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Decline in Cardiovascular Mortality: Possible Causes and Implications

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Abstract

If the control of infectious diseases was the public health success story of the first half of the 20th century, then the decline in mortality from coronary heart disease (CHD) and stroke has been the success story of the century's last 4 decades. The early phase of this decline in CHD and stroke was unexpected and controversial when first reported in the mid-1970s, having followed 60 years of gradual increase as the U.S. population aged. However, in 1978 the participants in a conference convened by the National Heart, Lung, and Blood Institute (NHLBI) concluded that a significant recent downtick in CHD and stroke mortality rates had definitely occurred, at least in the U.S. Since 1978, a sharp decline in mortality rates from CHD and stroke has become unmistakable throughout the industrialized world, with age-adjusted mortality rates having declined to about one-third of their 1960s baseline by 2000. Models have shown that this remarkable decline has been fueled by rapid progress in both prevention and treatment, including precipitous declines in cigarette smoking, improvements in hypertension treatment and control, widespread use of statins to lower circulating cholesterol levels, and the development and timely use of thrombolysis and stents in acute coronary syndrome to limit or prevent infarction. However, despite the huge growth in knowledge and advances in prevention and treatment, there remain many questions about this decline. In fact, there is evidence that the rate of decline may have abated and may even be showing early signs of reversal in some population groups. The NHLBI, through a request for information, is soliciting input that could inform a follow-up conference on or near the 40th anniversary of the original landmark conference in order to further explore these trends in cardiovascular mortality in the context of what has come before and what may lie ahead.

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Keywords

Coronary heart disease; Cardiovascular mortality rate; Risk factors; Disparities; Hypertension

Introduction

The first 60 years of the 20th century saw a remarkable transformation in health and longevity in the US and other industrialized countries. In 1900, life expectancy in the US was only 47.3 years (46.3 for men, 48.3 for women and only 33 for Blacks).[1, 2] Infectious diseases such as pneumonia, influenza, tuberculosis, and gastroenteritis were the leading causes of death and collectively accounted for more than twice as many deaths as heart disease and stroke, the next two leading causes of death. By 1960, improvements in sanitation and the development of vaccines and antibiotics had brought about dramatic declines in infectious disease mortality and concomitant increases in life expectancy to 69.7 years (ranging from 61 for black men to 74 for black women).[1, 2] Heart disease, cancer, and stroke replaced infectious diseases as the leading causes of death.

The increasing preeminence of heart disease among causes of death in the first half of the 20th century in part reflects the decline of infectious diseases and the resulting increase in life expectancy, with many more Americans living to an age when they are likely to suffer the sequelae of chronic atherosclerosis. Indeed, many physicians of that era viewed atherosclerosis as a "natural" and somewhat inevitable feature of aging and regarded only "premature" cardiovascular disease (CVD) (before age 60) as a legitimate target for preventive medicine.[3] However, even in the 1960s, it was evident from time trends in age-adjusted heart disease rates since 1940 that heart attack rates were on the rise and were not merely a spurious manifestation of an aging population.[4]

Then, in the early 1970s, epidemiologists in the US and Australia published an unexpected observation – that coronary heart disease (CHD) mortality rates, after peaking in 1968, had apparently begun to decline[5–7]. This observation was met with skepticism in many quarters. For example, a 1975 editorial in the *British Medical Journal* questioned "whether the decline, which is far from dramatic, may be considered real" and concluded that, at that time, "the prospects of an appreciable improvement in coronary mortality rates do not seem bright".[8]

To look further into whether the observed decline in CHD mortality and factors that might explain it, the National Heart, Lung, and Blood Institute (NHLBI) convened the 1978 Bethesda Conference on the Decline in Coronary Heart Disease Mortality.[9] The conference participants included a panel of international experts from the fields of CVD epidemiology, clinical cardiology, biostatistics and public health practice and research. Among the data examined and discussed at the conference were figures and tables on cause-of-death statistics and their comparability, as well as technical aspects of trends in mortality decline.[9, 10] The conferees concluded that the evidence supported a previously unappreciated and unexplained decline of the heart disease epidemic and that a range of factors acting together, from changes in risk factor profiles to improved clinical management, were all likely to have contributed to this new trend. The conference also confirmed that the declining

CHD mortality rates appeared to be confined to the US and that the evidence that similar trends were occurring elsewhere was equivocal.[9]

Now, nearly 40 years after the original conference on the decline in CHD mortality rates, it has become clear that CHD mortality rates have continued to decline in the US (Figure 1) in both men and women (Figure 2) and throughout the industrialized world.[11–14] Using the 1940 US population as reference, the age-adjusted annual heart disease mortality per 100,000 fell by 56% from 307.4 in 1950 to 134.6 in 1996, while age-adjusted annual stroke rates per 100,000 fell by 70% during this same period from 88.8 to 26.5.[4] Annual age-adjusted cardiovascular mortality rates have continued to decline thereafter, falling by 22% from 376 to 274 per 100,000 from 1990 to 2013. Similar declines have been observed in nearly all regions of the world, especially in high-income North America, Western Europe, Japan, Australia, and New Zealand.[12, 13, 15] In most of these countries, the declines in CVD mortality rates have been phenomenal - more than 70% decline in men and women in the Netherlands;[16] and over 60% decline in the United Kingdom and Ireland - from 1980 through 2009.[16]

However, despite the huge growth in knowledge and advances in treatment (Table 1), there remain some remarkable and unresolved issues about this decline. The NHLBI, through a request for information (RFI),[17] is soliciting input that could inform a follow-up conference on or near the 40th anniversary of the original landmark conference[9] which took place in Bethesda, Maryland on October 24–25, 1978. Such a follow-up conference could convene the expertise needed to further explore recent trends in the CHD and total CVD mortality decline in the US and abroad and anticipate their future trajectories worldwide.[17]

Contributions to the Declining Cardiovascular Disease Mortality Rate: Relative roles of Primordial, Primary, and Secondary Prevention

An important first step in exploring future trajectories of CVD mortality trends is the examination of contributors to the decline in CHD mortality. Ford et al. used a previously validated statistical model (IMPACT Coronary Heart Disease Model) to examine contributions to the decline in age-adjusted mortality rate for CHD in the US from 1980 through 2000.[18] The IMPACT model incorporates major CHD risk factors such as cigarette smoking, high blood pressure, elevated total cholesterol, obesity, diabetes, and physical inactivity and all established medical and surgical interventions for CHD. The model has been used to examine the relative contributions of medical and surgical interventions for CHD versus preventive strategies that target the reduction of major CHD risk factors. The model has been validated and replicated, and has been used specifically in efforts to explain CHD mortality trends in more than 15 countries worldwide[19–43] Using this model, Ford et al. estimated that approximately 47% of the decline in CHD mortality rate from that period was attributable to evidence-based medical and surgical treatments while reductions in major risk factors contributed about 44%.[18] As reported by Ford et al, the percentage contributions included “secondary preventive therapies after myocardial infarction or revascularization (11%), initial treatments for acute myocardial infarction or unstable angina (10%), treatments for heart failure (9%), revascularization for chronic angina (5%), and other

therapies (12%)"[18] and "approximately 44% was attributed to changes in risk factors, including reductions in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%)".[18] About 9% of the decline remained unexplained.[18] importantly, increases in the body-mass index (BMI) and the prevalence of diabetes accounted overall for an additional 59,500 deaths from CHD in 2000, suggesting that a greater decline in CHD mortality would have been seen had the rise in BMI and diabetes prevalence been controlled.[18]

Although most of the countries where the IMPACT model has been used are in high-income North America and Western Europe, it has been used recently to explain CHD mortality trends in developing countries. [39] Additionally, the model has been used to make future projections or predictions of expected deaths prevented or postponed as part of the European Heart Health Strategy II (Euroheart II) Project on CHD mortality projections to 2020 comparing different policy scenarios.[44] In these assessments, the agreement between future CHD mortality and explicitly observed mortality in four countries was high and varied between 80% and 106%.[44]

Gouda et al.[45] have recently demonstrated that in trying to explain the contributions to the decline in CHD mortality rates, the choice of the metric for comparisons matters. For example, analyses that use the metric of "number of deaths prevented" typically attribute about half the decline to disease treatments and half to preventive strategies that reduce risk factor levels.[45] However, when a time-based metric such as "life-years-gained" is used, the contribution from changes in risk factors typically increases significantly to over 60%.[45] They demonstrated that deaths averted before age 65 years through reductions in risk factors contribute only 15.9% of the total deaths prevented or postponed (DPP) but 36.2% of total life-years gained (LYG).[45] For the CHD mortality decline in the US between 1980 and 2000, reductions in major risk factors contributed 42% when DPP is used as the metric whereas a contribution of 79% is noted when LYG is the metric chosen.[45]

The importance of major risk factors in the prevention, pathogenesis, and clinical outcomes of CHD are well-establised;[46, 47] thus, it is not surprising that changes in risk factor levels are important contributors to the CHD mortality decline in the US[48, 49] However, the relative contribution of the role of primordial, primary, and secondary prevention in that decline has been very difficult to establish due to the lack of reliable data on time trends and incidence of cardiovascular events likely to be affected by those changes[50] and because they are likely to vary from country to country. [51, 52] Ideally, prevention studies need to account for the role and incidence of out-of-hospital sudden cardiac death (SCD) that is known to be the most common fatal cardiovascular event in most CHD patients. Thus, there is a need for reliable, large population surveillance data including administrative data, data on incidence of CHD risk factors and their treatment, and death certificate data with cause of death certification. Most primordial/primary prevention studies so far have used retrospective data analysis and modelling.

