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CLINICAL INVESTIGATIONS

Protecting the gains: What changes are needed to prevent a reversal of the downward cardiovascular disease mortality trend?

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Aims: Cardiovascular disease (CVD) mortality has decreased over 60% over the past 50 years in the United States; however, emerging data indicate CVD incidence may be rising because of shifting demographics, increasing risk factor prevalence, and competing needs for limited resources. We projected CVD mortality from 2015 to 2040 given varying informed assumptions regarding changes in risk factor prevalence, uptake of current therapeutic options, and future innovations.

Methods: A microsimulation model was used to project US CVD mortality trends. National Health and Nutrition Examination Survey data were used to estimate population-level trends in CVD risk factors. Risk factors were used to generate Framingham Risk Scores for cohorts of 1 000 000 individuals from the general population to determine each individuals' CVD risk. Annual cardiovascular incidence, prevalence, and mortality were projected for scenarios differing by uptake of current therapies, anticipated pharmaceutical innovations with variable efficacy, risk factor prevalence, and changes in health disparities.

Results: When incorporating a demographic shift, continued changes in risk factors, current treatment utilization, and no major innovations, we predicted the CVD mortality rate would increase 41% by 2040. If innovations providing incremental benefits equal to those associated with the introduction of statins are identified and widely utilized, CVD mortality could remain constant through 2040. With more efficacious innovations, CVD mortality could be further reduced.

Conclusions: Given demographic and risk prevalence changes, increasing access and adherence to current preventative therapeutics could slow the expected mortality increase, but new therapies may be needed to maintain the downward trend in CVD deaths.

KEYWORDS

cardiovascular disease, disease burden, microsimulation model, mortality, projections

1 | BACKGROUND

Cardiovascular disease (CVD) is the leading cause of mortality among adults in the United States, accounting for one-third of deaths.[1] While CVD burden remains high, annual age-adjusted mortality rates from heart disease and stroke decreased from 328.0 per 100 000 in 1999 to 206.1 per 100 000 in 2015.[2] This decrease was driven by reductions in CVD incidence and case fatality rate, and was significant for both sudden and nonsudden cardiac deaths.[3] In analyses exploring the mortality decline, one-half of the reduction was because of therapeutic improvements, and the remainder was because of risk factor changes including reductions in cholesterol, hypertension, and

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smoking.[4,5] However, emerging data suggests that mortality rates have recently stabilized and may be increasing.[1]

The total direct and indirect costs of CVD were $656 billion in 2015 and are projected to increase to $804 billion by 2020.[1] However, despite current spending levels, CVD remains a primary cause of mortality and morbidity in the United States. Moreover, the previous improvements in CVD mortality rate may be reversing because of an aging population,[6] increases in obesity,[7] and rising diabetes prevalence.[8] There has been an uptick in age-standardized stroke mortality from 36.2 per 100 000 in 2013 to 36.5 per 100 000 in 2014, and in non-CHD/non-stroke related CVD from 81.5 per 100 000 in 2011 to 84.6 per 100 000 in 2014.[1] Annual direct and indirect costs of CVD may exceed $1 trillion by 2030.[9]

Despite wide uncertainty ranges, projections can demonstrate the health and policy implications of population aging, risk factor changes, such as increasing prevalence of obesity and diabetes, treatment patterns and therapeutic restrictions, and the continued rise of health care costs. Projections are needed to guide policy, research, and therapeutic development to further improve cardiovascular health while efficiently utilizing limited resources.[10] Previous CVD projection studies did not consider mortality, used a short-time horizon, did not examine the impact of treatment development and uptake, or did not isolate factors that could drive changes in mortality.[10–16] In the present study, we project mortality rates given varying informed assumptions regarding changes in risk factor prevalence, uptake of current therapeutics, and future innovations.

2 | METHODS

2.1 | Overview

In this model-based analysis, we projected annual CVD mortality from 2015 to 2040. Incident and prevalent CVD cases were included in the model, which utilized the Framingham risk equation[17] to simulate individuals without a history of CVD, and combined with those experiencing new events and those with a history of CVD, to predict mortality for the US population. Model inputs included those required by the Framingham risk equation, such as age, sex, cholesterol, blood pressure, smoking status, and diabetes. Risk factor data was estimated through an analysis of the National Health and Nutrition Examination Survey (NHANES), and were supplemented with CVD prevalence and mortality data from the Centers for Disease Control and Prevention (CDC) and 2014 demographic data and projections from the US census.[18–21] Methods for estimating model inputs are described in detail in Section 2.3. Scenarios were explored to assess the impact of behavioral modifications and technological innovations.

