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IN DEPTH

Gender/Sex as a Social Determinant of Cardiovascular Risk

ABSTRACT: The social gradient for cardiovascular disease (CVD) onset and outcomes is well established. The American Heart Association's Social Determinants of Risk and Outcomes of Cardiovascular Disease Scientific Statement advocates looking beyond breakthroughs in biological science toward a social determinants approach that focuses on socioeconomic position, race and ethnicity, social support, culture and access to medical care, and residential environments to curb the burden of CVD going forward. Indeed, the benefits of this approach are likely to be far reaching, enhancing the positive effects of advances in CVD related to prevention and treatment while reducing health inequities that contribute to CVD onset and outcomes. It is disappointing that the role of gender has been largely neglected despite being a critical determinant of cardiovascular health. It is clear that trajectories and outcomes of CVD differ by biological sex, yet the tendency for sex and gender to be conflated has contributed to the idea that both are constant or fixed with little room for intervention. Rather, as distinct from biological sex, gender is socially produced. Overlaid on biological sex, gender is a broad term that shapes and interacts with one's cognition to guide norms, roles, behaviors, and social relations. It is a fluid construct that varies across time, place, and life stage. Gender can interact with biological sex and, indeed, other social determinants, such as ethnicity and socioeconomic position, to shape cardiovascular health from conception, through early life when health behaviors and risk factors are shaped, into adolescence and adulthood. This article will illustrate how gender shapes the early adoption of health behaviors in childhood, adolescence, and young adulthood by focusing on physical activity, drinking, and smoking behaviors (including the influence of role modeling). We will also discuss the role of gender in psychosocial stress with a focus on trauma from life events (childhood assault and intimate partner violence) and work, home, and financial stresses. We conclude by exploring potential biological pathways, with a focus on autonomic functioning, which may underpin gender as a social determinant of cardiovascular health. Finally, we discuss implications for cardiovascular treatment and awareness campaigns and consider whether gender equality strategies could reduce the burden of CVD for men and women at the population level.

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For decades, epidemiologists have consistently demonstrated that mortality and morbidity rates rise steadily as social status decreases.[1] Known as the social gradient, these striking trends have been observed for a range of health conditions including cardiovascular disease (CVD) onset and outcomes in countries around the world,[2] including the United States.[3] The social determinants of health model is now widely used in public health and health promotion as an established framework for understanding health inequities within and across countries. The application of a social determinants of health approach is particularly pertinent in the modern United States. The *Shorter Lives, Poorer Health* report states that "Americans are dying and suffering from illness and injury at rates that are demonstrably unnecessary," where adverse social and economic conditions are implicated as a contributing factor.[4] An unprecedented rise in death rates among middle-aged, white American men and women between 1999 and 2014 is thought to reflect a marked decline in their social and economic conditions in recent decades. This provides an example of the inverse relationship between transience in socioeconomic position and mortality outcomes.[5]

Data from the Whitehall II study first revealed the association between social and economic factors and coronary heart disease (CHD)[6] in the early 1990s. In their cohort of middle-aged, British, male civil servants, differences in 10-year mortality rates could be explained only in part by traditional risk factors, including smoking, obesity, physical activity, lipids, and blood pressure. Rather, age and the environments in which individuals lived and worked were shown to be critical for shaping cardiovascular health. Since then, there has been a notable decrease in cardiovascular-related mortality, largely because of medical and pharmacological advances, yet CVD still makes up one-third of all deaths in the United States.[7] In their position paper, "Social Determinants of Risk and Outcomes for Cardiovascular Disease," Havranek et al[8] advocate the need to look beyond breakthroughs in biological science toward the social determinants of cardiovascular health, focusing on socioeconomic position (encompassing wealth and income, education, employment/occupational status, and other factors), race and ethnicity, social support (including social networks), culture (including language), access to medical care, and residential environments. Indeed, the advantages of using a social determinants of health approach to curb the burden of CVD have the potential to be far reaching, enhancing the beneficial effects of advances in CVD related to prevention and treatment while reducing health inequities that contribute to CVD onset. Although not explicated in the position paper by Havranek et al,[8] gender and sex are critical determinants of cardiovascular health. In the 2011 summary by Mosca et al of the sex/gender differences in CVD prevention in the Unites States, the authors show the ways in which trajectories and outcomes of disease differ by sex.[9] Since 1984, there has been a greater absolute number of CVD deaths for women, but a greater number of men who live with and die of CHD. Improved awareness of CVD in women because of public health campaigns may have contributed to the reported increase in CVD deaths in women[9] by minimizing conventional detection and reporting bias. However, there are other contributing factors. For example, the sex-specific differential CHD and CVD mortality rates appear to be a reflection of population demographics in the United States (eg, women's longer life expectancy). Yet there are specific age groups for which the mortality attributable to CHD is increasing. Perhaps most striking is the rise in CHD mortality rates for women age 35 to 44 years: an annual increase of 1.3% between 1997 and 2002.[9] A recent analysis of World Health Organization mortality data also revealed stronger age-specific reductions in CHD in men than in women at the global level.[10]

Because etiologic models of cardiovascular medicine have been based on scientific research using male-dominated samples, we are only beginning to understand why sex-specific physiology might lead to differential CHD development, onset, symptom course, and outcomes, and importantly how we can ameliorate such risk. The seminal INTERHEART study (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries) provided an indication of a differential risk factor burden between men and women for incident myocardial infarction (MI) at the population level. With the use of case-control data from 52 countries, the population-attributable risk for MI owing to the modifiable risk factors of smoking, alcohol use, high-risk diet, and physical inactivity, was significantly higher among women than men (74.3; 95% confidence interval [CI], 67.9–80.7 versus 67.3; 95% CI, 63.9–70.8). Significant differences in the population-attributable risk because of psychosocial factors were also observed (25.7; 95% CI, 18.4–33.1 versus 21.7; 95% CI, 17–26.4).[11]