Mansverk et al.[53] reported data from a 15-year prospective study in the Norwegian town of TromsØ that consisted of three population surveys conducted between 1994 and 2008 that included 29,582 participants free of myocardial infarction at inclusion. Main results showed

that age and sex-standardized CHD mortality fell by 7.3% annually and CHD incidence fell by 3%. Thus the authors could demonstrate the changes in incidence and case-fatality contributed 43% and 57%, respectively, to the decline in CHD mortality.[53] Most importantly, the study showed that changes in risk factors contributed almost two-thirds of the change in CHD events, 64% in women and 61% in men. The prevalence of most risk factors decreased during that period, except for increases in BMI and diabetes. The major cause of the observed decline in CHD mortality was a cholesterol decrease of about one-third, thus accounting for about half of the observed CHD mortality decline. Changes in systolic blood pressure, smoking, resting heart rate and physical activity each accounted for 9% to 14% of the decrease in risk of CHD, while increases in BMI and diabetes prevalence accounted for a 7% and 2% increase, respectively.

Bjork et al.[37] also tried to quantify the relative contribution of primary and secondary prevention on cardiovascular mortality, as well as the part medical treatment played in the known reduction of CHD mortality rate observed in Sweden between 1986 and 2002. Using the IMPACT model, they reported that 75% of the mortality reduction was accounted for by reduction of the major risk factors (cholesterol, blood pressure and smoking) in the asymptomatic population, leading to their conclusion that the “largest effects on mortality came from primary prevention”.[37] This study also made the observation that the major contributors to the mortality reduction were dietary changes during that period in Sweden (because the use of statins at that time was very low in asymptomatic individuals) while the large decrease in cholesterol in the CHD population was due to both diet and use of statins.[37]

Other studies have tried to model the role of primordial prevention. For example, O’Flaherty, calculated that a more aggressive policy producing substantial dietary improvements such as the one already achieved in other countries, would result in an estimated 30,000 fewer cardiovascular deaths in the United Kingdom between 2006 and 2015 compared to 12,500 less cardiovascular deaths if the current trend continued.[54] Other recent studies analyzing European[55] or American[56] data are consistent with these numbers. These studies strongly suggest that primordial and primary prevention account for a large part of the observed reduction in the incidence and rate of cardiovascular events observed in the last 20–30 years. Data from the prospective WHO MONICA Project confirmed the importance of the main cardiovascular risk factors by showing at least a partial correlation between changes in those risk factors and changes in CHD event rates.[57] The proportion of the decline explained by the change in risk factors may be lower in countries where there is no provision for universal health care, and where national health policies for primordial and primary prevention of CHD are not in place. Conversely, the increase in CHD mortality observed in countries such as China appear to be related to an increase in smoking rates and higher cholesterol levels further emphasizing the importance of risk factor reduction overall, and primordial or primary prevention in particular.[21]

The role of other potentially modifiable risk factors in primordial and primary prevention, such as environmental stressors, remains to be determined but is assumed to play an important role.[58] In 2010, an American Heart Association scientific statement indicated that “the overall evidence is consistent with a causal relationship between PM2.5 exposure and

CVD morbidity and mortality."[59] There is also evidence that ambient noise and air pollution have a combined effect on the increased incidence of cardiovascular disease.[60, 61] However, there are no direct data showing that the decreases in these environmental stressors lead to a decline in the incidence of CVD events. These studies suggest an independent improvement in life expectancy and a reduction in cardiovascular events after reduction of the exposure.[60, 61]

Recent trends in the increased prevalence of obesity both in adults[62] and children[63] in the US and other developed countries, but also in developing countries,[52] are associated with corresponding trends in diabetes, again highlighting the need for primordial and primary prevention with emphasis on policy and environmental changes that support and facilitate healthy lifestyle and behavioral choices.

In addition to primordial and primary prevention strategies, improvement in the delivery of evidence-based therapies in patients with established CHD contribute significantly to the decline in CHD mortality. A historical study conducted on patients undergoing coronary artery bypass graft (CABG) surgery between 1970 and 1984 estimated that the surgical contribution to the annual decrease in CHD mortality increased from 0.2% to 6.6% during that period.[64] Wijeysundera showed that a 20% reduction in mortality could be achieved by meeting quality indicators of use, with the greatest benefit obtained by use of ACE-inhibitors in patients with stable CAD and beta-blocker use in heart failure.[65] In the WHO MONICA Project, Tunstall-Pedoe et al.[66] were able to show that the use of evidence-based therapies before and during acute myocardial infarction was strongly correlated with a decrease in coronary event rates, including CHD mortality.[66, 67] Other data from the MONICA-Australia cohort also showed that 28-day survivors of acute MI had a 28% lower relative risk reduction for the risk of death over 12 years after the incident admission, but the benefit completely disappeared when the analysis was further adjusted for medical treatment (thrombolysis, antiplatelet, β blocker, angiotensin converting enzyme inhibitor, and lipid lowering drugs) received after admission.[68]

Some recent studies conducted after 2000 may indicate the results obtained by the reduction of cardiovascular risk factors may not be sustained, especially in the US. For example, Plikerton and al.[69] analyzed the results of the Behavioral Risk Factor Surveillance System using a global Cardiovascular Health Index (CVHI) developed by the American Heart Association, combining the major seven cardiovascular risk factors. There was a small decrease in the mean CVHI, with an increase in the prevalence of "nonsmokers" and favorable diet status, but a decrease in the prevalence of "ideal" blood pressure, cholesterol, and a higher reported prevalence of lack of physical activity, as well an increase in BMI and high blood glucose. There were significant disparities by State and demographic groups. Despite the design limitations, this study suggests there may be a population-wide decrease in primordial prevention.[69] Again, as demonstrated in other studies,[53, 70–72] there were negative trends recorded in BMI and high blood glucose, whose long term consequences on the overall CV prevalence and mortality remain to be determined.

Adverse Impact of Obesity and Diabetes

The continuing global epidemic of obesity remains one of the greatest public health challenges of the present century.[73] It has been estimated that if current trends continue through 2025, the global obesity prevalence (BMI ≥ 30 kg/m2) will reach 18% in men and exceed 21% in women.[73] The profile in the US has paralleled the global pattern with a recent study finding 35% of men and 36% of women obese.[74] These trends have not been limited to adults – among children in the US, during the last 4 decades, alarming increases in overweight and obesity have also been found. In fact, it is estimated that nearly a third of children in the US are overweight or obese.[75]

These rising trends in the prevalence of obesity and diabetes have significant implications for CHD mortality rates because of the recognition that diabetes is a coronary risk equivalent[76] and obesity is a major CVD risk factor. In spite of this recognition, it remains challenging to fully appreciate the impact of diabetes and obesity on the CHD mortality decline, especially across the entire lifespan, and in particular, in reference to their role in the perceived deceleration of the CHD mortality rate declines. Three important studies have examined this issue in the US. In the first study, Ford et al,[31] demonstrated that although nearly half of the decline in CHD mortality over the period of 1980 −2000 was attributed to reductions in risk factors, increases in the body-mass index and the prevalence of diabetes accounted for an increased number of deaths (8% and 10%, respectively).[31]