2.2 | Model structure

A microsimulation model was developed in Microsoft Excel to project CVD mortality (Figure 1). A microsimulation model was selected to best capture the impact of heterogeneity and to allow for predicting the risks of CVD for individuals using the Framingham Risk Score. CVD was defined as conditions predicted by the Framingham Risk Score (ie, coronary death, myocardial infarction [MI], coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure). Individuals without a history of CVD were assigned demographic characteristics and CVD risk factors based on the NHANES analysis (described below), and simulated individually through the model. Hypothetical cohorts of 1 million individuals without CVD were created for each year from 2015 to 2040. We chose 1 million from that number decreased the impact of random low-frequency events while maintaining a reasonable computing time per simulation. Individuals experienced CVD events based on their calculated Framingham Risk Score. Those with prevalent CVD in 2015 were separately included in the model, and incident CVD events were added to existing cases to estimate the prevalence in a given year. Patients with CVD were at risk of CVD-related or competing-cause mortality. Those susceptible to CVD in a given year were calculated as the Census-projected population ages 25 to 85 minus those with prevalent CVD. While annual cohorts were considered independent and individuals within each cohort drew from separate probability distributions each year, common random numbers (CRN) were implemented to reduce stochastic variation. CRNs allow for counterfactual-like analyses in which the only varying factors between simulations are model inputs, and randomness beyond the impact of changing inputs is eliminated.[22]

2.3 | Model inputs

2.3.1 | Framingham risk equation

To calculate Framingham Risk Scores, we estimated age, sex, and population-wide CVD risk factors. The average age of the population, projected aging of the population, and distribution of men and women, were based on estimates from the US Census Bureau.[21] To estimate the prevalence of other risk factors for CVD, we assessed the previous six series of NHANES data (ie, 2003-2014). NHANES is a US-based survey program conducted by the National Center for Health Statistics every 2 years to assess the health and nutritional status of adults and children, and track temporal changes. We examined trends in the following risk factors required by the Framingham Risk Equation[17]: systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes prevalence, hypertension treatment, and smoking status.

While additional factors are known to influence CVD (eg, low-density lipoprotein (LDL) cholesterol, obesity), they are not explicitly included in risk equation, but are assumed to be captured indirectly through related measures (eg, HDL cholesterol and total cholesterol). The mean and SD for each clinical measurement (ie, systolic blood pressure, total cholesterol, and HDL cholesterol) were estimated for 16 distinct groups, defined by: diabetes prevalence, treatment for hypertension, smoking status, and sex. Additional risk factors, such as age, were included in the estimation of CVD risk but not used for stratification of clinical measurements.

The NHANES analysis was limited to those ages 25 to 85 years, consistent with the model population. Based on observations, we used linear regression to project clinical measurements for each of the 16 groups. The proportions of each annual cohort within a given

