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# US trends in premature heart disease mortality over the past 50 years: Where do we go from here? ☆☆

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## Abstract

Despite the premature heart disease mortality rate among adults aged 25–64 decreasing by 70% since 1968, the rate has remained stagnant from 2011 on and, in 2017, still accounted for almost 1-in-5 of all deaths among this age group. Moreover, these overall findings mask important differences and continued disparities observed by demographic characteristics and geography. For example, in 2017, rates were 134% higher among men compared to women and 87% higher among blacks compared to whites, and, while the greatest burden remained in the southeastern US, almost two-thirds of all US counties experienced increasing rates among adults aged 35–64 during 2010–2017. Continued high rates of uncontrolled blood pressure and increasing prevalence of diabetes and obesity pose obstacles for re-establishing a downward trajectory for premature heart disease mortality; however, proven public health and clinical interventions exist that can be used to address these conditions.

### Keywords

Heart diseases; Mortality; Premature; Risk factors; Public health

Heart disease (HD) has been the leading cause of death since 1933, when mortality data first became available for the entire nation [1]. The contribution of HD to overall mortality increased until the 1960s—from 21% of all deaths in 1933 to 39% of all deaths in 1963 [1]—but then began declining precipitously with the identification and management of key cardiovascular disease risk factors and advances in medical treatment [2-5]. Despite these successes, within the past decade trends in HD mortality have begun to stagnate, and—even more disturbing—HD mortality rates among younger adults may be rising [6-9].

The substantial health and economic impact of HD in the United States warrants monitoring of the entire population. However, it is particularly important to monitor its burden among younger adults. Around half of cardiovascular events among men and almost one-third of

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events among women occur before age 65 [10]. Furthermore, this group is instrumental in the US work-force and as caregivers, and having an event at an early age can negatively impact their ability to serve in these roles [11]. This paper provides a review of the history of HD mortality among younger US adults over the past 50 years (1968–2017) and its relationship to trends in key cardiovascular disease risk factors. We refer to deaths among adults aged 25–64 years collectively as being premature [12,13]. These deaths were further classified as premature HD deaths if they had an underlying cause per the specifications outlined by the National Vital Statistics System [1,14]. We also highlight public health and clinical activities that could be used to address the worrisome trends observed.

## Trends in premature HD mortality

The overall, age-standardized premature HD mortality rate decreased by 70%, from 206 per 100,000 in 1968 to 62 deaths per 100,000 in 2017 (Fig. 1), and the percentage of all premature deaths attributable to HD decreased from 33% during 1968–1977 to 19% during 2008–2017 (Fig. 2) [15]. However, the burden remains high—126,842 deaths occurred in 2017, or around 1 death every 4 min—and no appreciable change has been observed in event rates since 2011.

These overall findings mask important differences and continued disparities observed by demographic characteristics. For example, while premature HD mortality rates decreased among both sexes and among blacks and whites (Fig. 3), in 2017, overall age-standardized rates were 134% higher among men (88 deaths per 100,000) compared to women (38 per 100,000) and 87% higher among blacks (108 per 100,000) compared to whites (58 per 100,000). Moreover, the rate of decline has stagnated across all age groups and even increased among adults aged 55–64 by 4% from 183 deaths per 100,000 in 2011 to 191 per 100,000 in 2017 (Fig. 1). Furthermore, while the proportion of premature deaths attributed to HD has decreased each decade for most groups, it remained unchanged among adults aged 25–34 (around 7% of all deaths during each decade) and it has remained stagnant during the two most recent decades among adults aged 35–44 and blacks (Fig. 2).

Findings at the national level also mask important differences observed by geography and by level of urbanization [7,16-20]. For example, HD mortality among younger adults has consistently been highest in the area from eastern Texas and Oklahoma through the Southeast and into Appalachia (Fig. 4a) [7,16-19]. However, recently, widespread increases have occurred [7], including almost two-thirds of US counties experiencing an increase among adults aged 35–64 during 2010–2017 (Fig. 4b). Furthermore, HD mortality among younger adults remains considerably higher in rural compared to metro areas, especially among blacks [20].

### Coronary heart disease and heart failure

Deaths attributed directly to coronary HD still have the greatest overall impact on premature HD mortality [1,14,15]. However, the percentage of deaths attributable to coronary HD has been decreasing and deaths attributable to heart failure and hypertensive HD, which is often associated with heart failure [21], have been on the rise [22,23]. This change appears to be driven by multiple factors. First, less severe myocardial infarctions (Mis) appear to be

occurring [24]. This includes rates decreasing for ST-elevation MI (STEMI) hospitalizations and increasing for non-STEMI hospitalizations, which have lower case fatality rates; this finding is likely driven in part by the increased sensitivity of troponin testing in identifying non-STEMI events [25,26]. Second, advances in care, including increased use of early invasive strategies and decreasing the average time-to-revascularization, have led to improved survival [9,26,27]. Additionally, heart failure prevalence and related healthcare utilization appear to be on the rise [28,29]. During 2013–2016, an estimated 6.2 million US adults aged ≥20 had heart failure [29], and a projected 8.5 million will have it by 2030, almost one-third (29%) of which, are expected to be aged 18–64 [30]. This change in heart failure prevalence appears to be driven, in part, by advances in treatment that improve survival after having a coronary HD event [31] and changing demographics. For example, Hispanics are the fastest growing minority group in the United States and are more likely to develop heart failure before age 65 compared to non-Hispanic whites [30,32]. Furthermore, the overall premature heart failure mortality rate is negatively impacted by the recent increase observed among younger black men who, along with black women, have heart failure-related mortality rates 2.5-to 3-fold greater than those observed among similar aged white men and women, respectively [22].

