change in deaths which the model then attempts to explain. It applies only to the final year of the period (2006 in Syria, 2008 in Turkey, 2009 in oPt and Tunisia).

Table 3: Risk factor trends and consequent mortality changes in the four Eastern Mediterranean countries (men & women combined)

Country	Risk Factor	Prevalence		Absolute change in risk factor*	Changes in deaths (increases or decreases)*			% of total mortality trend
		Initial year	Final year		Estimated	Min	Max	
Tunisia (1997 – 2009)	Smoking	23.9	22.7	-1.2	-14	-53	24	-2.1
	SBP (mmHg)	130.4	131.0	+0.60	+166	+20	+350	+24.3
	Cholesterol (mmol/l)	4.59	4.73	+0.14	+273	+204	+384	+40.0
	BMI (kg/m ²)	26.0	27.5	+1.44	+86	+60	+112	+12.6
	Diabetes %	12.1	17.3	+5.2	+62	+4	+123	+9.2
	Physical inactivity%	98	85	-13	-35	-48	-23	-5.1
	Total				+538	+368	+777	+78.9%
Syria (1996 -2006)	Smoking	33	37	+4	+171	-216	+549	+2.7
	SBP (Systolic BP)	122.2	130.9	+8.7	+2073	+1209	+3576	+32.5
	Cholesterol	5.05	5.34	+0.29	+1348	+1006	+1508	+21.2
	BMI	28.0	29.7	+1.8	+373	+266	+479	+5.9
	Diabetes	9	13	+4	+636	+242	+1013	+10.0
	Physical inactivity%	-	-	-	-	-	-	-
	Total				+4601	+3428	+6186	+72.2%
oPt (West Bank) (1998 -2009)	Smoking	32%	22%	-10	-29	-78	+11	-23.7
	SBP (Systolic BP)	121.4	121.3	-0.10	-33	-235	155	-27.3
	Cholesterol	5.0	4.94	-0.06	-39	-140	46	-32.3
	BMI	28.0	31.0	+3	+2	-23	+28	+1.7
	Diabetes %	9	12	+3	+28	-16	+71	+22.7
	Physical inactivity%	84	92	+8	+16	+8	+17	+10
	Total				-56	-160	+294	-45.7%
Turkey (1995 – 2008)	Smoking%	27	16	-11	-8423	-10205	-6679	-23.6
	SBP	127.2	124.6	-2.6	-8723	-12453	-4763	-24.4
	Cholesterol	4.96	4.97	+0.01	+310	-2238	+2797	+0.9
	BMI	27.4	29.0	+1.6	+3310	+2783	+3878	+9.3
	Diabetes %	15.5	18.7	+3.2	+4456	+2236	+6651	+12.5
	Physical inactivity%	70	65	-5	-1683	-2418	-1085	-4.7
	Total				-10763	-16191	-4955	-30.1%

*Footnote: A positive value denotes an increase in the risk factor and an increase in deaths attributed to the risk factor increase. A negative value denotes a decrease in the risk factor and a consequent decrease in deaths attributed to the risk factor. Physical activity data not available from Syria. Individual rows may not sum to their sub-totals due to rounding.

Table 4a: Treatment contributions: numbers of patients in specific groups and CHD deaths prevented or postponed in Tunisia and Syria where CHD mortality was rising
(men and women combined)

1.