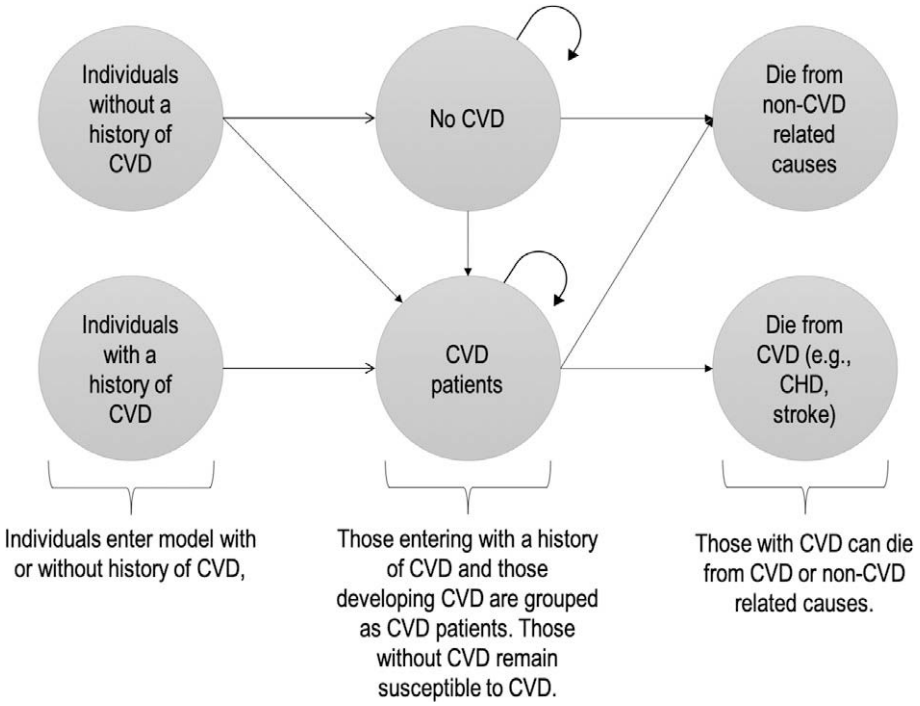

FIGURE 1 Model schematic. CHD, coronary heart disease; CVD, cardiovascular disease

group were based on distributions observed in NHANES and the US census.[21]

2.3.2 | Prevalent cases

The Framingham Risk Score is only applicable to CVD-naïve individuals; therefore, we separately included those with a history of CVD into the model. CVD prevalence in 2015 was estimated from NHANES by extrapolating reported rates of myocardial infarction, stroke, angina, congestive heart failure, or other coronary heart disease. Prevalence among men in 2013 was 10.6%, and among women was 8.8%.

2.3.3 | CVD mortality

Individuals with CVD faced an increased mortality risk, which we kept constant for each year of the analysis, but we separately estimated for each sex and 10-year age group. The case fatality rate was calculated by dividing observed deaths because of included CVD-related conditions from the CDC in 2015[19] by the individuals at risk from NHANES prevalence projections and US census data.[6,18] Both those with a previous CVD event, and those experiencing an incident event during a given year, were at risk of dying. Competing cause mortality rates were based on CDC data.[20]

2.4 | Analyses

Initially, we projected CVD mortality using risk factor values from 2015, with the only temporal shift being an aging US population. In subsequent scenarios, each risk factor varied individually as projected by authors using NHANES data, to determine which factor was most influential. We also conducted a scenario in which all risk factors simultaneously shifted as projected. These results represented expected mortality trends given behavioral modifications but without significant changes in the pace of innovation.

We also explored the impact of therapeutic innovations, which alter risk factors, CVD incidence, or CVD mortality. In such scenarios, we combined projected shifts in risk factors with variations in other model parameters. We first considered the impact of the introduction and uptake of interventions, which reduced total cholesterol or blood pressure. These scenarios were designed to consider hypothetical treatments, as opposed to specific therapies; therefore, the impacts of varying theoretical decreases in each clinical measurement were assessed. We separately considered scenarios in which CVD incidence was lowered by fixed increments, and when varying the case fatality rate.

In all scenarios, we projected CVD prevalence, total CVD deaths, and mortality rate per 100 000 population. The latter metric has been more frequently reported, given the expectation that there will be an increase in CVD deaths because of a growing population regardless of other changes. Although age-standardized rates are often reported in literature, we chose not to do so as this analysis was designed to provide population-level outcomes. Such outcomes are driven in large part by the aging population, and standardizing would prevent policymakers from understanding the full burden of CVD.

3 | RESULTS

In the first scenario, risk factor prevalence was fixed at 2015 levels and the average age of the population increased from 49.6 to 51.5 years based on projections from 2015 to 2040. CVD mortality rate in 2015 was projected to be 218 per 100 000 individuals, and would increase to 256 per 100 000 in 2020, 315 per 100 000 in 2030, and 355 per 100 000 in 2040. This 62% increase in mortality

from 2015 to 2040 was driven by an increase in CVD prevalence from 9.8% to 16.0%. When additionally considering the growing population as projected by census estimates, annual CVD deaths were projected to increase from 462 122 in 2015 to 916 014 in 2040.