## Trends in major modifiable risk factors for HD

Fig. 5 shows prevalence changes for many modifiable HD risk factors. improvement in several of these factors has been associated with around half of the decrease in HD mortality observed during the latter half of the 20th century [2,4]. However, there remains a low prevalence of ideal cardiovascular health in the United States [33,34]. In fact, over 90% of adults aged 18 to 59 years who have an initial acute MI hospitalization have at least one documented HD risk factor [35].

### Hypertension

Hypertension is the risk factor associated with the largest percentage of cardiovascular deaths [33,36]. Overall hypertension prevalence increased from the mid-1980s through the turn of the century, but has remained steady since [37-39]. Application of the updated blood pressure thresholds recommended in the 2017 national guideline [40] results in an estimated 23% of US adults aged 18–44, 47% of adults aged 45–54 and 66% of adults aged 55–64 currently having hypertension [41]. While hypertension control increased considerably since the 1970s, it has plateaued during the past decade [37-39]. Currently, around 56 million US adults aged 18–64 have uncontrolled blood pressure per the 2017 guideline criteria and are in need of initiating or intensifying non-pharmacologic and, possibly, pharmacologic treatment [41]. One potential barrier to improving blood pressure control is the significant amount of sodium consumed in the United States [42]. Mean daily sodium intake among adults has increased greatly during the last several decades from around the recommended amount of 2300 mg/day in the 1970s to over 3500 mg/day in 2015–2016 [42-44].

### Dyslipidemia

The prevalence of high low-density lipoprotein cholesterol and high total cholesterol levels have improved considerably over the past decades [45,46]. However, during 2013–2014,

only around half of US adults aged 35–64 eligible for statin use for cholesterol management were taking them [47]. Although not everyone eligible for taking statins are prescribed them. Furthermore, familial hypercholesterolemia, an inherited condition affecting about 1 in 250 US adults, often remains undiagnosed [48] and is a frequent cause of heart attacks in younger adults. Adults aged 20–39 who have this treatable condition and are not receiving statin therapy have around a 100-fold increased risk for death compared to those without the condition [49].

## Smoking

Smoking prevalence and secondhand smoke exposure have decreased considerably since the 1970s [50-53]. However, smoking remains a prevalent condition among those aged 18–44 who have had a MI [35]. Despite smoking cessation rapidly lowering coronary HD risk [54], an estimated 16.1% of US adults aged 25–44 and 16.5% of adults aged 45–64 currently smoke cigarettes [55]. Additionally, the use of e-cigarettes has increased substantially among youth and young adults [56,57]. The long term health effects of e-cigarettes are still largely unknown [58]. However, most e-cigarettes contain nicotine, and there is substantial evidence for the negative effect of nicotine on increasing heart rate, blood pressure, and myocardial oxygen demand [50,57].

## Obesity and diabetes

The increasing prevalence of both obesity and diabetes have been major barriers to decreasing the prevalence of other HD risk factors and making continued improvements in HD mortality [2,34,59-61]. They are frequently found among younger adults who experience their first acute MI [35]. During 2015–2016, around 40% of US adults aged 20–74 had obesity, of whom one-in-five had severe obesity [59]. In 2017, approximately 13% of adults aged 45–64 had diagnosed diabetes [60]. Associated with the high prevalence of obesity and diabetes is the growing rate of chronic kidney disease [62] and the continued high rates of poor diet quality [33] and physical inactivity [47,63]. During 2015–2016, over one-fourth (28%) of US adults aged 35–64 were physically inactive, defined as never getting 10 min or more of leisure-time physical activity [47].

## Other heart disease risk factors

Other pertinent risk factors include: exposure to poor air quality, which has improved at the population level but still poses a threat to certain populations, especially those with pre-existing HD [64-66]; consumption of foods containing trans-fatty acids, which has reduced remarkably with the introduction of mandatory food processing requirements [67]; and stress, for which no consistently measured values are available over time, but has been shown to be a contributor to cardiovascular disease [29], especially among women [68]. Moreover, the rates of hypertensive disorders during pregnancy have increased significantly, placing the mothers at increased lifetime risk for cardiovascular disease-related morbidity and mortality [69,70].

## Premature HD mortality projections

Despite the recent plateau noted in HD death rates, some projections have the United States experiencing small decreases in overall premature HD mortality during the next couple of decades [12]. However, no change is expected among women and substantial increases are expected among American Indians or Alaska natives, especially males in that group [12]. Furthermore, these projections may be negatively impacted by the cardiovascular health profile of the US adolescent population being less than ideal [71]. This includes adolescents having low rates of physical activity and quality diets potentially leading to further increases in the prevalence of obesity and diabetes and, as this cohort becomes adults, increased cardiovascular disease risk [71].