A second study examined CVD mortality rates between 1979 and 2011 and the variation across age and sex groups. In this study, adults ≥65 years of age showed consistent CHD mortality declines while younger men and women (<55 years of age) initially had declines in CHD mortality between 1979 until 1989, followed by two decades of stagnation with minimal improvement.[77] The reasons for this stagnation among younger persons are not clearly understood. The authors speculated that many factors, including the ongoing obesity epidemic, may have contributed to the findings. A third and more recent study, that used US national epidemiology data, found declines in CHD mortality from 2000–2014.[78] However, a deceleration in the CVD mortality rate decline was noted after 2011. Importantly, this deceleration occurred in males, females, and all race/ethnicity groups. The authors expressed concern about the adverse impact of obesity and diabetes on the mortality rate declines, especially considering the national epidemiological data showing that the prevalence of adult obesity increased from 22.9% in 1988–1994 to 34.9% in 2011–2012, while diabetes prevalence nearly tripled, between 1990 and 2013.[78] As shown in Figure 3, it has been estimated that if current trends continue unabated, there will be nearly 7.3 million incident cases of coronary artery disease and stroke in the US and UK by 2030.[79, 80] There will also be an estimated 65 million more obese adults in the USA and 11 million more in the UK by 2030 resulting in.[79, 80]

The challenge of attributing causality in the relationship between rising prevalence of obesity and deceleration in the CHD mortality decline is made even more complex by the lack of adequate understanding of the combined impact of fatness and fitness and the related confounding influence of exercise capacity on CVD mortality trends in diverse populations. For example, in study of more than 29,000 ethnically diverse participants, McAuley et al.[81]

identified reduced exercise capacity as a powerful predictor of total mortality independent of the impact of BMI or obesity. Although the endpoint in this was not CHD or CVD mortality, this finding is informative and quite consistent with previous data showing that fitness may reduce the all-cause and cardiovascular hazards of obesity[82] and that low cardiorespiratory fitness and physical inactivity imposes an adverse impact independent of the impact of obesity.[83, 84] Continued rigorous research on the impact of obesity and diabetes on CHD mortality trends is needed.

Dynamics of the Decline in Coronary Heart Disease Mortality Rates

Trends in CHD mortality rate are dynamic and reflect changing contributions from the prevention and control of major CHD risk factors, effective treatment of established CHD, and possibly the role of other factors yet to be identified. Additionally, because the magnitude of contributions from these factors and their degree of success in preventing CHD deaths vary among different populations and sub-groups, important differences in CHD trends may be noted by age, sex, race, ethnicity, geographic location, and other socio-demographic categories. As a result, CHD mortality rates may be continuing to decline in some groups at the initial dramatic rates observed in the US in the early 1970s[31] while rates of decline may be decelerating, stagnating, or even reversing elsewhere. This has been demonstrated using the IMPACT CHD model.[19, 23, 38, 39, 42, 78, 85–88]

Ezzati et al.[52] have provided a comprehensive assessment of the contributions of risk factors and medical care to CVD mortality trends in many countries with a special focus on the established risk factors such as smoking; blood glucose and diabetes mellitus; raised blood pressure; and serum cholesterol for which reasonably robust data on trends exist in many countries. They also address the contributions of adiposity, certain aspects of diet, and alcohol intake. In the present article, we explore current understanding of these contributions and their relationships to known CHD mortality trends that have slowed, stagnated, or reversed in different countries in order to examine recent trends in the US.

Where Have Trends Decelerated?

In 2007, Ford and Capewell[89] provided the first evidence suggesting that CHD mortality rates for young adults less than 55 years old in the US might be leveling off or even showing early non-significant signs of a rise. Using mortality data from 1980 to 2002 to calculate age-specific mortality rates from CHD for US adults aged ≥35 years and a validated Joinpoint analysis software, they examined changes in the annual percentage change in mortality rates from CHD. The key parameter determined in this exercise was the estimated annual percentage change (EAPC). Overall, they observed that age-adjusted CHD mortality rate had declined from 1980 through 2002 by 52% in men and 49% in women. The decline in the overall EAPC for the entire American adult population was fairly constant over the 20-year period from 1980 to 2000, and foreshadowing the decade of 2001 and 2010, the EAPC accelerated in the 2000 to 2002. This study suggested that although the overall EAPC had declined at a fairly steady rate, the trend for younger compared to older adults differed during the 1980 to 2002 period. For example, among women 35 to 54 years old, the EAPC for CHD mortality decreased significantly from - 5.4% in 1980 to 1989, to EAPC of - 1.2%

in the 1990's, and similarly among men age 34 to 54 the EAPC also decreased significantly from −6.2% in the 1980's to −2.3% in the 1990's. In contrast to the younger adults, US adults older than 55 years had the opposite pattern with greater mortality rate declines in the 1990's than in the 1980's.[89]

Since the Ford and Capewell publication in 2007, more evidence on the trend in younger adults has emerged. One analysis in Australia found that for both men and women between ages 25 and 54 years, the decline in CHD mortality slowed starting in the early 1990s in comparison to the prior two decades.[19] The authors concluded that the most likely explanations for the reduction of the CHD mortality decline were attenuations of the earlier declines in major traditional risk factors and diabetes mellitus.[19] In another study, Wilmot and colleagues, also using Joinpoint analysis, found that from 1989 to 2004, the EAPC for CHD mortality in women younger than 55 years of age was 0.2 (95% Cl −0.1 to 0.4) while men in the same age group during a nearly identical period of 1989 to 2005 showed a modest decline of −0.9 (95% CI −1.1 to −0.8).[77] But in the latter part of the decade, the CHD mortality rates in this age group improved slightly to −2.9 (2005–2011, CI −3.5 to −2.3) in men and to −2.0 (2004–2011, CI −2.7 to −1.3) in women. In contrast, during the period of 2002 to 2011, CHD EAPC mortality rates for both men and women older than 65 years continued to decline at five percent or greater.

The most recent study of trends in CVD mortality in the US concluded that the rate of decline in heart disease mortality which includes CHD mortality has substantially slowed for the 2011–2014 period for both sexes and for all race/ethnic groups.[78, 85] Since this period only contains four years, the pattern of the decline by age group is not yet clear and it is probably too early to determine whether the pattern since 1990 in which the older adults had more rapid declines in CHD mortality than the younger adults will persist. The modest upturn in the magnitude of decline among the younger adults in the last part of the last decade suggests a need for caution in predicting the trend of CHD mortality rates by age group for the rest of this decade, although careful monitoring and further study is definitely warranted.

Where are Trends Likely to Reverse or Are Already Rising?

Comparison of trends in CHD mortality decline at the international level is complex because challenges in definitions of metrics used, differences in data quality and methods of acquisition, and consistency in cause of death recording and certification. Additionally, information from countries undergoing social and political change can show results due to process rather than cause of death. Nevertheless, data from countries that exhibit unusual changes can be informative in understanding the dynamics of mortality changes.

In an analysis of trends in CVD mortality from 1980 to 2009 in Europe, Hartley et l.[16] found substantial variation in the declines by country. Declines in ischemic heart disease (IHD) were more than 60% over this time period for Western Europe whereas Eastern European states had much less decline.[16] There were periods in the decade of the 1990s where countries like Croatia, Latvia, and Slovenia showed substantial increases in IHD mortality. The authors suggested that these increases were influenced by the social and political

changes following the fall of Communism.[16] Social constructs also play a role in trends in mortality in England.[90] Using data from 1982 and 2006 as well a prediction model to 2030, Allen et al. noted that all economic groups demonstrated declining IHD mortality rates, but those in the lowest economic groups were projected to decline the least.[90] Thus, while absolute inequalities were decreasing, relative inequalities were projected to widen further, reflecting slower mortality declines in the most deprived groups.[90] Differences by sex are also important and concerning. In their assessment of possible plateaus in the CHD mortality decline over the 20th century in England and Wales, Allender and colleagues noted that the rate of improvement in CHD mortality "appears to be beginning to decline and may even be reversing among younger women."[23] These may not always be entirely explained by differences in risk factor burdens.

Using data from vital statistics and from risk factor survey data, Critchley et al.[39] described trends in CVD mortality for Syria, Tunisia, occupied Palestinian territories (oPt), and Turkey. In the periods from the late 1990's to the late 2000's, age standardized rates of CHD rose by 20% in Tunisia and 62% in Syria, but declined by 17% in oPt and 29% in Turkey. BMI and diabetes increased in all of these areas over this time period, though cholesterol and blood pressure increased only in Tunisia and Syria, the countries where the CHD mortality rates increased.[39] Cigarette smoking declined substantially in Turkey and oPt, the countries where the CHD mortality rates decreased. Thus, these findings are suggestive but somewhat inconsistent regarding risk factor explanations for the CHD mortality rate changes.