To date, the influence of gender on these risk factors and thus the onset and progression of CVD have seldom been considered, much less the notion that gender is a potentially modifiable target for CVD prevention. This may be because of the tendency for sex and gender to be used interchangeably, contributing to putative thinking that both are constant or fixed.[12] The relational theory posits that gender is a performative and dynamic process that is shaped by the social context in which one is embedded. The ways in which gender is expressed differ across domains (eg, domestic, economic, political) at the individual level, and are embedded in the structures and practices of society.[13] Gen-

der can interact with other social determinants, such as ethnicity and socioeconomic position, to shape cardiovascular health from conception, through early life when health behaviors and risk factors are shaped, into adolescence and adulthood. In 1997, Elizabeth Barrett-Connor wrote a seminal piece published in *Circulation* that demonstrated the importance of evaluating both gender and sex differences in relation to CVD risk.[14] Our article builds on the multidisciplinary evidence presented by Barrett-Connor from 2 decades ago by discussing gender as a modifiable determinant of cardiovascular health using key risk factors identified in the seminal INTERHEART study.[11]

Given the cumulative burden of these risk factors to the overall population, the gender-specific differential in population-attributable risk, and their potential to be modified, this article will illustrate how gender shapes the early adoption of health behaviors in childhood, adolescence, and young adulthood focusing on physical activity, drinking, and smoking behaviors (including the influence of role modeling). We also discuss the role of gender in psychosocial stress with a focus on trauma from life events (childhood assault and intimate partner violence), and work, home, and financial stresses. We conclude by exploring potential biological pathways that may underpin sex and gender as determinants of cardiovascular health, with a focus on autonomic functioning; discuss implications for cardiovascular treatment and awareness campaigns; and consider whether gender equality strategies could reduce the burden of CVD for men and women at the population level.

EARLY ADOPTION OF HEALTH BEHAVIORS

In comparison with men, the clinical onset of heart attack is delayed 9 years in women.[15] Although women's estrogen and therefore high-density lipoprotein production was considered to be largely cardioprotective (at least up until menopause), population data show that this delay in disease manifestation is narrowing, possibly because of the changes in Western lifestyles of younger women.[16] Identifying the role of gender in the early adoption of health behaviors could be pivotal for reversing this trend.

Socialization of Boys From Infancy Encourages Greater Pursuit of Physical Activity

Physical inactivity and sedentary activity are both risk factors for CVD across the lifespan. From birth, boys are encouraged to be more physical than girls, reflective of underlying assumptions regarding inherent sex-based physical characteristics and aptitude. The early socialization process places emphasis on boys developing physical strength and girls developing emotional and verbal skills.[17] This may be emblematic of differences in parenting style. Indeed, parenting style has been shown to be associated with children's' attraction to physical activity, in particular, in those who are overweight.[18] This socialization begins in the early years and continues throughout later childhood and adolescence. As early as 6 to 8 years of age, girls are more sedentary than their male counterparts.[19] Data from 2002 suggest that, as they transitioned into adolescence, girls' activity levels reduced by up to 83%,[20] with the majority of girls partaking in almost no physical activity, with the exception of school gym classes. As women age, this differential persists. A more recent 2017 analysis of various sources of US government data demonstrates that in children, as well as adults age >18, girls and women are less likely to meet 2008 federal physical activity guidelines (aerobic and muscle-strengthening activities) across every age group (high school students, 18–24, 25–64, 65–74, 75+ years)[21] in comparison with men of the same age groups. As women progress through age categories, a progressive decline in adherence to physical activity guidelines (aerobic through leisure-time activity and muscle-strengthening activities) was also observed.

Reasons for this gradual and persistent decline in activity in women are complex. Adolescence is the period where young girls and women become aware of, and alerted to, physical and sexual threats to their safety. A critical implication of this is that women are less physically mobile—that is, less likely than men to exercise in public spaces at night[22] or ride a bike through cities.[23] Women are also more likely to be harassed or abused while in public,[24] thereby limiting their ability to remain as freely physically active as men. For example, a survey of women in Seattle, where, in 2012, 28% of bike commuters were women, revealed that safety issues were the biggest barrier to them cycling.[25] Fostering girls' ability to become and remain active from birth to adolescence is critical in the context of life-course CVD prevention in view of evidence that inactivity in adolescence predicts inactivity in adulthood.[26] This accumulation of risk may subsequently elevate girls' and women's cardiovascular risk markers like cholesterol and blood pressure levels, and incident CHD, stroke, high blood pressure, and type 2 diabetes mellitus, as well. Indeed, the lifetime cardiovascular and other health-related benefits of targeting the physical activity levels of girls during schooling years has been demonstrated historically. For example, a 2010 analysis of a seminal school-based intervention designed to increase physical activity (Title IX of the Education Amendments of 1972) resulted in (1) a 600% increase in girls' sports participation (between 1972 and 1978) and, (2) in comparison with those who did not participate, a lower body mass

index and obesity rates 20 to 25 years later.[27] However, issues remain with measuring physical activity across the life course, in particular, in older women. Conventional measures of activity are often flawed with an inability to discriminate between incidental and purposive exercise. New approaches (eg, digital devices, exhaled breath condensate) are being investigated for this population to more accurately capture physical activity in populations such as older women.