Country	Treatment group	Eligible Patients	Deaths prevented or postponed (estimates)			Estimated % reduction in CHD mortality attributed to treatments		
			Best	(Min)	(Max)	Best	(Min)	(Max)
Tunisia	Acute Myocardial Infarction (AMI)	4505	89	78	101	7.8	6.9	8.9
	Unstable Angina	6755	77	67	88	6.8	5.9	7.8
	Secondary Prev Post AMI	24058	95	87	103	8.4	7.7	9.1
	Secondary Prev Post CABG/PCI	1300	3	2	3	0.3	0.2	0.3
	Chronic Angina	53436	0	-19	15	0.0	-1.7	1.3
	Hospital Heart Failure	3614	37	22	55	3.3	2.0	4.9
	Community Heart Failure	25298	49	43	55	4.3	3.8	4.9
	Hypertension Treatment	1496744	80	38	138	7.1	3.4	12.2
	Statins primary prevention	601743	21	18	24	1.9	1.6	2.1
	Total*		448	376	530	39.7	33.2	46.9
Syria	Acute Myocardial Infarction (AMI)	18002	287	250	321	3.4	2.9	3.8
	Unstable Angina	22877	150	142	158	1.8	1.7	1.9
	Secondary Prev Post AMI	78976	372	280	481	4.4	3.3	5.7
	Secondary Prev Post CABG/PCI	26316	65	46	84	0.8	0.5	1.0
	Chronic Angina	319974	803	638	1013	9.4	7.5	11.9
	Hospital Heart Failure	6927	84	-9	168	1.0	-0.1	2.0
	Community Heart Failure	52251	332	279	376	3.9	3.3	4.4
	Hypertension Treatment	863425	45	17	78	0.5	0.2	0.9
	Statins primary prevention	307295	6	4	10	0.1	0.0	0.1
	Total*		2145	1648	3170	25.2	23.0	27.4

Footnotes:

The denominator is the estimated total number of CHD deaths in the absence of any treatments i.e. Tunisia 1130 (680+450) and Syria 8515 (6370+2145).

For Tunisia, chronic angina treatment in the community (best estimate) is zero since aspirin use was already high in the model base year (1997), and hence there was little scope for increase over time.

*The totals row does not represent the sum of each treatment component due to the bootstrap methodology.

KEY:

AMI = Acute myocardial infarction

CABG = Coronary artery bypass graft surgery

PCI = Percutaneous intervention

Table 4b: Treatment contributions: numbers of patients in specific groups and CHD deaths prevented or postponed in the oPt and Turkey where CHD mortality was falling (men and women combined)

Country	Treatment group	Eligible Patients	Deaths prevented or postponed (estimates)			% of the mortality change explained		
			Best	(Min)	(Max)	Best	(Min)	(Max)
oPt	Acute Myocardial Infarction (AMI)	489	2	2	2	1.9	1.3	1.7
	Unstable Angina	489	1	1	1	1.1	1.0	1.2
	Secondary Prev Post AMI	2266	8	6	10	7.3	5.0	8.6
	Secondary Prev Post CABG/PCI	1974	2	2	3	1.9	1.5	1.9
	Chronic Angina***	22180	10	9	11	8.4	7.2	8.8
	Hospital Heart Failure	468	2	2	3	1.5	1.5	2.1
	Community Heart Failure	2342	7	5	8	5.3	4.5	6.2
	Hypertension Treatment	81894	5	4	6	4.1	3.1	6.2
	Statins primary prevention	7030	0	0	0	0	0	0.0
	Total		38	29	46	31.5	23.4	37.7
Turkey	Acute Myocardial Infarction (AMI)	91317	1677	1448	1930	4.7	4.1	5.4
	Unstable Angina	45658	638	562	722	1.8	1.6	2.0
	Secondary Prev Post AMI	759071	4570	4100	5088	12.8	11.5	14.2
	Secondary Prev Post CABG/PCI	273379	1752	1401	2160	4.9	3.9	6.0
	Chronic Angina***	103293	2622	2046	3265	7.3	5.7	9.1
	Hospital Heart Failure	46511	1025	891	1144	2.8	2.5	3.2
	Community Heart Failure	424511	2338	2074	2632	6.5	5.8	7.4
	Hypertension Treatment	10553133	2153	1899	2427	6.0	5.3	6.8
	Statins primary prevention	4483287	41	32	53	0.1	0.1	0.1
	Total		16794	16026	17598	47.0	44.9	49.3

KEY:

AMI = Acute myocardial infarction

CABG = Coronary artery bypass graft surgery

PCI = Percutaneous intervention