The prevalence of CVD risk factors as observed in NHANES, and projected using historic trends are shown in Table 1 and Figure A1. Briefly, we found that smoking, total and HDL cholesterol, and systolic blood pressure have decreased since 2003, whereas diabetes prevalence and the use of hypertension medications have increased. While the total projected changes in risk factors between 2015 and 2040 were large, the annual changes in each risk factor were less dramatic, resulting in substantial overlap in the distributions of risk factors when comparing consecutive years. When average total cholesterol in the population decreased between 2015 and 2040 from 191 mg/dL to 163 mg/dL as projected, mortality in 2040 was estimated to be 323 per 100 000 individuals, compared to 355 per 100 000 individuals when remaining constant (see Figure 2). When the average systolic blood pressure decreased from 122.0 mm Hg to 115.8 mm Hg, mortality was 327 per 100 000 in 2040. In the scenario in which diabetes prevalence increased from 14% to 24%, CVD mortality increased to 364 per 100 000 in 2040. When smoking and HDL cholesterol varied, the mortality shift was less pronounced.

In the scenario varying all risk factors, CVD mortality was expected to increase by 15% in 2020, 34% in 2030, and 41% in 2040, compared to 2015 rates. Prevalence of CVD was similarly expected to increase from 9.8% to 13.2% in 2030 and 14.0% in 2040. The mortality increase is lower than when only incorporating an aging population, but risk factor variations were not enough to prevent a rise in CVD mortality compared to the model-projected 2015 rate. The projected mortality rates in 2040 in the status quo scenario, when varying each risk factor individually, and when varying all risk factors simultaneously, are shown in Figure 2.

Compared to the scenario in which risk factors varied and CVD mortality increased to 309 per 100 000, the introduction of cholesterol lowering therapies that could reduce average cholesterol by 20% would lead to a CVD mortality rate of 260 per 100 000 by 2040. For perspective, a meta-analysis of 27 trials comparing statins to placebos was conducted and included studies published between 1994 and 2010 that assessed both men and women with and without a history of vascular disease.[23] This meta-analysis found that the average reduction in LDL was 28.6%.[23] Reducing average systolic blood pressure by 5% would lead to a mortality rate of 286 per 100 000 in

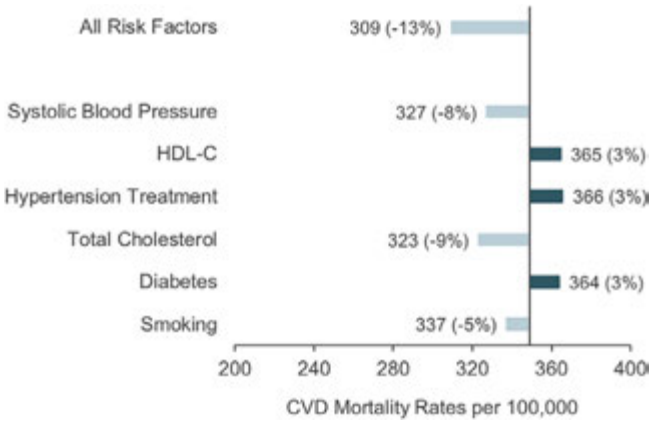

FIGURE 2 A 2040 mortality rates based on projected changes in risk factors. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol. Solid vertical line reflects projected mortality rate of 355 per 100 000 individuals with current risk factors. Dark bars indicate risk factor changes that will increase mortality compared to no changes in risk factors, light bars indicate those that will decrease mortality. Numbers beside bars show the CVD mortality rate per 100 000, percentages indicate the change compared with mortality rate with current risk factors. For comparison, the model-projected mortality rate for 2015 is 218 deaths per 100 000 individuals and depicted with the dotted vertical line. Results reflect the following changes in risk factors, as projected from NHANES from 2015 to 2040: smoking prevalence: decrease from 18% to 4%; diabetes prevalence: increase from 14% to 24%; total cholesterol: projected decrease from 191 to 163 mg/dL; hypertension treatment: increase from 27% to 40%; systolic blood pressure: decrease from 122.0 to 115.8 mmHg; HDL-C: decrease from 52.4 to 49.6 mg/dL