Socialization of Boys in Teenage Years Encourages Development of Social Support Networks and Promotes Antisocial Behaviors Like Drinking

Social isolation is a potent risk factor for CVD across the life course, whereas social support is a well-established protective factor.[28,29] From the time boys are newborns, caregivers spend less time verbally interacting with them, which can predict social-behavioral deficits in a range of interpersonal contexts (with peers, romantic partners, family).[30] Evidence from the field of social psychology suggests that boys maintain good friendships throughout childhood, yet despite a continuing, strong desire to maintain close friendships, many change or disappear in mid- to late adolescence.[31] Adolescent boys perceive their male peer group culture and their socialization toward dominant masculine norms to compromise the development and maintenance of close male friendships.[32] However, boys who develop and maintain close male friendships can feel more capable of resisting the social pressures of their peer group.[32] Comradery that comes from close male friendships and the confidence to reject peer pressure are critical in the formation of health and other risk-taking behaviors. Conventionally, boys have been considered predisposed or biologically determined to partake in risk-taking behaviors, whereas girls are predisposed to be risk-averse. Yet according to some,[33] there is very little evidence to support this proposition; the socialization process including caretakers' responses to gendered norms increases the likelihood of boys exhibiting delinquent and antisocial behavior in adolescence.[34] Evidence from the field of criminology indicates that antisocial behaviors may induce cardiovascular risk factors in boys with personality disorders.[35] In comparison with healthy controls, offenders with antisocial personality disorders have markedly lower glucagon and nonoxidative glucose metabolism.[35]

More generally, the socialization of boys to display stoicism and reject strong and intimate friendships can lead to emotional dysregulation that compromises one's stress response. It is interesting to note that gender roles and traits (masculinity in particular) have been found to explain part of the gender differences in stress and coping, social constructions of gender that specifically influence the risk of CVD. One study found that men who scored higher on conventional femininity attributes had a lower risk of CHD death (hazard ratio [HR] per unit increase in femininity score, 0.65; 95% CI, 0.48–0.87; P=0.004) after adjustments for smoking, binge drinking, body mass index, systolic blood pressure, household income, and psychological well-being.[36] From a biobehavioral perspective, poor coping skills or maladaptive stress responses can manifest in anger and hostility, both risk factors for incident CVD. Indeed, data from the Framingham Offspring Study show that measures of anger and hostility predict the development of atrial fibrillation in men.[37] Although social support is a strong protective factor against incident and recurrent CVD, loneliness is associated with lifetime illicit drug use (with the exception of marijuana) among boys (odds ratio [OR], 3.09; CI, 1.41–6.77). For girls, loneliness has been associated with past 30-day alcohol consumption (OR, 1.80; CI, 1.18–2.75), lifetime marijuana use (OR, 1.79; CI, 1.26–2.55), and past 30-day binge drinking (OR, 2.40; CI, 1.56–3.70).[38] Often used as self-medication or coping mechanisms, all are lifestyle-related risk factors for CVD. In addition, excessive use of drugs can induce or elevate the risk for serious mental disorders, to which men are more susceptible, like schizophrenia, schizo-affective disorders, substance abuse, or antisocial disorders.[39] These are associated with both CVD and very short life expectancy.

Adolescents, Particularly Girls, Use Smoking as a Weight Loss or Maintenance Tool

Cigarette smoking is one of the most potent risk factors for CVD onset. Most commonly initiated in adolescence, smoking during this critical period of development is a strong predictor of continuation during adulthood.[40] Traditionally, boys were significantly more likely to smoke cigarettes than girls; however; in more recent times, this gap has narrowed. Indeed, in high-income countries, like the United States, women now smoke at rates comparable to men.[41] Previous studies show the most common reasons for adolescents smoking is stress reduction and relaxation.[42] The most influential role model for initiation in girls is an immediate family member, particularly of the same sex, whereas boys were most influenced to smoke by peers in the school setting.[42] It has been argued that such findings may reflect the influence of dominant gendered norms; prior research suggests girls are more strongly influenced by the domestic sphere, whereas boys' influences are derived from environments outside the home.[43] Analysis of NESARC data (National Epidemiologic Survey on Alcohol and Related Conditions)[44] shows no

gender differences in CHD onset for children with an age of smoking initiation <16, but for those age 16+, females were more likely to develop hypertension (OR, 1.24; CI, 1.09–1.41) and heart disease (OR, 1.20; CI, 1.00–1.45). During adulthood, role modeling had an impact on smoking cessation for women. In their analysis of the Original Cohort and the Offspring Cohort of the Framingham Heart Study, Darden (2010) modeled 30-year smoking behaviors of adult offspring alongside parental behaviors and outcomes.[45] Despite limited evidence that offspring smoking behaviors were not sensitive to parent health during adulthood, women significantly reduce their smoking intensity following a smoking-related cardiovascular event of a parent. This suggests that the influence of role modeling on smoking behaviors of girls and women may be more pronounced than in boys and men, in particular as they relate to the risk of CVD.