## What can be done to address current trends in premature HD mortality?

To address these alarming trends in premature HD, public health and clinical systems can implement proven effective strategies and innovative promising practices across the spectrum of HD prevention. Million Hearts®, a national initiative co-led by the Centers for Disease Prevention and Control (CDC) and the Centers for Medicare & Medicaid Services, is focused on making gains within both sectors [72] with the ultimate goal of preventing one million heart attacks, strokes, and other acute cardiovascular events in five years [18,47]. Because of the growing burden of premature HD, Million Hearts® has prioritized taking action to address modifiable HD risk factors among younger adults.

## Public health interventions

### Decreasing tobacco use

Multiple evidence-based public health strategies have been shown to reduce the prevalence of tobacco use [73], including comprehensive smoke-free policies which include e-cigarettes [57,74], increasing price [75], and implementation of mass media campaigns [76,77]. Each of these approaches deter initiation and encourage cessation. Widespread mass media campaigns, like the CDC *Tips From Former Smokers*® campaign [76], are being used to show the impact that smoking can have on health and quality of life in order to spur tobacco cessation and connect people who use tobacco with cessation resources [77].

### Supporting physical activity

To combat physical inactivity, initiatives like Active People Healthy Nation℠ [78] and Million Hearts® recommend that communities and streets be designed to support physical activity through activity-friendly routes to everyday destinations. This approach combines interventions to improve transportation systems with land use and community design interventions to make it safe and convenient for people of all abilities to be physically active [79]. Places for physical activity can be created or have their access enhanced through actions such as shared use agreements or workplace facilities or policies [80]. Social supports, for example, promising peer support programs such as the Arthritis Foundation's Walk with Ease and GirlTrek, have been shown to be effective for encouraging walking and other forms of activity [81-83].

### Decreasing sodium intake

National initiatives like the National Salt and Sugar Reduction Initiative [84] and Million Hearts® are working to increase the availability of lower-sodium options for consumers. This can be accomplished by instituting healthy food procurement and nutrition policies to reduce average daily sodium intake and improve overall nutrition, which has been demonstrated in hospitals and other localities [85]. In addition, gains can be made through the gradual and voluntary reduction of sodium in commercially packaged and prepared foods, as described in the U.S. Food and Drug Administration's (FDA) draft proposed guidance to the food industry [86].

### Coverage for evidence-based services

Access to comprehensive health insurance coverage among younger adults can influence their receipt of HD risk factor management services and improve their health outcomes [87]. To support clinical teams, public health and health advocacy groups are working with insurers to expand coverage and reimbursement for evidence-based services and prevention strategies [88]. These include reducing or eliminating barriers such as out-of-pocket costs for antihypertensive medications and statins and prior authorization and annual and duration limits for tobacco cessation treatments (including individual, group, and telephone counseling and seven FDA-approved cessation medications) to increase their use [73,89-91]; obtaining coverage for validated home blood pressure monitors and reimbursement for clinicians to provide patient training and interpretation of home blood pressure readings to improve hypertension control [92]; expanding access to the National Diabetes Prevention Program for lifestyle modification [93]; and expanding coverage with reduced patient copays for cardiac rehabilitation to improve participation [94].

## Clinical interventions

### Standardized treatment protocol adoption

Studies have suggested that younger adults are less likely than older adults to have their hypertension diagnosed and treated or to use statins as recommended, and are more likely to use combustible tobacco products [47,55,95]. Moreover, studies suggest that siblings and children of people with premature coronary heart disease are not routinely screened for risk factors, provided therapeutic treatment, or recommended lifestyle modifications, even with their increased risk [96]. Clinicians and their patients, especially younger adults, may hesitate to start a medication regimen that could be life-long, despite a strong indication to do so. A systems-approach to care, using protocols, teams, and timely data, is useful in overcoming these barriers and protecting this group from largely preventable HD events. Treatment protocols can help systematically identify all patients who are eligible for clinical management, reduce unwarranted variation, simplify medication initiation and intensification, reinforce lifestyle counseling, routinize timely patient follow up, and enable all members of the clinical team to contribute to patient management [97]. Healthcare systems that have improved their performance on chronic disease indicators including hypertension control often attribute their success, in part, to protocol implementation [98-101].

### Self-measured blood pressure monitoring

Self-measured blood pressure (SMBP) monitoring, also known as home blood pressure monitoring, with additional clinical support, is an evidence-based strategy for lowering blood pressure and increasing control rates in patients with hypertension. There is strong evidence showing that SMBP, with co-interventions such as counseling, telephonic support, or telemonitoring, is an effective strategy for managing patients with hypertension [102-104]. It may also help with medication adherence and overcoming therapeutic inertia [105,106]. There is a growing body of evidence that supports its use in confirming an initial hypertension diagnosis, a new indication in recent clinical guidelines [40,107]. Many available SMBP devices are Bluetooth- or Wi-Fi-enabled and clinical systems can be set up that allow remote transmission of readings to the clinical team through patient portals or telemonitoring modes. However, clinicians should be aware that smart phone devices, wearable sensors, cuffless monitors, and finger cuffs intended for blood pressure measurement have not, at this time, been proven accurate or validated [108].

### Lifestyle modifications

The U.S. Preventive Services Task Force recommends referring adults who are overweight or have obesity with additional HD risk factors to behavioral counseling to improve nutrition, including decreasing sodium and saturated fat intake, and increase level of physical activity [109]. Lifestyle modifications are also an integral component of the most recent hypertension and cholesterol management guidelines [40,110]. Evidence suggests that patients are more likely to make a lifestyle modification if their clinician recommends they do so [111]. One readily available evidence-based lifestyle modification program is the National Diabetes Prevention Program [93,112]. Patients can also be referred to registered dieticians, exercise physiologists, or promising community-based programs like Walk With a Doc or the ParkRx initiative [113,114].