Continuing to complicate the picture of identifying clearly the causes of CHD declines is a study of trends in Japan.[91] The age-adjusted trend in CHD mortality was described for Japan and seven other countries. Although there were large differences in the CHD mortality rates by country, all showed declines from 1980–1983 to 2004–2007. Japan showed the smallest percent decline but even by the last period, their mortality rates were one-third of the US for men and one-fourth in women.[91] The key issue in this study, however, is that despite the CHD mortality declines, the cholesterol levels in Japan are rising whereas in every other country they are declining. Although cigarette smoking is very high in Japan (35% in 2012) it has shown a substantial decrease from the high of 61% in 2008.[91]

Trends from CHD in England were analyzed among those with or without diabetes.[92] In those without diabetes mentioned on the death certificate, the deaths from CHD dropped consistently from 1995 to 2010 with an average annual percent change of 4.5%. However, CHD mortality rates either remained constant over time, or increased slightly for those with a mention of diabetes on the death certificate.[92] This result could have several meanings, one of which could be that diabetes is being added more frequently on the death certificate without any real change in the disease impact. However, the other suggestion is that mortality from the combination of diabetes and CHD remains stubbornly unchanged and substantial improvements are needed in prevention and treatment of diabetes.

The foregoing examples illustrate the difficulty of concretely attributing causes to changes in CHD mortality rates but they don't negate the likely role of traditional risk factors. However, it is also important to consider other changes such as increases in economic disparity or

social change that disrupts secure well-being. From all of the data from the US presented earlier in this paper, there is likely a deceleration of the CHD mortality decline in some age groups but it will be unclear if it is a major change or one of the short term level periods seen when reviewing the long trend line from 1965.

Disparities in the Declining CVD Mortality Trends

The decline in CVD mortality rate in recent years has neither been uniform for all population subgroups nor for all causes of CVD death.[49, 93–95] In addition, despite the decades of the decline, substantial disparities in mortality rates continue by race, ethnicity, and sex (Figures 4a and 4b). Unequal access to preventive interventions is one of the contributing factors. The Medical Expenditures Panel Survey of more than 157,000 adults showed that, although statin use among US adults increased by nearly 80% between 2002 and 2013, statin use was significantly lower in women, racial/ethnic minorities and the uninsured.[96] Differences in CVD mortality also exist by geographic location and socioeconomic status and are often attributed to related differences in risk factor status; social and environmental differences; and inequities in access to care and the quality of care received. Because of their close association with CVD events and mortality, it is of interest to examine their influence on the decline of CVD mortality in the US and internationally.

A comprehensive assessment of cardiovascular health disparities using national surveys of adults aged 18 years and older demonstrated that disparities by race/ethnicity, sex, education level, socioeconomic status, and geographic location were pervasive in the US.[97] In fact, disparities were common in all risk factors examined. Hypertension prevalence was high among blacks (39.8%) regardless of sex or educational status, and hypercholesterolemia was high among white and Mexican American men and white women in both groups of educational status. CVD mortality at all ages tended to be highest in blacks. The highest prevalence of obesity in men (29.2%) was found in Mexican Americans who had completed a high school education. In women, the highest prevalence of obesity (47.3%) was noted in black women with or without a high school education.[97]

In spite of the steady decline in smoking since the publication of the first Surgeon General's Report on Smoking and Health in 1964,[98] smoking still continues to influence CVD risk. Although the prevalence of smoking was significantly lower in 2010–2013 than in 2002–2005 in many subgroups in the US, differences between various population subgroups span more than an order of magnitude.[99] For example, only 2.5% of Chinese women smoke, compared to 32.5% pf Puerto Rican Men and 25% of Puerto Rican women. Even among different Hispanic subgroups there is a three-fold difference in smoking rates.[99] Moreover, for the overall US adult population the rate of decline has slowed and appears to have reached an asymptote at just above 18%.[100] Thus, although there is significant variation in smoking rates among different subgroups of the US population, the overall trend has been stable for the last decade. To the extent that the decline in prevalence of smoking, long considered one of the most toxic CVD risk factors has stalled, it should not be surprising that the rate of decline in CVD deaths has also slowed.

Considerable geographic, racial, ethnic, and socioeconomic variation exists in the prevalence of seven common indices of cardiovascular health, defined by the American Heart Association (AHA) as including smoking, physical inactivity, obesity, poor diet, hypertension, high cholesterol and diabetes.[101] Although no study has evaluated trends in their collective prevalence, five of the AHA seven indices of cardiovascular health (serum cholesterol, blood pressure, BMI, diabetes and smoking) were included in the definition of low-risk for CVD in the Hispanic Community Health Study (HCHS).[102] A striking variation was found in the prevalence of low-risk status by Hispanic/Latino background (Cuban, Dominican, Mexican, Puerto Rican, Central American and South American), as well as among the five individual components that constitute the risk metric in the HCHS. Additional variation in risk was also observed by age, sex, acculturation and age at immigration. For example, Puerto Rican women had the highest percentage with a high risk profile, while South American women had the lowest (43.9 vs. 18.1%). Cuban women had the highest proportion with a low-risk profile, with Mexican men having the lowest proportion in the low-risk category (15.0 vs. 4.6%).[101] Thus, the limited classifications of racial and ethnic groups usually seen in the literature do not portray the nuances of Hispanic/Latino subgroup health status adequately, obscuring an understanding of their underlying causes. Finally, an insufficient granularity in defining important subgroups impedes a sufficiently refined understanding of the preventive interventions needed to optimize improvement in risk factors in underserved subgroups of the population.

Considerable disparities also exist by geography and State within the US.[103, 104] One such study is an examination of trends in heart disease mortality in Mississippi, the State with the highest cardiovascular mortality rates in the US.[105] In the most recent years described in the analyses (late 1990s to 2013), mortality in all race and sex group declined by an average of 3 to 4 percent annually. This is important, since their heart disease death rate in 2014 is twice that of the state with the lowest mortality[106] and improvement is certainly needed. Comparing age-adjusted heart disease death rates for the 50 states in 2010 and 2014 showed declines in all states with a few exceptions.[107, 108] The top 10 states with the highest heart disease mortality all showed declines, but 5 states throughout the range showed no decline over this time period. This may be due to variation in mortality rates and possibly regression to the mean, but attention needs to be given to assure the improvements in heart disease are met throughout the US. Gillum et al. also showed in an earlier analysis that between 1999 and 2007, the level and rates of decline in CHD mortality were greater in the Ohio and Mississippi River region than in other geographic regions of the US.[104]

An often overlooked CVD risk factor is infection by the influenza virus, a risk that has been shown in randomized trials to be ameliorated by vaccination, reducing CVD mortality by 55% in secondary prevention trials.[108] Vaccination rates were highest among non-Hispanic whites, followed by Hispanics and non-Hispanic blacks (66% vs. 54% vs. 48%). Rates increased in all subgroups of the population between 1989 and 1999, but declined slightly for non-Hispanic whites until 2003.[110] In 2011, vaccinations among those over the age of 65 reached 72.1% among non-Hispanic whites, vs 57.2% among Hispanics and 53.3% among non-Hispanic blacks.[111] Given the significant impact of influenza vaccination on secondary prevention of CVD death, the 18% vaccination differential between major population subgroups contributes significantly to disparities in CVD mortality.

Successful preventive intervention on CVD risk factors, including novel ones such as influenza infection, is key for accelerating a decline in CVD mortality. Strategies must take into account a more nuanced understanding of subgroups of the population, including differences between urban, inner city and rural populations, as well as a more granular classification of ethnic and at-risk population subgroups. Greater detail is needed in surveillance programs in order to optimize prediction and the optimal application of resources. Modeling future CVD mortality is more successful when trends in changing demographics are included.[111] It can be even more successful if detailed data become available on trends in prevalence of specific risk factors among subgroups of the population.

International data also suggest that differences in CVD risk factors may be the major contributor to disparities in mortality. In Scotland, decline in mortality rates flattened between 1986 and 2006, with the decline confined to younger men and women in the two most deprived fifths in socioeconomic status.[113] These are also the groups with the highest prevalence of CVD risk factors, especially smoking. When 30-year CVD mortality trends are compared among countries in the European Union, it is evident that there is a considerable East-West disparity for ischemic heart disease and CVD,[16] attributed to a differential prevalence of cardiovascular risk factors. In Lithuania for example, smoking prevalence increased 1985–2013 in both sexes, as well as hypertension and obesity, which contributed to a slowing decline in CVD mortality.[114]

Implications for Clinical and Public Health Research and Practice

The data on CVD mortality trends in the US presented throughout this review have been derived from a variety of sources, including national surveys, regional surveillance efforts, and cohort studies. Most of these data sources act independently of one another. A coordinated surveillance system can serve many functions such as providing benchmark data for local, regional, state, and national policies and programs, thereby helping to direct the allocation of limited resources.[115, 116] A system that includes the capability for methodically and accurately capturing key factors underlying health disparities by race, ethnicity, socioeconomic status, and geographic region would further enable more effective goal setting for programs and policies aimed at eliminating health disparities.