Body image pressure is also likely to play a role in the uptake of smoking in adolescence. Although body dissatisfaction is prevalent in both boys and girls, the socialization process prioritizes the esthetic value of girls and women from a very young age. Indeed, an Australian study of 600 girls age 15 to 19 found that they feel that they are seldom or never valued for their brains over their looks.[46] This perception subsequently shapes girls' health behaviors at vulnerable periods of both emotional and physical development such as adolescence, a period of development that can coincide with rapid weight gain for some girls (particularly those from low socioeconomic backgrounds and those exposed to environmental chemicals during childhood[47]). To counter this, smoking initiation and other weight loss and control tactics, as well, such as disordered eating[48] or overexercising, are common in adolescent girls. Age of onset for anorexia nervosa is 10 to 14 years, and the age of onset for bulimia nervosa is 15 to 19 years.[48] Stice and Shaw[49] found that body dissatisfaction and eating disturbances markedly increase a girl's risk for smoking initiation. A behavioral economic approach has recently been applied to quantify the extent to which smoking behaviors are related to weight control. Using nationally representative data in which adolescents were directly asked whether they smoke to control their weight, Cawley et al[50] found that, of those who frequently smoked, almost half (46%) of girls and 30% of boys smoked in part to control their weight. This was particularly true for those who described themselves as too fat. The authors concluded that the demand for cigarettes is less price-elastic among those who smoke for weight loss, all else being equal. It is interesting to note that the World Health Organization found that, in countries where women have higher empowerment, women's smoking rates are higher than men's, independent of the level of economic development and of the level of income inequality. In fact, the gender empowerment measure was by far the strongest predictor of the gender smoking ratio, even after including the other 2 competing predictors in the model. That is, women's empowerment as measured by economic participation and decision making, political participation and decision making, and power over economic resources, was found to be associated with the ratio of female-to-male cigarette smoking prevalence.[51]

PSYCHOSOCIAL STRESS

Life Events: Traumatic Events Predict CHD mortality, With Young Girls and Women Most Commonly Victimized

Adverse childhood events are robust predictors of cardiovascular problems in later life, including onset[52] and recurrent CVD.[53] Although ≈50% to 80% of this relationship is mediated by traditional cardiovascular risk factors, psychological factors[54] and neighborhood affluence,[55] chronic and maladaptive stress responses as a result of adverse childhood events also elicit a cascade of stress-induced alterations in immunoinflammatory, autonomic, and endocrine responses that elevate cardiovascular later-life risk. One of the most severe forms of adverse childhood events is physical, sexual, and emotional abuse. National data show that 1 in 5 girls are victims of sexual abuse, in comparison with 1 in 20 boys.[56] In 2011, a national survey of high school students demonstrated that 11.8% of grade 9 to 12 girls and 4.5% of boys reported they had been forced to have sexual intercourse at some time in their lives.[57] Almost half (42.2%) of female victims were first raped before age 18, 1 in 3 (29.9%) between 11 and 17 years of age.[57] Developmentally, trauma that occurs in early life—particularly during critical growth periods before the age of 16 years—is a potent predictor of later life cardiovascular health. A meta-analysis of 24 studies found a large effect size (Cohen d=0.66) for adult CVD attributable to physical and sexual abuse that occurred in childhood.[58] Similarly, intimate partner violence (IPV) victimization in adulthood has been associated with deleterious cardiovascular risk behaviors and outcomes.[59] Young women age <25 years are most vulnerable to IPV victimization.[57] This subgroup of women is most likely to be victimized for a number of reasons. One is that young people are beginning to negotiate their intimate relationships, influenced by longstanding gender roles that see the sexualization of girls from a very early age and the socialization of boys to include dominant, heteronormative masculinity. The cardiovascular effects of IPV victimization have been extensively researched and include higher rates of carotid atherosclerosis, Takotsubo cardiomyopathy (broken heart syndrome), obesity, high triglycerides, and low high-density lipoprotein cholesterol, cigarette, drug, and alcohol

consumption in comparison with women who are not exposed.[59] IPV can have cardiovascular consequences for perpetrators[60] in addition to victims.[61] Forms of IPV including coercive control can have adverse cardiovascular outcomes for perpetrators by way of health behaviors and psychological and physiological factors. Baron et al[62] found that behaviors characterized by higher trait control (ie, dominance) predicted higher systolic and diastolic blood pressure in men. Interestingly, evidence from laboratory studies illustrates the immediate effects of IPV perpetration on aspects of the cardiovascular system during buildup, enactment, and aftermath of a violent incident such as pulse rate, heart rate, and arousal levels.[63] Surprisingly, these relationships were not always linear. Approximately 80% of IPV perpetrators experienced hyperarousal characterized by elevated cardiovascular markers during buildup and enactment before returning to baseline levels. In contrast, the remaining 20% exhibit hypoarousal, reflected via a dramatic drop in heart rate during the buildup and execution phases of violence before elevating to baseline levels in the aftermath. This suggests that emotional dysregulation is not shared by all IPV perpetrators, and the use of IPV may be driven by other factors. This is important considering how persistent IPV may impact the cardiovascular system in the long term. Although there is limited research on the long-term impact of gendered violence perpetration on incident CVD, preliminary data suggest that IPV perpetration that occurs in late adolescence and young adulthood increases the risk of CVD in the ensuing 7 to 14 years.[60] Although the mechanisms underpinning this relationship are unclear, it is plausible that persistent behavioral patterns associated with IPV perpetration, victimization, or both triggers a cascade of stress-induced alterations in immunoinflammatory, autonomic, and endocrine responses that elevates cardiovascular later-life risk.