### Treatment of tobacco use and dependence

Recent data show that while approximately 70% of adults aged 25–64 who smoke wanted to quit, less than one in ten were able to quit for six months or more in the past year [115]. While around half of smokers aged 25–44 and two-thirds of those aged 45–64 report having received a health professional’s advice to quit, very few have received cessation counseling (6% and 9%, respectively) or used cessation medication (26% and 38%, respectively). Clinical interventions that work to help adults who use tobacco quit include asking about tobacco use at every visit, advising all users to quit, and providing FDA-approved medications, counseling, and quitline referrals; all of which can be included in tobacco cessation treatment protocols [90,116].

The U.S. Preventive Services Task Force found that the current evidence is insufficient to recommend e-cigarettes for tobacco cessation in adults [117], and e-cigarettes are not currently approved by the FDA as a smoking cessation aid. Moreover, their health impacts are not well understood and little evidence is available about how to help patients quit e-cigarette use [58,118].

## Medication adherence strategies

For both management of HD and many of its related risk factors, medications are an integral treatment component. Yet nonadherence to these medicines is common [119-121]. There are a number of evidence-based or promising practices that clinicians can employ or encourage their patients to use to improve adherence; their current implementation varies by strategy and clinician type [122].

Whenever possible, clinicians should prescribe in a way that minimizes patient cost, reduces barriers for obtaining medications, and simplifies regimens. Consulting a patient's insurance formulary and selecting generic formulations can help to reduce or eliminate patient co-pays, a proven facilitator for adherence [89]. Prescribing medication electronically reduces the likelihood that prescriptions will be lost by the patient and supports the use of pharmacy-initiated text reminders and automated refills. Issuing prescriptions of longer duration, i.e. 90 vs. 30 days, using fixed-dose combination pills where two or more medications are combined into one pill, and synchronizing medication regimens, where all prescriptions are received during a single pharmacy visit, make it more convenient for patients to adhere to medication regimens, particularly if they are complicated [123,124]. Moreover, lower dosing frequency can improve adherence [125-127].

To ensure that needed medications are taken as directed, the care team can suggest ways for patients to be reminded to take their medications, such as through use of pill boxes or mobile-health interventions like daily calendar reminders in phones, text messages, or reminder apps [128]. Educating patients on how medications should be taken and why is fundamental. Potential side effects should be thoroughly reviewed but clinicians should be mindful of the nocebo effect, where a patient experiences side effects because they were told they might, which has been well documented for muscle pain with statins [129].

Pharmacists can be integral members of the care team, especially for hypertension control and cholesterol management [130-132]. They can play a unique role in educating patients through medication therapy management, which encompasses a range of services to help patients take medications as directed and has been shown to improve medication adherence [132,133]. Clinicians may work directly with pharmacists employed by their health system or put collaborative practice agreements in place for delivery of these types of services by community-based pharmacists.

## Cardiac rehabilitation

For adults who have already had a HD-related event, cardiac rehabilitation is an evidence-based, comprehensive secondary prevention program designed to improve cardiovascular health following a cardiac event or procedure through supervised exercise training, education and skills development for heart-healthy living, and psychosocial counseling [134-139]. Participation can reduce the risk of death from any cause and cardiac causes, as well as decrease hospital readmissions, and improve functional status, quality of life, and mood [140-143]. Yet despite these benefits, participation remains low, ranging from 10% to 34% in national analyses, with variation by geography, cardiac diagnosis, and demographic characteristics, including being lower among adults aged <65 compared to those aged ≥65

[144-148]. Clinicians can play a critical role in optimizing participation rates by emphasizing its value, ensuring referral of eligible patients, and encouraging completion of a full course of treatment.

## Future directions

Innovation to go beyond the status quo and utilize different interventions, modalities, and delivery sites will be needed for HD prevention among younger adults. This may include using interventions that leverage technology to improve cardiovascular health. In the age of smartphones and personal health monitoring devices, younger adults are accustomed to tracking their activity, heart rate, and sleep patterns. Technology, at a minimum, can be directly pertinent in SMBP monitoring, treatment of tobacco use and dependence, and medication adherence. Interventions like cardiac rehabilitation, which is traditionally delivered by attending 36 one-hour sessions in an outpatient clinic during usual business hours, may need to invest in home-based programs with remote monitoring, develop flexible models, including accelerated programs or open-gym concepts, or offer expanded hours that can better accommodate work and caregiver demands [149-151]. Younger adults spend about a third of their lives at work, and the negative HD-related trends observed in this age group are costly to the private sector with regard to health care costs and lost productivity [29]. Because of this potential financial burden, it behooves employers to move beyond traditional ‘worksite well-ness’ into community-level policy, systems, and environmental changes, which may have a bigger impact on HD and related sequelae. Lastly, how we discuss and evaluate cardiovascular disease risk needs to be expanded outside of traditional risk calculators, which are largely driven by age. This includes assessing for and acting on risk factors for hypertensive disorders of pregnancy and family history of premature HD among younger adults, as well as addressing cardiovascular disease risk and modifiable risk factors in youth [10,152,153]. If not, current trends in premature HD are likely to continue and possibly worsen.