TABLE 1 Trends in CVD risk factor prevalence in men and women

	2013 value (observed)	2020 value (projected)	2030 value (projected)	2040 value (projected)
Men				
Smoking prevalence	0.21	0.16	0.10	0.03
Total cholesterol (mg/dL)	188.2	180.2	167.0	153.8
HDL cholesterol (mg/dL)	47.6	46.8	46.1	45.4
Systolic blood pressure (mm hg)	124.0	122.8	121.0	119.2
Hypertension treatment (%)	0.25	0.29	0.33	0.38
Diabetes prevalence	0.15	0.18	0.23	0.28
Women				
Smoking prevalence	0.18	0.14	0.09	0.05
Total cholesterol (mg/dL)	194.4	190.8	181.8	172.8
HDL cholesterol (mg/dL)	58.8	56.9	55.3	53.8
Systolic blood pressure (mm hg)	120.8	118.6	115.5	112.4
Hypertension treatment (%)	0.29	0.33	0.38	0.43
Diabetes prevalence	0.14	0.15	0.18	0.21

Abbreviations: HDL, high-density lipoprotein.
Risk factor prevalence in 2013 as reported in NHANES. Projections based on extrapolating observed trends in NHANES from 2002 to 2013.

2040. Such a decrease would require significant effort, as a 4% decrease was observed between 1980 and 2000.[5] When the projected interventions were more efficacious, such that cholesterol was reduced by 40%, we found that mortality levels would be 210 per 100 000 in 2040, compared to 309 per 100 000 in the base case scenario. The population wide systolic blood pressure would need to be reduced by >20% to maintain the current rate of CVD mortality through 2040. Results when varying projected total cholesterol and systolic blood pressure levels are shown in Figure 3A,B, respectively.

When considering interventions that would reduce CVD through any mechanism of action, we found that a 20% reduction in incidence led to mortality rates of 255 per 100 000 individuals in 2030 and 262 per 100 000 in 2040. If the incidence reduction was 40%,[24] similar to the benefit found with the introduction of statins, CVD mortality rates remained constant through 2040. The predicted changes in