In the absence of ideal data, the results of modeling studies can be invaluable but they must be interpreted cautiously given that both the heterogeneity of the data sources, as well as of the models used lead to great imprecision, a limitation that has been well-recognized by most investigators. For example, in the analysis by Ford et al.[31] the best estimate of the reduction in CHD deaths due to therapies was 47%, but could have been as low as 19% or as high as 94%. However, other recent studies using the same model seem to confirm that about half of the reduction in CHD deaths may indeed be due to medical or surgical treatments.[117] These data again highlight the benefit of collecting prevalence data on a large scale, coupled with longitudinal surveys to better understand trends in cardiovascular risk factors as well as provide data on cardiovascular events. The National Institutes of Health (NIH) All of Us Research Program[118] (formerly the Precision Medicine Initiative) Cohort Program that intends to build a national research cohort of one million or more US participants may be one way to achieve this goal.[119]

Expanding the Research Evidence to More Precisely Prevent and Treat CVD

Despite all the accomplishments in cardiovascular research to date, only a small proportion of clinical CVD guidelines are based on high-quality evidence.[120] There is a critical need to support the continued generation of research findings to guide evidence-based decision making, both in CVD prevention and treatment. Whenever feasible to conduct randomized clinical trials to generate gold-standard evidence on new interventions, such efforts should be pursued. In other incidences, such as when evaluating impacts of harmful behaviors or environmental exposures, population-based cohort studies are invaluable.[121] Observational studies from clinical settings, including those based on platforms provided by disease registries or electronic health records, represent another rich source of research evidence. Yet another often underappreciated but valuable method is research that generates "practice-based evidence" (as opposed to the well-known concept of "evidence-based practice"). Instead of shying away from analyzing complicated factors that often occur in real-life settings, practice-based research embraces these variables in the analyses to generate evidence that better reflects the complex reality rather than cover it.[122] Recently, in light of advancing technologies in genomics, high throughput molecular assays, wearable and mobile devices, electronic health records, and data sciences, precision medicine has appeared on the forefront of many areas of research. Precision medicine is defined by the National Institutes of Health as an "emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[123] In his January 20, 2015 State of the Union address, President Obama announced his plan to launch the Precision Medicine Initiative® (PMI), including NIH funding starting from fiscal year 2016 to build a national cohort study of one million or more US volunteers.[119, 124] The PMI Cohort Program will be inclusive of participants from diverse racial/ethnic, social, and geographic backgrounds and health statuses. The large sample size and the multiple types of data to be collected are intended to have the statistical power to detect associations between genetic, behavioral, environmental exposures, and other individual variability to a variety of health outcomes.[125] Given the high prevalence and incidence of CVD, a substantial portion of the cohort is expected to have risk factors or existing CVD at the outset or to develop CVD during the course of follow up. One can readily envision the potential of leveraging the PMI Cohort Program to enable deeper observational investigations or targeted trials to enable more precise prevention and treatments of CVD. Examples of scientific opportunities might include, but not limited to: a) advancing the field of pharmacogenetics in managing CVD, b) improving risk stratification of a variety of CVD and conditions, c) developing new disease classifications for CVD, especially heterogeneous conditions such as heart failure, and d) tailoring behavioral interventions based on one's genomic and molecular profile as well as environmental exposures.

Toward Effective Implementation in Clinical Care and Public Health

Critics have raised concerns that ongoing attention to precision medicine detracts from public health efforts.[126–129] One criticism is that a heightened focus on improving clinical care will not address the fundamental social and economic problems that play huge roles in driving health disparities.[125] Others, however, view precision medicine and public health as

complementary rather than opposing efforts. One such area of complement is that advances in precision medicine could improve population health by refining the risk stratification of populations for multiple chronic diseases including CVD to enable more efficient prevention strategies and potentially reduce cost of care.[129, 130] Nevertheless, it is well established that generating the evidence and developing strategies for prevention and treatment does not necessarily lead to changes in clinical practice. The learning health care system has been identified as one key approach envisioned in real-world clinical settings to foster the integration of genomics and other precision medicine interventions with implementation science.[130] Indeed, it should be recognized that implementation science is a crucial element and a potential catalyst in the translation of research findings into routine clinical and public health practice.[132, 133]

In brief, this section has laid out several ways in which population science might be advanced to further understand and promote the continued decline in CVD mortality rates in the US. The approaches include developing a coordinated national surveillance system to obtain CVD incidence and mortality data at local, state, and national levels, and expanding the current research evidence base through a wide-spectrum of clinical research methods, ranging from traditional clinical studies to novel approaches such as precision medicine. Moreover, to continue to bend the CVD mortality curve, multi-dimensional efforts are required that go beyond solely focusing on generating research evidence to also applying implementation science for successful adoption, scale-up, and spread of effective clinical and public health interventions.[132–134]

Summary and Conclusions

Viewed from the perspective of the early 21st century, the 20th century dramatically reshaped the public health profile of the US and the rest of the world. The first half of the century saw a remarkable 25-year increase in longevity in the US, fueled mainly by control of communicable diseases through improvements in sanitation and the development of vaccines and antibiotics. However, this improvement was mitigated somewhat by a concurrent rise in mortality from CVD and other non-communicable diseases. This rise partly reflected population growth and aging, as well as real increases in age-specific CVD mortality rates driven most likely by the increasing prevalence of tobacco use and socioeconomic changes permitting a more atherogenic diet and more sedentary lifestyle. The second half of the 20th century brought about an at-first unexpected sharp decline in cardiovascular mortality in the US, attributed almost equally to risk factor control and major pharmacological and technological advances in both the acute and long-term treatment CHD and stroke. This decline has given Americans an additional decade of longevity, pushing life expectancy into the late 70s and early 80s. While less apparent at first, it has become clear that similar changes have occurred elsewhere. Indeed, many other high-income countries throughout the world have surpassed the US and report even lower CVD mortality rates and greater life expectancy.

But the picture is not altogether rosy. Prevalence of obesity, metabolic syndrome and type 2 diabetes have increased during the past 20 years, and the decline in CHD mortality rates seem to have decelerated. Advances in the prevention and treatment of CVD have become

more incremental during this period. While patients who suffer a heart attack often survive their initial events and may live into their 80s, many go on to develop and die of chronic heart failure, and we have had very little success in preventing or treating this end stage outcome. In fact, as shown in Figure 5, the age-adjusted mortality rate for heart failure during the period of 2012–2015 appears to be on the rise after more than a decade and a half of gradual declines since 1999. Finally, many segments of the US population have been unable to access the remarkable advances made in CVD prevention and treatment and marked inequities in cardiovascular health and healthcare remain pervasive.[97] While these disparities may not be as stark as they were in 1900, much work remains to be done towards the elimination of health inequities.

Through a published RFI, the NHLBI is soliciting information that could inform a follow-up conference on or near the 40th anniversary of the landmark 1978 conference where the decline in CHD mortality in the US was first recognized. Areas of major emphasis for such a conference could include: worldwide trends in CHD mortality and morbidity since 1978; major contributors to acceleration or deceleration of the CHD mortality rate decline, especially in young adults; national, regional, and global patterns in the geographic, socioeconomic, racial, and ethnic disparities in the trends in CHD mortality declines at the national and international levels; impact of the continuing epidemic on obesity, metabolic syndrome, and type 2 diabetes on CHD mortality trends; potential strategic targets for research likely to lead to transformative advances in prevention, early detection, treatment, and control of CHD. Consistent with the NHLBI Strategic Vision,[135, 136] the conference could also explore additional unanswered questions or poorly understood areas of CHD research and related critical challenges that require NHLBI facilitation to ensure scientific progress.