## Conclusion

We have achieved significant progress over the past 50 years in decreasing the burden of premature HD mortality in the United States. However, the continued high or increasing prevalence of some HD risk factors has stalled the previously decreasing trends and may lead to a reversal in the gains made. Fortunately, there are powerful, concrete, and complementary actions available to both public health and healthcare professionals. By focusing attention on and pooling the resources of both sectors to make gains among younger adults, the downward trajectory in premature HD mortality could be re-established, improving the health of the country.

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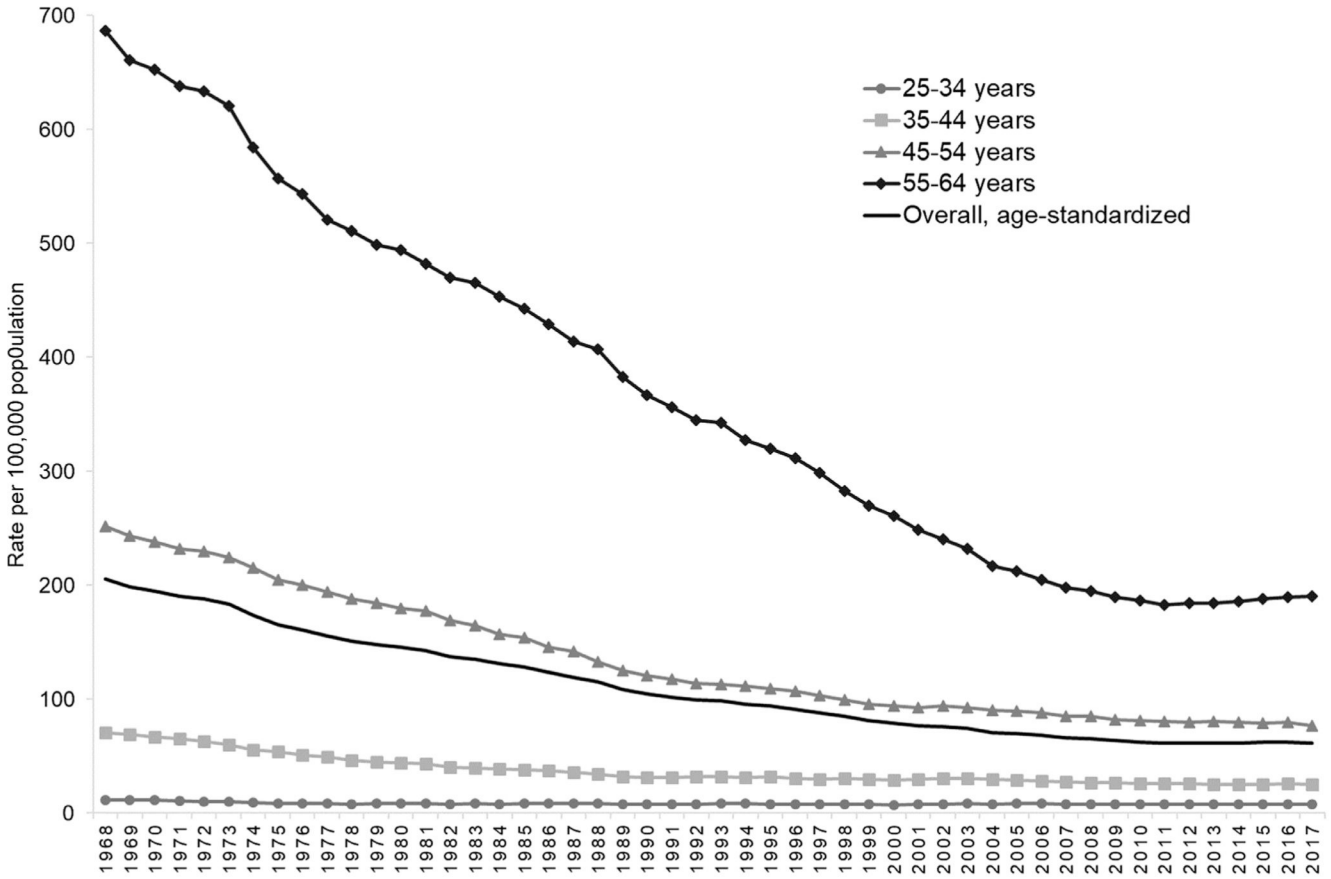


**Fig. 1.**

Age-standardized overall and age-specific premature heart disease mortality rates* among adults aged 25–64 years, 1968–2017.

*Source:* Centers for Disease Control and Prevention WONDER Online Database [1,14,15].

*Deaths with underlying-cause-of-death *International Classification of Disease, Eighth Revision* (1968–1978) codes: 390–398, 402, 404, 410–429; *Ninth Revision* (1979–1998) codes: 390–398, 402, 404–429; or *Tenth Revision* (1999–2017) codes: I00–I09, I11, I13, I20–I51. Overall rate standardized by age to the 2000 standard US population.