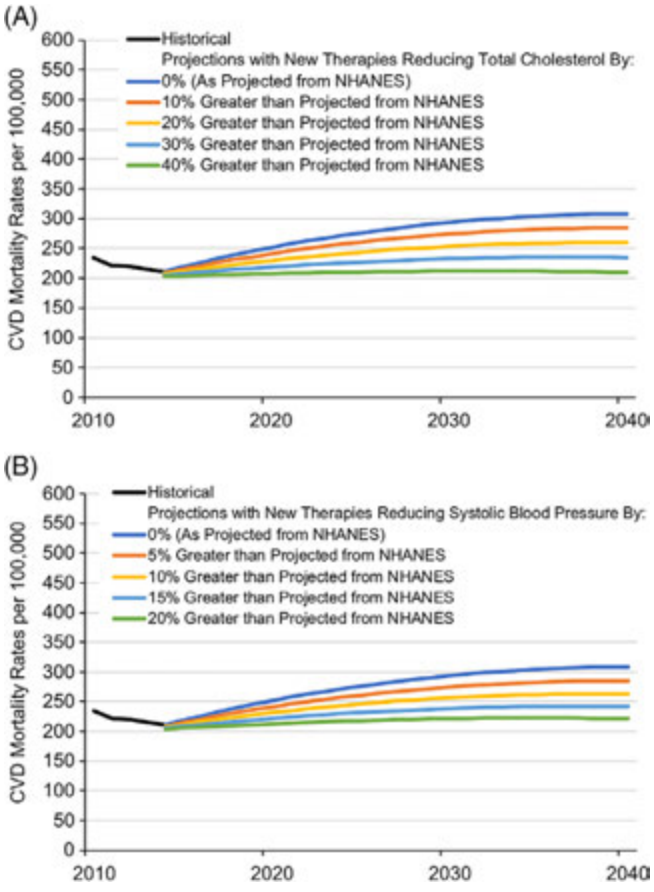

FIGURE 3 A, Cardiovascular disease mortality projections following innovations reducing total cholesterol. CVD, cardiovascular disease; NHANES, national health and nutrition examination survey. Figure depicts the CVD mortality trends given differing assumptions regarding future total cholesterol levels. The top line reflects changes in cholesterol as projected by NHANES. Each subsequent line reflects a decrease in total cholesterol beyond the change projected by NHANES. B, CVD mortality projections following innovations reducing systolic blood pressure. CVD, cardiovascular disease; NHANES, national health and nutrition examination survey. Figure depicts the CVD mortality trends given differing assumptions regarding future systolic blood pressure levels. The top line reflects changes in systolic blood pressure as projected by NHANES. Each subsequent line reflects a decrease in systolic blood pressure beyond the change projected by NHANES

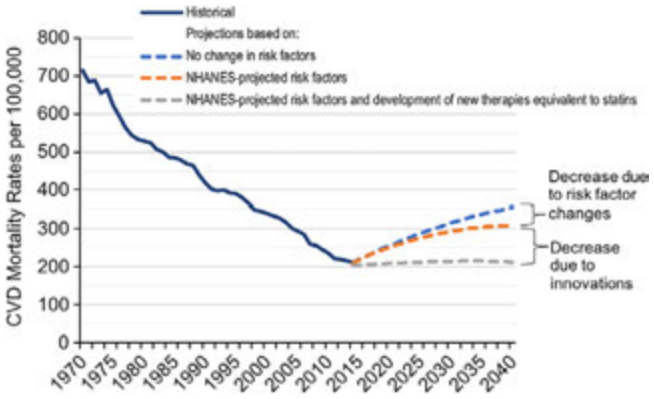

FIGURE 4 Mortality projections for three scenarios. CVD, cardiovascular disease; NHANES, national health and nutrition examination survey. Figure depicts the historical rates of CVD mortality, and the projected rates under three scenarios. Historical data based on publication by Ma et al.[25] Future increases without innovations driven by a rapidly increasing CVD prevalence rate

CVD mortality with an innovation similar to statins is found in Figure 4, compared to the expected trends with no changes in risk factors, or changes in risk factors without innovations.

In scenarios exploring interventions that decrease the case fatality rate for patients experiencing a CVD event, we found that a 10% reduction would lead to 289 deaths per 100 000 in 2040, compared to 309 per 100 000 in 2040 assuming the current rate.

4 | DISCUSSION

There may soon be a meaningful increase in CVD prevalence and mortality. In scenarios with projected changes in risk factors, but without significant pharmacological or technological advances, CVD deaths will rapidly rise in the near future. However, if development of therapeutic alternatives is prioritized and new treatments are used effectively in the right patient populations, the decline in CVD mortality could continue.

Nevertheless, death is inevitable. As progress is made in one disease area, more individuals are susceptible to competing causes of mortality. In the setting of economic development, the phrase "epidemiologic transition" is used to describe the trend in which a decrease in infectious diseases leads to an increase in cancer and CVD mortality.[26,27] While the typical shifts associated with an epidemiologic transition have already occurred in the United States, a different yet related change in common causes of mortality is underway. Specifically, increases in cancer screening and new oncology therapies have lengthened overall survival, but have resulted in a larger pool of older individuals susceptible to CVD.[28] While successes in healthcare are encouraging, we must be prepared for demographic and epidemiological changes causing an increased CVD burden.

In addition to the impact of demographic changes, the rising incidence and prevalence of obesity and type 2 diabetes among most racial and ethnic groups, and the disproportionate increase among African-Americans, Latinos,[29–31] and some Asian[32] and Pacific Islander groups,[33,34] is cause for concern. Diabetes and obesity are significant risk factors for CVD, as well as contributing to other CVD

risks including hypertension.[35] In addition, the average age among those diagnosed with obesity and type 2 diabetes is decreasing.[36] The impact of an earlier age of diagnosis remains unclear. While evidence has shown that CVD risk increases with an increased duration of diabetes,[37] earlier diagnosis leading to effective treatment could allow glucose levels to be controlled before individuals become elderly and face an elevated age-related risk. These shifts were addressed in the models to some degree, but these ongoing epidemics may worsen more than expected.