Work, Home, and Financial Stress: Traditional Gender Roles Within and Across the Domestic and Workplace Settings Can be Cardiotoxic, Particularly for Women

Everyday harassment and discrimination can be considered a chronic stressor that erodes cardiovascular health. In their scientific statement, Havranek et al[8] detail the multiplicative effects of marginalization attributable to ethnicity on CVD risk. Indeed, the adverse physiological responses to perceived racism are well documented, via its effects on nocturnal blood pressure recovery[64] and higher daytime systolic and diastolic blood pressure.[65] Compelling statistics show that 33% of women and 9% of men report sexual harassment over the lifetime, with 4 of 5 of perpetrators being male.[66] Gendered violence, discrimination, and harassment can be a chronic and persistent stressor that compromises cardiovascular health in the same manner as other forms of subjugation, with intersectional effects for women of color, minority religions, or nonheterosexual orientation. Longitudinal data reveal that exposure to workplace sexual harassment more than doubles the likelihood of psychological distress after 2 years for women (OR, 2.03; 95% CI, 1.2–3.39) but not men (OR, 1.32; 95% CI, 0.72–2.43).[67] Possible pathophysiologic mechanisms linking gendered violence at work and CVD include pronounced daytime systolic blood pressure,[68] a mediator of various forms of CVD and cardiovascular risk factors, including cortisol secretions, pulse rate, and changes in heart rate variability. For men, poor workplace conditions that affect cardiovascular health are more likely to be characterized by low job control and high demand, a combination known to have cardiotoxic effects. The Whitehall II study found that low decision latitude predicted incident CHD (1.55; 95% CI, 1.26–1.90) and heightened risk of fatal CHD/nonfatal MI for men less so than women.[69] Despite being much less researched, gender role expectations in the domestic sphere are also of relevance to cardiovascular health. In Western culture, boys are often socialized from a young age to believe they are financially responsible for a family, whereas girls are more likely to be socialized to be emotionally responsible. Despite this, a recent study conducted with 3000 married couples over 15 years[70] revealed that acting as a sole breadwinner can be detrimental to a man's health and well-being. When women took more financial responsibility, the impact on both their husband's and their own health and well-being increased by up to 5% for couples with less rigid gender role expectations. Related to gender role expectations, the effects of marital tension seem to be particularly pronounced for women. Women with poor-quality marriages have higher rates of several markers for CVD,[71] including low high-density lipoprotein cholesterol, high triglycerides, and higher body mass index, blood pressure, depression, and anger. In a study following 292 women for 5 years after an MI, women reporting high levels of marital conflict were nearly 3 times more likely to have a recurrent event.[72] Another 13-year longitudinal study of married women found that unsatisfying marriages increased cardiovascular risk over the study period.[73] Expectations around women as caregivers can also have deleterious health consequences. Almost two-thirds of caregivers of parents and children in the United States are women, with the average caregiver a 49-year-old married woman caring for her mother.[74] High-intensity caregiving has been associated with the highest levels of self-reported stress in comparison with low or no caregiving responsibilities.[75] Moreover, there is some evidence that long hours of caregiving could be an independent risk factor

for incident nonfatal CHD for middle-aged women (HR, 1.98; 95% CI, 1.27–3.08), but not men (HR, 1.35; 95% CI, 0.67–2.71). Poor mental health more generally is a risk factor for incident CVD, particularly in women,[76] because the prevalence of common mental disorders (depression, anxiety) is higher in women. Since 1997, there has been an increase in cardiac-related mortality for young and middle-aged women 35 to 54 years,[77] the age group in which the strongest association of depression and CHD has been observed. There is, however, a dearth of intervention research regarding how best to reduce or prevent the associated unnecessary burden associated with CHD in these women.

DISCUSSION

The American Heart Association has published 3 sex-specific, evidence-based guidelines for the prevention of CVD.[9,78,79] Their impact on physician behavior or sex-specific patient outcomes is not yet clear.[9] Arguably, progress in this area of cardiology has been slow because of the prioritization of the reproductive system in women's health (sometimes referred to as bikini medicine). Evidence from the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction [AMI] Patients) indicates that both health practitioners and women themselves continue to neglect or remain uneducated about women's CHD risk factors and CHD development.[80] It appears likely that these guidelines will have a suboptimal impact on the absence of a broader approach to CVD prevention that considers gender as a social determinant of cardiovascular health across the lifespan. This article provides examples of the ways in which gender, a social construct, can directly and indirectly influence individuals' cardiovascular risk, as outlined in the Figure. The directions of these relationships are complex and likely differ, depending on the extent to which they interact with other domains and demographic factors. To date, it is unclear whether reducing gender inequities at the broader societal level (ie, upstream) or lessening strict gendered roles that shape cardiovascular-related behaviors at the individual level (ie, downstream) would improve the cardiovascular risk of populations.

Indeed, it is plausible that challenging the ways in which boys and girls are socialized could have a cascade of beneficial health effects over the life course at the individual level. The key risk factors discussed in this article that link gender to CVD risk and onset share common biological, stress-related pathways. Physical inactivity, excessive drinking, smoking behaviors, and psychosocial stress are all known to promote immunoinflammation,[81] oxidative stress, cell ageing, neuroendocrine hormones, and possibly poor gut health, which may contribute to intermedial thickening, atherosclerotic disease, diabetes mellitus, and hypertension. In recent years, the role of the autonomic nervous system specifically has garnered attention as a key indicator of optimal health. The autonomic nervous system is pivotal for regulating how one responds to stressors and the body's ability to induce homeostasis. Comprising sympathetic activity (the flight or fight response) and parasympathetic activity (vagal activity that stimulates responses that occur at rest), cardiac sympathovagal balance is a marker of good cardiovascular health. It is commonly measured by heart rate variability (HRV) and is a known prognostic indicator, particularly for women,[82] following MI.[83] In early life, impairments in HRV can be influenced by genetics, childhood illness, and preterm birth.[84] However, there is emerging evidence that HRV changes because of lifestyle factors in a manner that may precipitate or mirror cardiovascular pathology. A review article by Valentini and Parati[85] identified physical activity, smoking, alcohol, and psychosocial stress as key determinants of HRV and therefore neural cardiovascular modulation. Indeed, sex-specific differences in both heart rate and HRV have been consistently observed in (premenopausal) women who have a higher resting heart rate and lower HRV than men.[86] Although Valentini and Parati argue that sex is a nonmodifiable determinant of HRV, we have demonstrated here the ways in which gender, overlying sex, shapes key stress and lifestyle behaviors that may induce or protect against CVD via autonomic nervous system pathways. Targeting gender as a means of modifying biobehavioral aspects of CVD may be an avenue worthy of further investigation.