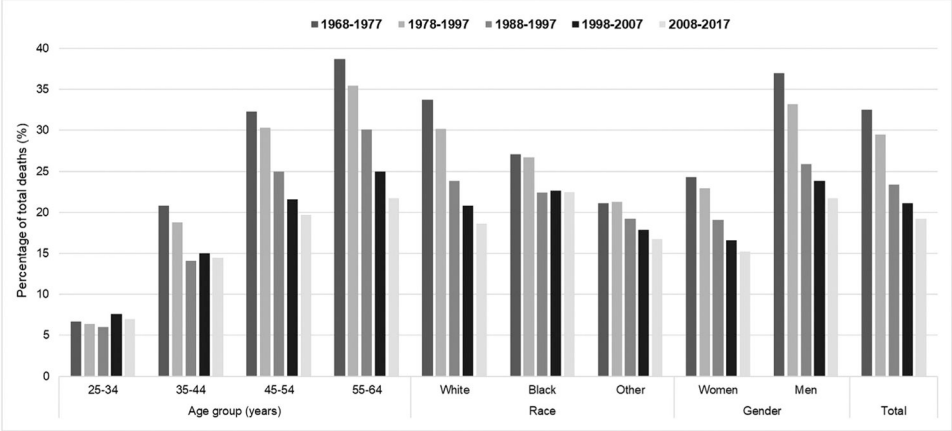


**Fig. 2.**

Percentage of total premature deaths attributed to heart disease* among adults aged 25–64 years within five 10-year periods, by age group, race and sex, 1968–2017.

*Source:* Centers for Disease Control and Prevention WONDER Online Database [1,14,15].

*Deaths with underlying-cause-of-death *International Classification of Disease, Eighth Revision* (1968–1978) codes: 390–398, 402, 404, 410–429; *Ninth Revision* (1979–1998) codes: 390–398, 402, 404–429; or *Tenth Revision* (1999–2017) codes: I00–I09, I11, I13, I20–I51.

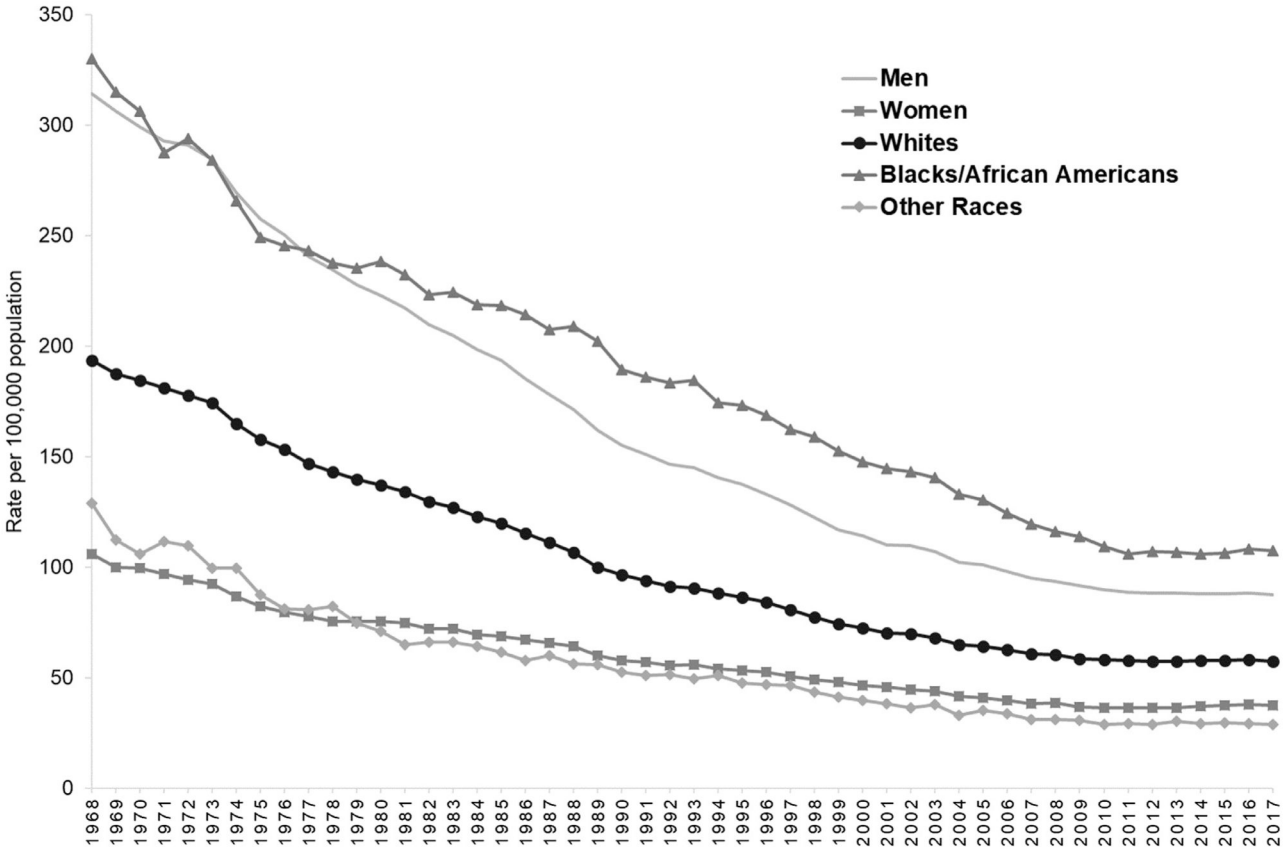


**Fig. 3.**

Age-standardized premature heart disease mortality rates* among adults aged 25–64 years, by race and sex, 1968–2017.