Additional risk factors for CVD include poor access to healthcare. Deaths due to CVD are higher among adults without health insurance or regular access to health care.[38,39] With the advent of the Affordable Care Act (ACA), more adults have health insurance,[40] but many may still limit utilization due to deductibles, copayments, and conflicting priorities.[41] With ongoing legislative changes and uncertain access to healthcare, we may see another increase in the number of uninsured adults.

This study aimed to provide exploratory analyses to assess hypothetical changes without specifying the driver of such changes. The specific interventions required to reduce mortality will probably include a combination of therapies, including some that are under-utilized, some under investigation, and others that have not yet been developed. A current approach that could contribute to a decline in CVD mortality include improved initial treatments for MI and unstable angina, which were found to be responsible for 10% of the mortality decline from 1980 to 2000,[4] and use of optimal treatments following stroke. Another approach that could improve CVD outcomes is use of monoclonal antibody therapies, such as PCSK9 inhibitors among adult patients with established CVD, high risk of cardiovascular events, and LDL-C ≥ 70 mg/dL and/or non-HDL-C ≥ 100 mg/dL despite high- or moderate-intensity statin therapy. Such therapies were shown in a recent study to decrease the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization when added to statins, vs statins alone (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.79-0.92).[42] In addition, continued improvements in acute interventions to prevent sudden mortality could save lives, as these have been highlighted as a key driver of mortality gains over the past 50 years. Identification of genetic variations that are more amenable to treatment and further operationalizing of transcatheter valve replacement could also reduce mortality.[43–46] Finally, the extent of uncertainty in making projections to 2040 leaves open the possibility that the most beneficial innovations have not yet been developed or even considered.

These analyses are unique in that we based projections on the most recent NHANES data, incorporated behavioral and therapeutic changes, and predicted outcomes to 2040. In cases of overlap between this study and previous studies, results are similar. A 2013 analysis projected a rise in CVD 10-year risk from 2015 to 2030, and projected CVD prevalence would increase to 12.5% by 2030, compared to 13.2% in our study. However, that analysis did not explore the impact this would have on CVD mortality.[16] Studies using another model to quantify the impact of policies predicted an increase in CVD in the absence of changes, and a decrease with efficacious interventions.[10,12] These trends were consistent with our findings; however, direct comparisons are impossible to give these outcomes which were projected for 2010 and 2020. Other analyses explored the impact of changing risk factor profiles and demographics, but did not consider innovations.[13–15]

Results should be considered in light of limitations. The model relies on historical data, and there is uncertainty in projecting future events. The relationships between risk factors and CVD were based on the Framingham Risk Score, which widely used, is not a perfect predictor. Other risk equations exist, and comparing the outcomes projected from this model with similar results when using alternative risk equations could be an interesting area for future research to determine whether results vary by equation used. This model relied on the best available data, including NHANES and a nationwide mortality registry; however, there are simplifying assumptions required in modeling. In this study, we assumed men and women had equivalent case-fatality rates, the 1-year risk of CVD was 10% of the 10-year risk predicted by the Framingham Risk Score, and those with an incident CVD event had the same mortality risk as those with a previous event.

5 | CONCLUSION

Following an extended period of decline in CVD mortality, there has been a recent stabilization in deaths attributed to CVD. Changing demographics including longer life expectancy, competing needs for limited resources, and decreases in other fatal medical conditions, suggest there could be an impending increase in CVD mortality. Model projected outcomes indicate behavioral interventions targeting CVD risk factors will be insufficient to maintain the gains observed over the past 50 years and could result in >330 000 additional deaths in 2040. Preventing an increase in CVD mortality will require either dramatic shifts in risk factor prevalence or development and diffusion of additional efficacious treatments.