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Non-standard Abbreviations and Acronyms

AHA	American Heart Association
BMI	body-mass index
CABG	coronary artery bypass graft
CHD	coronary heart disease
CVD	cardiovascular disease
CVHI	Cardiovascular Health Index
DPP	deaths prevented or postponed
EAPC	estimated annual percentage change

Euroheart	European Heart Health Strategy
HCHS	Hispanic Community Health Study
IHD	ischemic heart disease
IMPACT	IMPACT Coronary Heart Disease Model
LYG	life-years gained (LYG)
MONICA	Multinational monitoring of trends and determinants in cardiovascular disease
NHLBI	National Heart, Lung, and Blood Institute
PMI	Precision Medicine Initiative
RFI	request for information
SCD	sudden cardiac death
US	United States

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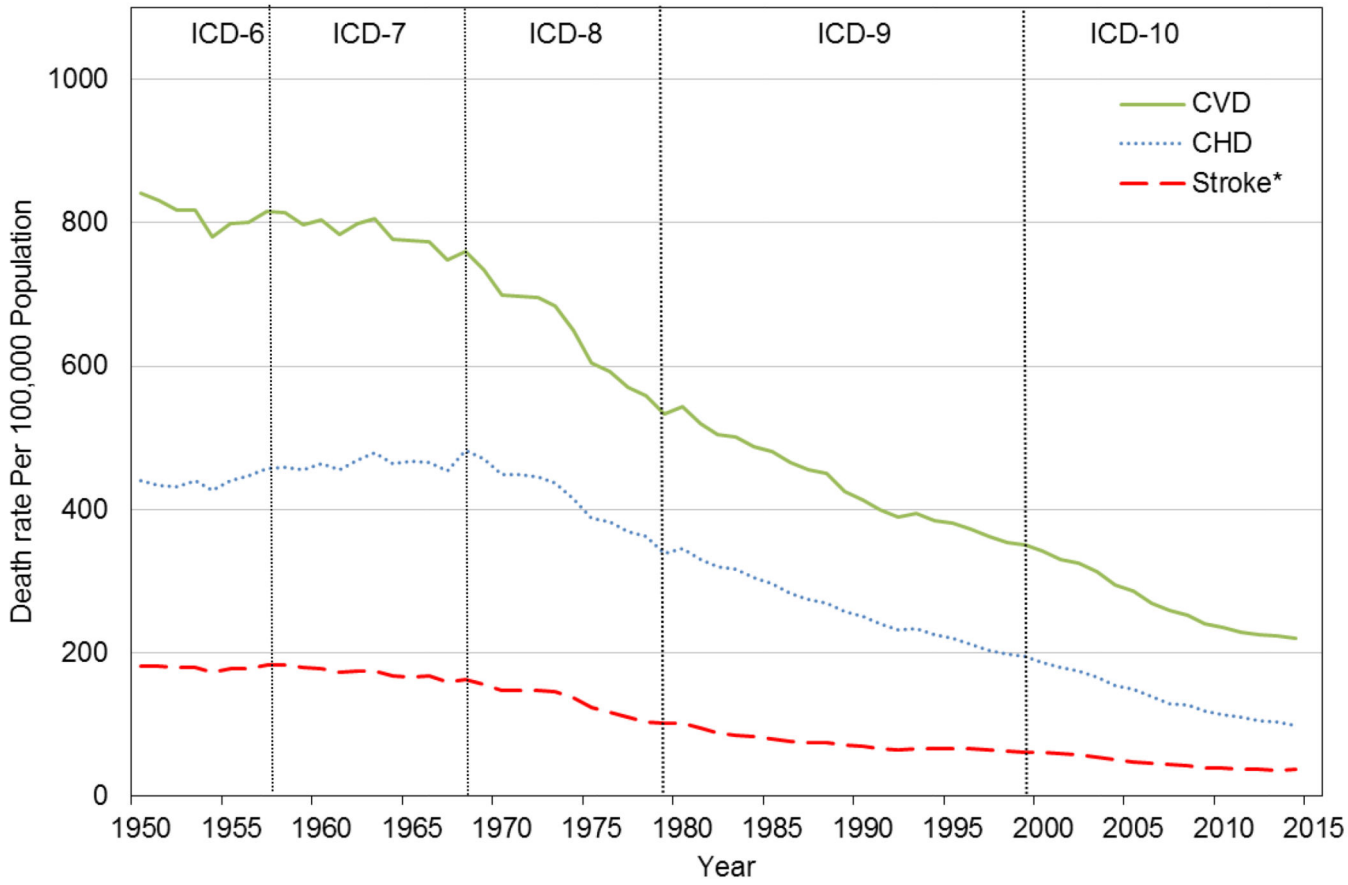


Figure 1. Age-adjusted CVD Mortality Rates, 1950–2014

*The comparability ratio 1.0502 was applied to the death rates reported in vital statistics for 1979-1998. Source: CDC/NCHS, National Vital Statistics System, Mortality Multiple-Cause-of-Death. These data represent underlying cause of death only.

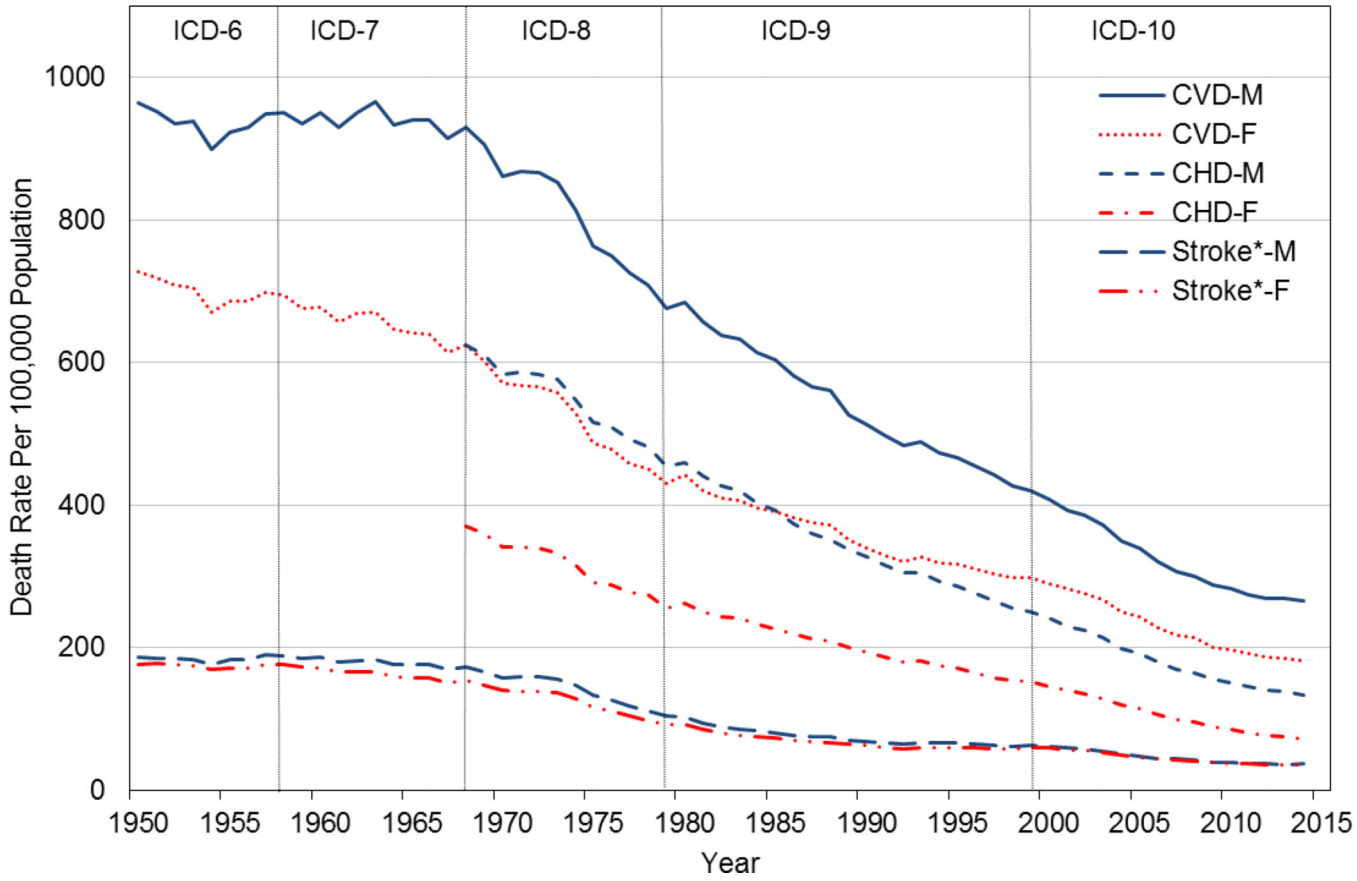


Figure 2. Age-adjusted CVD Mortality Rates by Sex, 1950–2014

*The comparability ratio 1.0502 was applied to the death rates reported in vital statistics for 1979-1998. Source: CDC/NCHS, National Vital Statistics System, Mortality Multiple-Cause-of-Death. These data represent underlying cause of death only. CVD: cardiovascular disease; M: male; F: female