*Source:* Centers for Disease Control and Prevention, National Center for Health Statistics. CDC WONDER Online Database [1,14,15].

*Deaths with underlying-cause-of-death *International Classification of Disease, Eighth Revision* (1968–1978) codes: 390–398, 402, 404,410–429; *Ninth Revision* (1979–1998) codes: 390–398, 402, 404–429; or *Tenth Revision* (1999–2017) codes: I00–I09, I11, I13, I20–I51. Rates standardized by age to the 2000 standard US population.

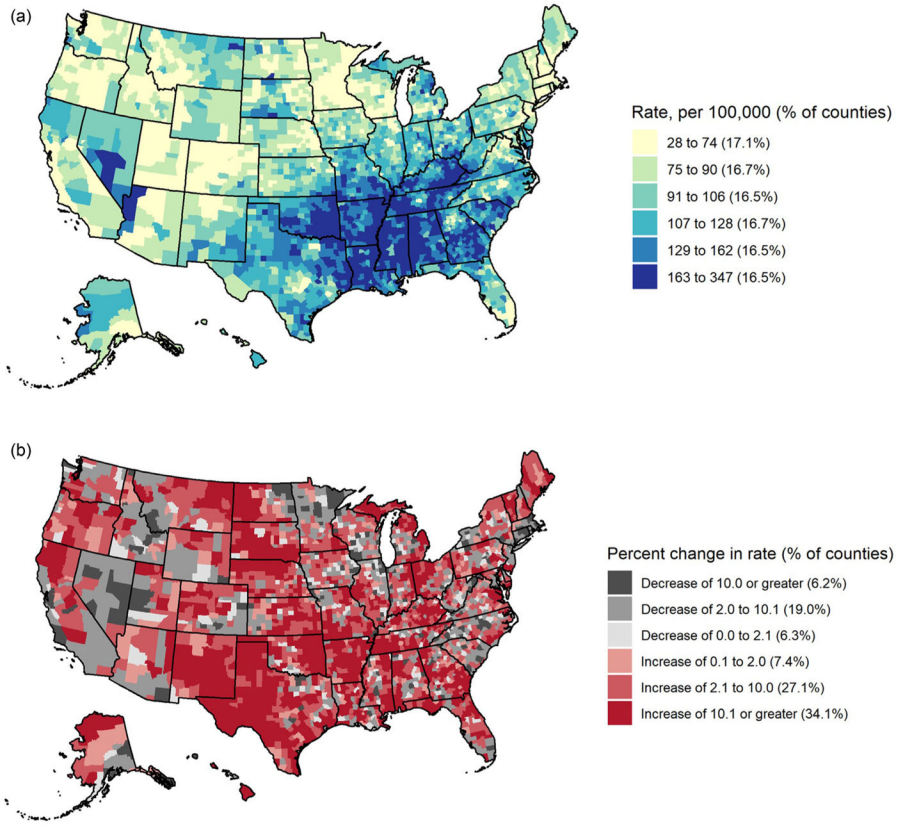


**Fig. 4.**

County-level heart disease mortality rates in 2017 (a) and percent change in heart disease mortality rates from 2010 to 2017 (b) among US adults aged 35 to 64 years.

*Source:* Initially reported in Vaughan et al. [7]. Updated with data through 2017.

*Standardized by age to the 2010 US Standard Population.