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Author contributions

JO, DC, and MB were involved in the conception and design of this study. JO, AH, MB, PT, and AD were involved in conducting the analysis and interpreting the data. All authors were involved in drafting the paper and revising it critically for intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

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APPENDIX

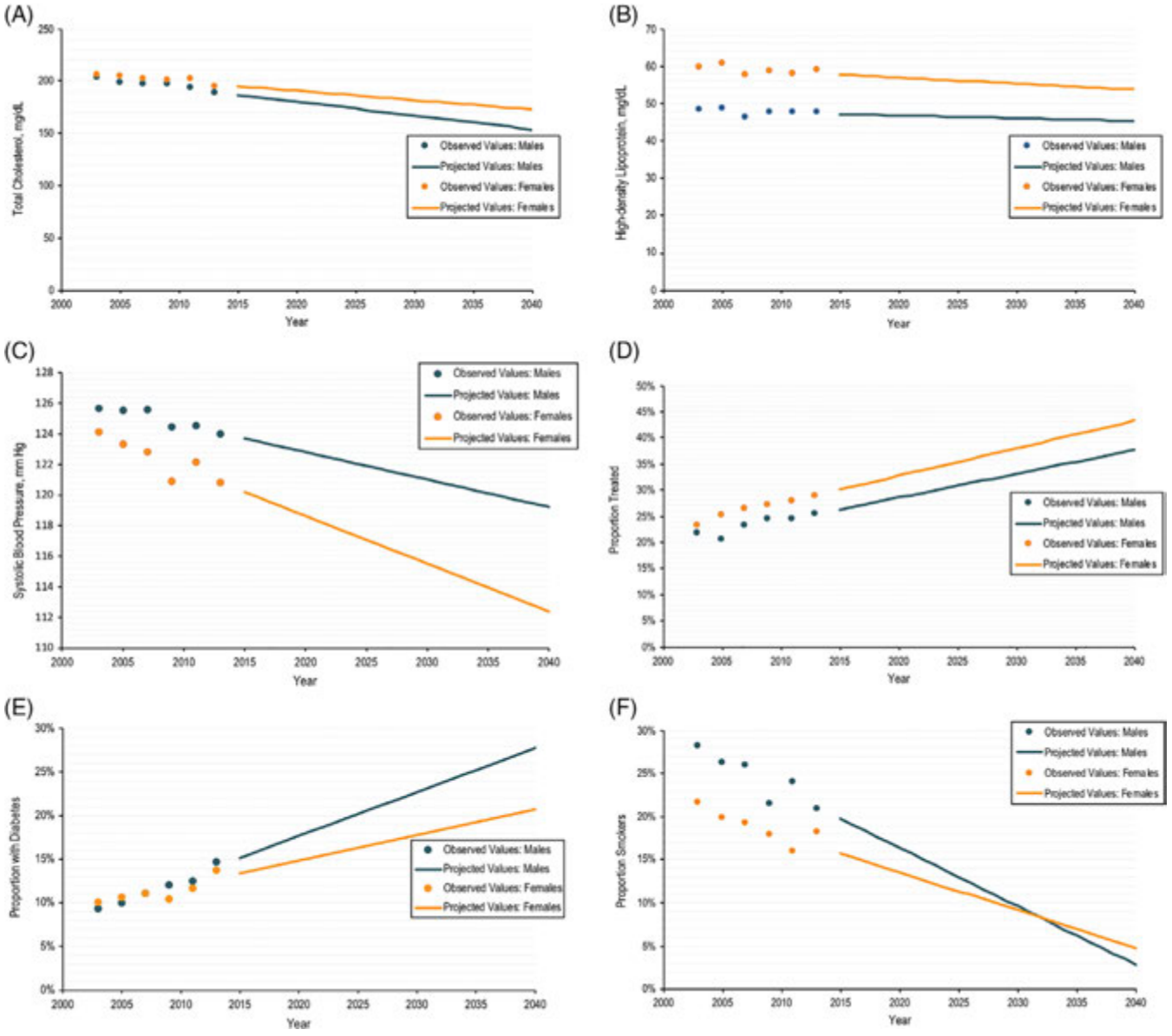

FIGURE A1 Historical and projected risk factor values: total cholesterol. A, The decrease in total cholesterol based on an analysis of NHANES data from 2003 to 2014. B, The decrease in high-density lipoprotein based on an analysis of NHANES data from 2003 to 2014. C, The decrease in systolic blood pressure based on an analysis of NHANES data from 2003 to 2014. D, The increase in systolic blood pressure treatment based on an analysis of NHANES data from 2003 to 2014. E, the increase in diabetes prevalence based on an analysis of NHANES data from 2003 to 2014. F, The decrease in smoking rates based on an analysis of NHANES data from 2003 to 2014