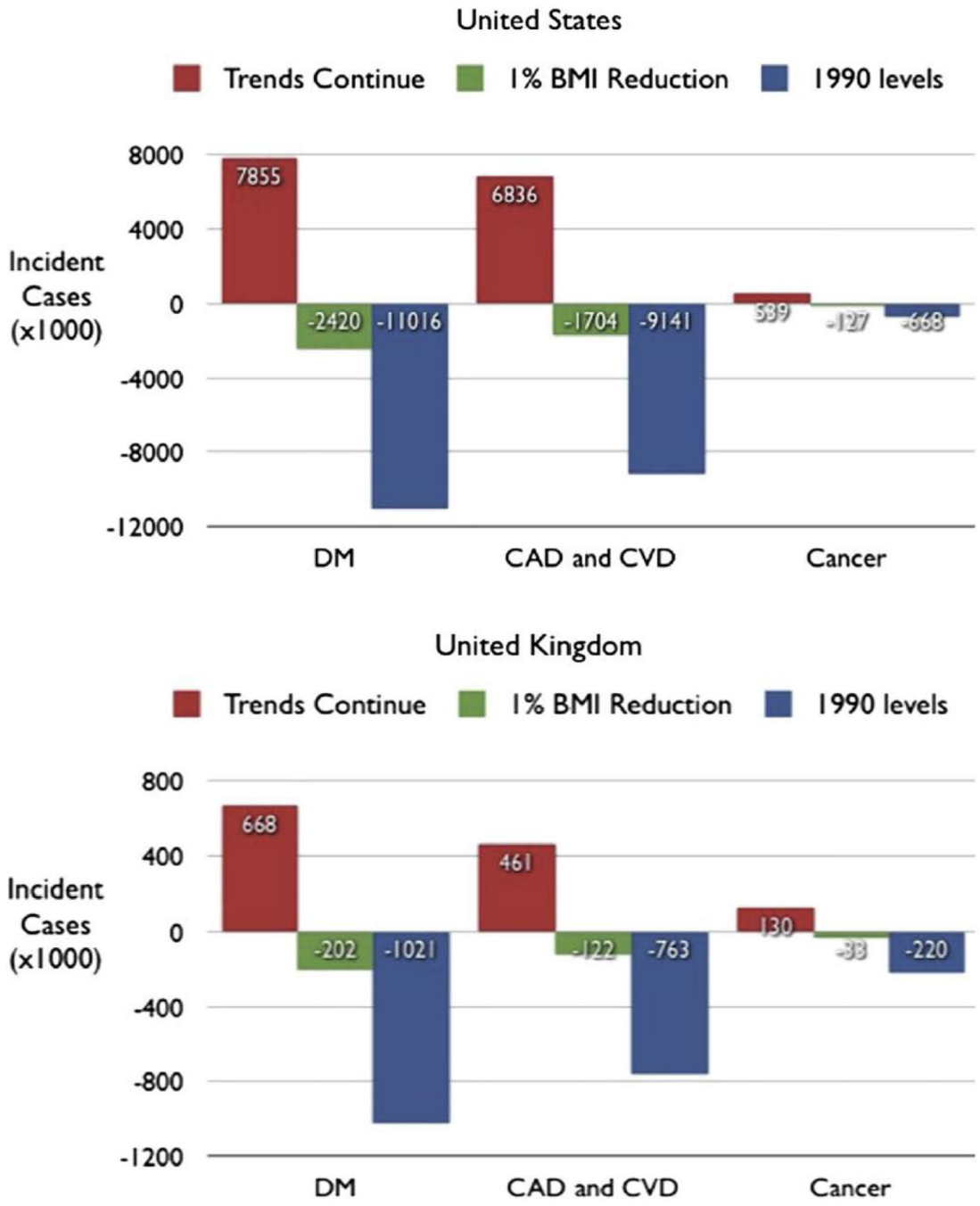
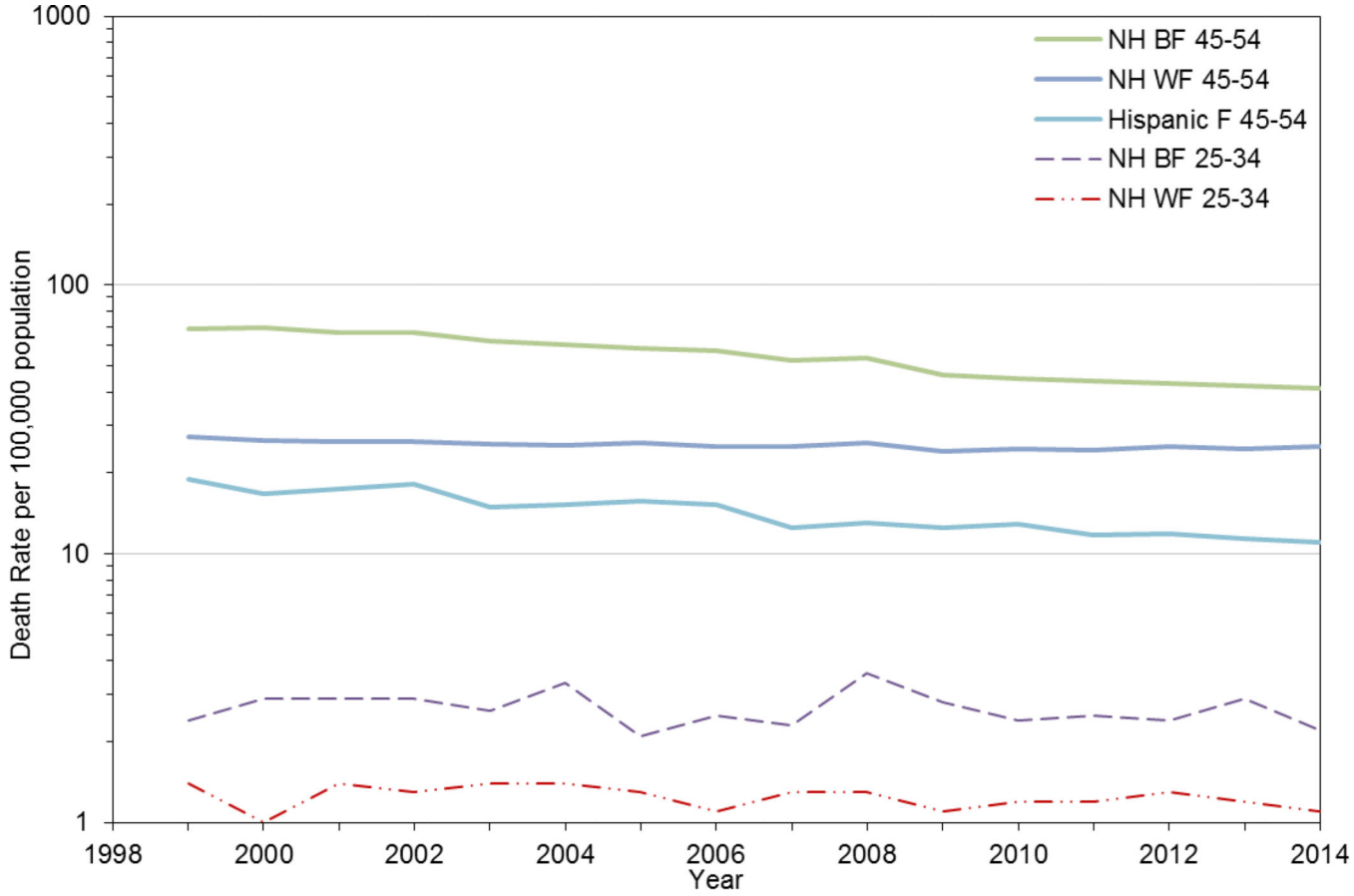
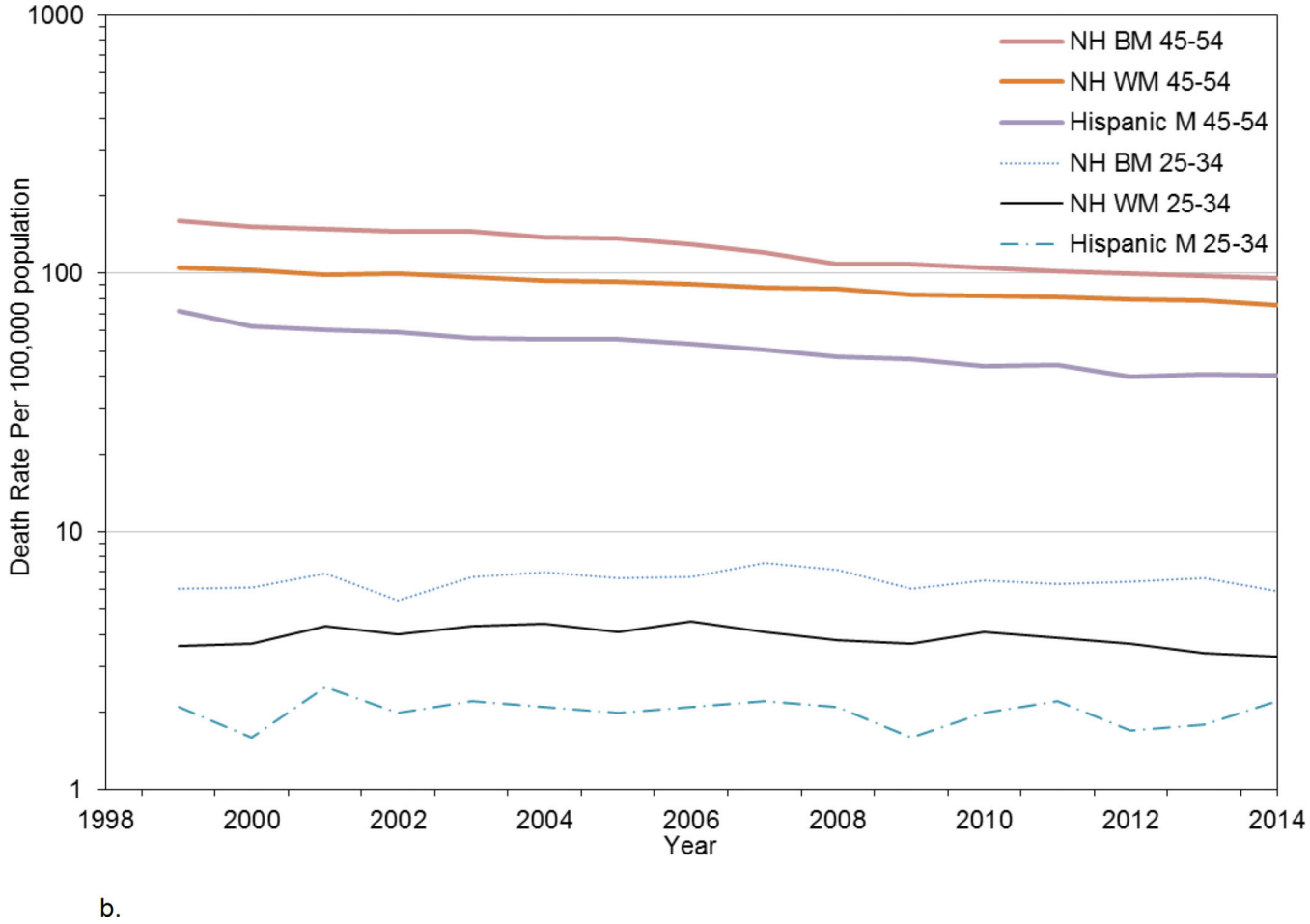