Upstream determinants of health such as employment, domestic, and political contexts that promote gender equality could theoretically benefit cardiovascular health.[87] According to the United Nations, an indication of a nation's level of gender equality specifically includes (1) attainment of higher education, (2) labor force participation, (3) maternal mortality rate, (4) adolescent fertility rate, and (5) parliamentary representation. It is important to note that countries with the highest levels of gender equality have reported some of the greatest reductions in 40-year CHD mortality rates in Western countries. For example, between 1981 and 2006, these rates dropped by 80% in Iceland in both men and women age 25 to 74 years.[88] This average of 3.2% per year is one of the largest reductions recorded in Western populations, comparable to Finland (4.2% per annum) and Sweden (3.3%);[88] both countries also rank in the top 10 for gender equality, whereas the United States recorded a decline of 2.5%.[88] This decline in Iceland was largely because of secular reductions in cholesterol (32%; predominantly from dietary intake, not lipid-lowering drugs), systolic blood pressure (22%), and smoking (22%), and a further 5% came from increases in physical activity. All of these, as demonstrated in this article, can be heavily shaped by gender.

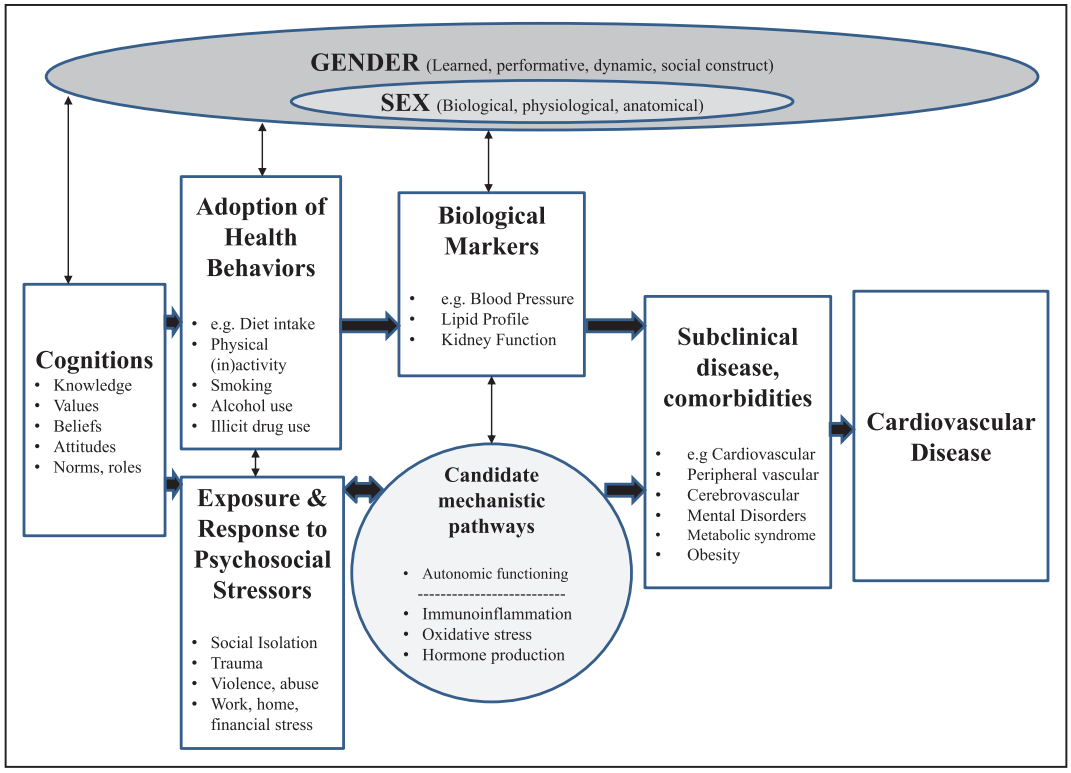

Figure. Gender and sex as determinants of cardiovascular health.

Indeed, economic development is inextricably linked to gender equality, thereby making these concepts difficult to disentangle. Common features of countries with higher gender equality (such as the Nordic countries) are policies that promote gender equality, focusing on financial independence in both domestic and work settings. For decades, these countries have had a history of implementing key policies around paid maternity leave,[89] extensive day care services, and a parental leave scheme that provides quotas for couples to negotiate their own combination of absence from their employment.[90] First introduced in Sweden, Iceland, and subsequently Finland in 1974, 1981, and 1985, respectively, this dual earner/dual care model has supported equal labor force and domestic participation for both women and men[91] and is now socially and politically institutionalized because of the widespread acknowledgment of its importance.[90] Ultimately, this model has been successful in its attempt to remove key structural barriers that otherwise preclude the freedom of choice around domestic and labor participation, thereby perpetuating gender inequalities that are deleterious to cardiovascular health. It is indeed plausible that equality-based initiatives that focus on gender would have other positive effects on the cardiovascular health of both genders and further generations. For example, encouraging and teaching men to participate in an egalitarian manner in the domestic sphere could foster the emotional intelligence and well-being of both fathers and boys, thereby reducing the risk of delinquency or social isolation, both CVD risk factors.