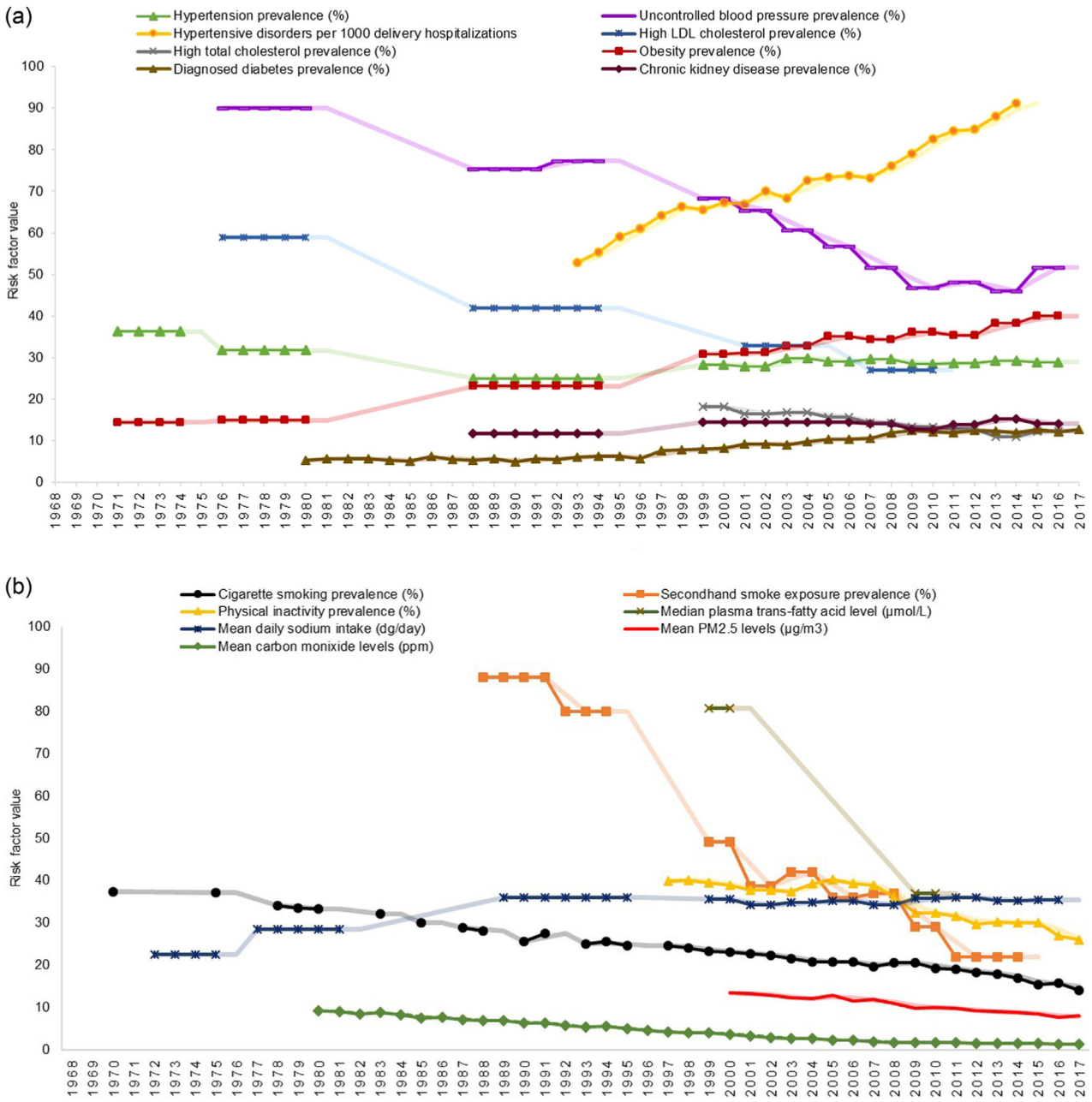


**Fig. 5.**

Trends* in the leading modifiable heart disease risk factors during 1968–2017, by risk factor type: biological† (a) and behavioral or environmental‡ (b).

Abbreviations: LDL: low-density lipoprotein; $PM_{2.5}$: particulate matter 2.5.

*Estimates are derived from the published literature and provided for as close to the 25–64 age group and for as much of the 50-year period as available. Estimates for a period containing multiple years are repeated for each year in the period. The semi-transparent lines included for each risk factor represent 2-year moving averages and are provided to assist with the visual inspection of each trend, however, no formal statistical assessments were

conducted. Uncertainty in the point estimates is not described in the figure; reference the source material for confidence intervals.

[†]Biological risk factors defined as: hypertension (blood pressure ≥140/90 mm Hg or using antihypertensive medication) and uncontrolled blood pressure (blood pressure <140/90 mm Hg among those with hypertension) among US adults aged 18–74 and age-adjusted to the 1990 US Standard Population for years 1971–1980 [37] and those aged ≥18 and age-adjusted to the 2000 US Standard Population for years 1988–2016 [38,39]; hypertensive disorders during pregnancy (includes gestational hypertension, preeclampsia and eclampsia) is expressed per 1000 delivery hospitalizations [69,70]; high LDL cholesterol (above the treatment goals established by the National Cholesterol Education Program's Adult Treatment Panel III guidelines) among US adults aged 40–74 and age-adjusted to the 2000 US Standard Population [45]; high total cholesterol (≥240 mg/dL) among adults aged ≥20 and age-adjusted to the 2000 US Standard Population [46]; diagnosed diabetes (self-reported) among US adults aged 45–64 [60]; obesity (body mass index ≥30.0 $kg/m^2$) among US adults aged 20–74 years (except during 1960–1962: among 18–79 years) and age-adjusted to the 2000 US Standard Population [59]; and chronic kidney disease (Stages 1 and 2 defined by single assessment of albuminuria [i.e., no estimation of persistence] and eGFR ≥90 and 60–89 ml/min/1.73 $m^2$, respectively; or stages 3 and 4 defined as 30–59 and 15–29 ml/min/1.73 $m^2$, respectively) among adults aged ≥20 years (unadjusted) [62].

[‡]Behavioral or environmental risk factors defined as: smoking (report use every day or some days) among adults aged ≥18 during 1970–1997 [51] (unadjusted) and during 1998–2017 age-adjusted to the 2000 US Standard Population [52]; secondhand smoke exposure (nonsmokers who had a serum cotinine level ≥0.05 ng/mL and ≤10 ng/ml) among adults aged ≥20 [53]; median plasma trans-fatty acid levels (measured in μmol/L) among US adults aged ≥20 [67]; mean daily sodium intake (measured in dg/day [typically described in g/day or mg/day]) among US adults aged 20–74 and age-adjusted to the 2000 US Standard Population during 1971–2000 (male and female values were combined using a population-weighted average) [43] and among US adults aged ≥20 (unadjusted) during 2001–2016 [44]; physical inactivity (report that they never do, or are unable to do, physical activity for at least 10 min) among adults aged ≥18 [63]; and mean $PM_{2.5}$ (measured in $\mu g/m^3$) and carbon monoxide (measured in ppm) levels [65].