Figure 3. Variations in the number of projected incident cases of obesity-related complications between 2010 and 2030, according to 3 hypothetical scenarios of population-wide BMI change

The first column assumes that past trends continue unabated; the middle column assumes an immediate population-wide 1% BMI reduction; and the third column assumes that population BMIs had remained at 1990 levels. BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; DM, diabetes mellitus. From Padwal RS. Canadian J Cardiol. May 2014;30(5):467-472 based on data presented by Wang et al. Lancet. 2011 Aug 27;378(9793):815-25. Reproduced with Permission from Elsevier, Inc.



a.



b.

Figure 4.

a. Coronary Heart Disease Mortality by Race-ethnicity, and sex, ages between 25 and 34 years, US, 1999 – 2014. NH, non-Hispanic. Data for Hispanic females are unreliable and not shown. Source: CDC/NCHS, National Vital Statistics System, Mortality Multiple-Cause-of-Death. These data represent underlying cause of death only.

b. Coronary Heart Disease Mortality by Race-ethnicity, and sex, ages between 45 and 54 years, US, 1999 – 2014* NH, non-Hispanic. Source: CDC/NCHS, National Vital Statistics System, Mortality Multiple-Cause-of-Death. These data represent underlying cause of death only.

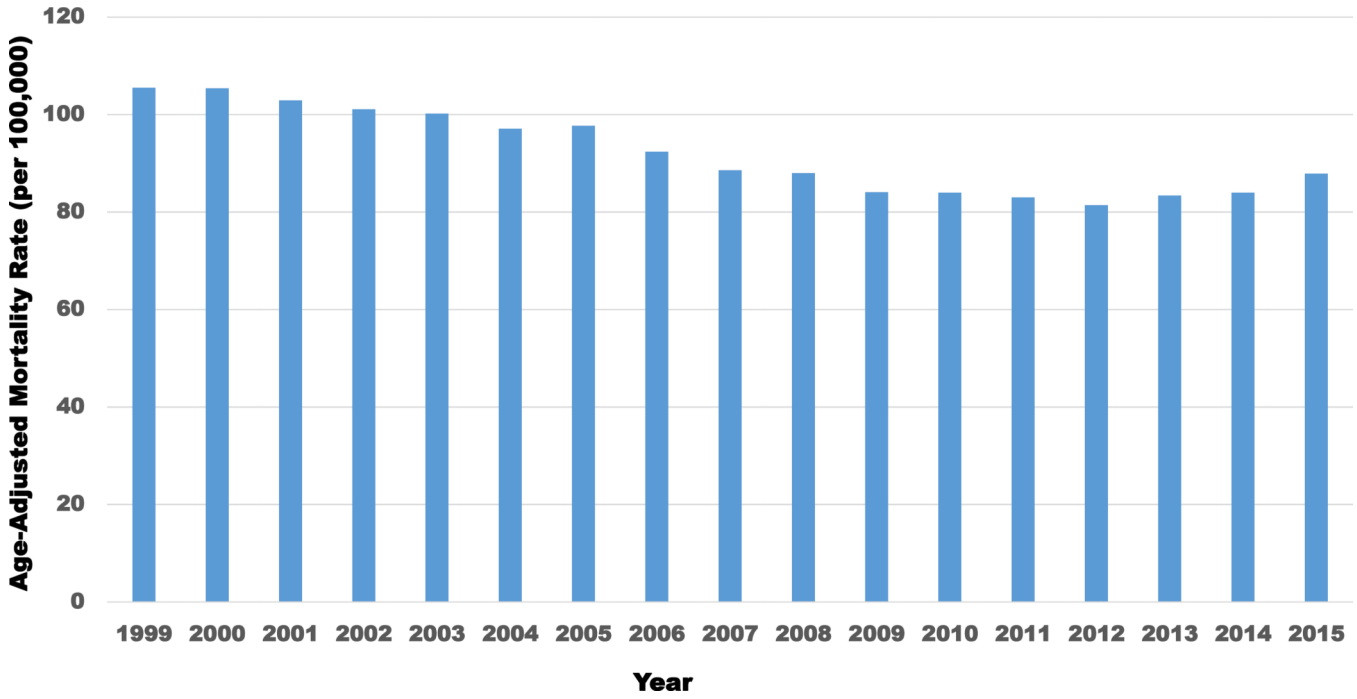


Figure 5. Age-Adjusted Death Rates for Heart Failure (Multiple Cause), 1999–2015

Source: Centers for Disease Control and Prevention / NCHS 1999–2015 Multiple Cause-of-Death, United States, ICD-10 Code I50.

Table 1

Examples of major advances in the prevention and treatment of coronary heart disease

Advance	Year or Period	Impact on the Prevention and Treatment of Coronary Heart Disease and Risk Factors
Framingham Heart Study identified smoking, high blood pressure (BP), and high blood cholesterol as major cardiovascular risk factors	1960s	New targets for atherosclerotic coronary heart disease prevention and treatment
First coronary artery bypass surgery	1960	Surgical procedure to bypass clogged arteries
Surgeon General's Report on Smoking and Health	1964	Publicized dangers of cigarette smoking
Hypertension Detection and Follow-up Program (HDFP)	Early 1970s	Demonstrated benefit of treating even moderate hypertension
First percutaneous transvascular coronary angioplasty	1977	Successful restoration of perfusion in occluded coronary arteries via percutaneous catheter
Discovery of the low-density lipoprotein (LDL) receptor	1970s	Michael Brown and Joseph Goldstein laid the groundwork for statins
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)	1984	Established benefit of cholesterol lowering
National clinical practice guidelines for high BP and high blood cholesterol	1987	Established standards and targets for blood pressure (BP) and cholesterol
Development of statins, angiotensin-converting enzyme inhibitors and calcium channel blockers	1987–8	New powerful drugs for managing cholesterol and blood pressure
Thrombolysis in Myocardial Infarction (TIMI) Trial	1987	Thrombolysis in acute myocardial infarction
First coronary stent	1988	Made angioplasty more durable
Scandinavian Simvastatin Survival Study (4S)	1994	First statin end point trial showed reduction in mortality. Many other statin trials followed.
Systolic Hypertension in the Elderly (SHEP)	1996	Established the benefit of treating isolated systolic hypertension in elderly. Many other BP trials followed.
Systolic Blood Pressure Intervention Trial (SPRINT)	2015	Established the benefit of intensive BP control (to target systolic BP less than 120 mmHg) in high risk patients without diabetes