Yet evidence that gender equality is beneficial to the health of men and women is far from unequivocal. Although women's financial independence is greatest in countries with the highest gender equality, we have highlighted how gender empowerment has been associated with an increase in some cardiovascular risk behaviors for women, such as smoking. Another unexpected consequence of gender equality is referred to as the Nordic paradox,[92] the disproportionally high prevalence rates of IPV against women occurring in Nordic countries. IPV victimization rates in the European Union average 22%, while they range from 28%, 30% and 32% in Sweden, Finland, and Denmark, respectively. Gracia and Merlo[92] postulate reasons for this unanticipated trend, which should be taken into consideration in the context of social determinants of CVD. Evidence from other high-income countries suggests that women with higher economic status (relative to their partners) are at greater risk of IPV victimization, particularly if their partner holds traditional gender beliefs and expectations. Negative perceptions and responses to gender equality may also incite a backlash effect against women in powerful positions.[93] Also plausible is men's sense of resistance or resentment toward gender-based social progress that manifests in the form of IPV in the privacy of the domestic sphere. Of course, an alternative explanation for this trend may be higher reporting

of IPV. Progressive cultural expectations and standards encourage, or may at least alleviate, the stigma associated with IPV reporting, meaning that the adverse consequences of reporting are fewer. As generations become more accustomed to the expansion of egalitarianism and fluidity of gendered roles, we might expect rates of IPV to decline.

It should be noted that, although cardiovascular risk as it specifically relates to lesbian, gay, bisexual, transgender, queer, questioning, and intersex populations was beyond the scope of this article, it is indeed important when considering gender and sex as a social determinant of CVD and an area that warrants greater attention in both a research and a public health sense. An intersectional, gendered approach to CVD prevention that considers lesbian, gay, bisexual, transgender, queer, questioning, and intersex populations is therefore required.

In conclusion, gender (as it overlies biological sex) should be considered a social determinant of CVD that is modifiable through efforts to improve gender equality. This approach warrants the attention of government and health professionals. Indeed, the most recent social determinants of CVD risk and outcomes position paper should be updated to reflect this and the contexts in which CVD develops for women and men. Research is required to determine whether gender equality policies at the national level, such as those introduced in countries that have also experienced major reductions in CVD mortality, would impact the cardiovascular health of the US population.

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REFERENCES

1. Wilkinson RG, Marmot M. *Social Determinants of Health: the Solid Facts*. 2nd ed. Copenhagen, Denmark: World Health Organization; 2003.
2. Marmot M. Social determinants of health inequalities. *Lancet*. 2005;365:1099–1104. doi: 10.1016/S0140-6736(05)71146-6.
3. Murray CJ, Michaud C, McKenna M, Marks J. US patterns of mortality by county and race: 1965–1994. *US Burden and Injury Monograph Series*. Cambridge, MA: Harvard Center for Population and Development Studies; 1998.
4. Institute of Medicine and National Research Council. *U.S. Health in International Perspective: Shorter Lives, Poorer Health*. Washington, DC: The National Academies Press; 2013.
5. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci USA*. 2015;112:15078–15083. doi: 10.1073/pnas.1518393112.
6. Marmot MG, Smith GD, Stansfeld S, Patel C, North F, Head J, White I, Brunner E, Feeney A. Health inequalities among British civil servants: the Whitehall II study. *Lancet*. 1991;337:1387–1393.
7. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. doi: 10.1161/CIR.0000000000000485.
8. Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, Davey-Smith G, Dennison-Himmelfarb CR, Lauer MS, Lockwood DW, Rosal M, Yancy CW; American Heart Association Council on Quality of Care and Outcomes Research, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, Council on Lifestyle and Cardiometabolic Health, and Stroke Council. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132:873–898. doi: 10.1161/CIR.0000000000000228.
9. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. 2011;124:2145–2154. doi: 10.1161/CIRCULATIONAHA.110.968792.
10. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health*. 2017;2:e000298. doi: 10.1136/bmjgh-2017-000298.
11. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S; INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:953–962. doi: 10.1016/S0140-6736(04)17019-0.
12. Krieger N. Genders, sexes, and health: what are the connections—and why does it matter? *Int J Epidemiol*. 2003;32:652–657.
13. Hammarström A, Johansson K, Annandale E, Ahlgren C, Aléx L, Christianson M, Elwér S, Eriksson C, Fjellman-Wiklund A, Gilenstam K, Gustafsson PE, Harryson L, Lehti A, Stenberg G, Verdonk P. Central gender theoretical concepts in health research: the state of the art. *J Epidemiol Community Health*. 2014;68:185–190. doi: 10.1136/jech-2013-202572.
14. Barrett-Connor E. Sex differences in coronary heart disease. *Circulation*. 1997;95:252–264.
15. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008;29:932–940. doi: 10.1093/eurheartj/ehn018.
16. Vogel B, Farhan S, Hahne S, Kozanli I, Kalla K, Freynhofer MK, Jarai R, Kautzky-Willer A, Huber K. Sex-related differences in baseline characteristics, management and outcome in patients with acute coronary syndrome without ST-segment elevation. *Eur Heart J Acute Cardiovasc Care*. 2016;5:347–353. doi: 10.1177/2048872615585514.
17. McLean CP, Anderson ER. Brave men and timid women? A review of the gender differences in fear and anxiety. *Clin Psychol Rev*. 2009;29:496–505. doi: 10.1016/j.cpr.2009.05.003.
18. Lau PWC, Lee A, Ransdell L. Parenting style and cultural influences on overweight children's attraction to physical activity. *Obesity*. 2007;15:2293–2302.
19. Lampinen EK, Eloranta AM, Haapala EA, Lindi V, Väistö J, Lintu N, Karjalainen P, Kukkonen-Harjula K, Laaksonen D, Lakka TA. Physical activity, sedentary behaviour, and socioeconomic status among Finnish

girls and boys aged 6-8 years. *Eur J Sport Sci*. 2017;17:462–472. doi: 10.1080/17461391.2017.1294619.
20. Kimm SY, Glynn NW, Kriska AM, Barton BA, Kronsberg SS, Daniels SR, Crawford PB, Sabry ZI, Liu K. Decline in physical activity in black girls and white girls during adolescence. *N Engl J Med*. 2002;347:709–715. doi: 10.1056/NEJMoa003277.
21. Katzmarzyk PT, Lee IM, Martin CK, Blair SN. Epidemiology of physical activity and exercise training in the United States. *Prog Cardiovasc Dis*. 2017;60:3–10. doi: 10.1016/j.pcad.2017.01.004.
22. Wesely JK, Gaarder E. The gendered "nature" of the urban outdoors: women negotiating fear of violence. *Gender Soc*. 2004;18:645–663.
23. Aldred R, Dales J. Diversifying and normalising cycling in London, UK: an exploratory study on the influence of infrastructure. *J Trans Health*. 2017;4:348–362.
24. Macmillan R, Nierobisz A, Welsh S. Experiencing the streets: harassment and perceptions of safety among women. *J Res Crime Delinq*. 2000;37:306–322.
25. Haustein S, Møller M. E-bike safety: individual-level factors and incident characteristics. *J Trans Health*. 2016;3:386–394.
26. Gordon-Larsen P, Adair LS, Nelson MC, Popkin BM. Five-year obesity incidence in the transition period between adolescence and adulthood: the National Longitudinal Study of Adolescent Health. *Am J Clin Nutr*. 2004;80:569–575.
27. Kaestner R, Xin Xu. Title IX, girls' sports participation, and adult female physical activity and weight. *Eval Rev*. 2010;34:52–78. doi: 10.1177/0193841X09353539.
28. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart*. 2016;102:1009–1016. doi: 10.1136/heartjnl-2015-308790.
29. Kamarck TW, Manuck SB, Jennings JR. Social support reduces cardiovascular reactivity to psychological challenge: a laboratory model. *Psychosom Med*. 1990;52:42–58.
30. Brown BB. Adolescents' relationships with peers. *Handb Adolesc Psychol*. 2004;2:363–394.
31. Way N. Boys' friendships during adolescence: intimacy, desire, and loss. *J Res Adolesc*. 2013;23:201–213.
32. Chu JY, Porche MV, Tolman DL. The adolescent masculinity ideology in relationships scale: development and validation of a new measure for boys. *Psychol Men Masc*. 2005;8:93–115.
33. Maxfield S, Shapiro M, Gupta V, Hass S. Gender and risk: women, risk taking and risk aversion. *Gender Mgmt Int J*. 2010;25:586–604.
34. Huselid RF, Cooper ML. Gender roles as mediators of sex differences in expressions of pathology. *J Abnorm Psychol*. 1994;103:595–603.
35. Virkkunen M, Rissanen A, Naukkarinen H, Franssila-Kallunki A, Linnoila M, Tiihonen J. Energy substrate metabolism among habitually violent alcoholic offenders having antisocial personality disorder. *Psychiatry Res*. 2007;150:287–295. doi: 10.1016/j.psychres.2006.01.013.
36. Hunt K, Lewars H, Emslie C, Batty GD. Decreased risk of death from coronary heart disease amongst men with higher 'femininity' scores: a general population cohort study. *Int J Epidemiol*. 2007;36:612–620. doi: 10.1093/ije/dym022.
37. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB, Benjamin EJ. Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. *Circulation*. 2004;109:1267–1271.
38. Stickley A, Koyanagi A, Koposov R, Schwab-Stone M, Ruchkin V. Loneliness and health risk behaviours among Russian and U.S. adolescents: a cross-sectional study. *BMC Public Health*. 2014;14:366. doi: 10.1186/1471-2458-14-366.
39. McGlashan TH, Bardenstein KK. Gender differences in affective, schizoaffective, and schizophrenic disorders. *Schizophr Bull*. 1990;16:319–329.
40. Paavola M, Vartiainen E, Haukkala A. Smoking, alcohol use, and physical activity: a 13-year longitudinal study ranging from adolescence into adulthood. *J Adolesc Health*. 2004;35:238–244. doi: 10.1016/j.jadohealth.2003.12.004.
41. World Health Organization. WHO Report on the Global Tobacco Epidemic, 2008: The MPOWER package. Geneva, World Health Organization, 2008.
42. Nichter M, Nichter M, Vuckovic N, Quintero G, Ritenbaugh C. Smoking experimentation and initiation among adolescent girls: qualitative and quantitative findings. *Tob Control*. 1997;6:285–295.
43. Abbott-Chapman J, Robertson M. Home as a private space: some adolescent constructs. *J Youth Studies*. 1999;2:23–43.
44. Thompson AB, Tebes JK, McKee SA. Gender differences in age of smoking initiation and its association with health. *Addict Res Theory*. 2015;23:413–420. doi: 10.3109/16066359.2015.1022159.
45. Darden M. Smoking, expectations, and health: a dynamic stochastic model of lifetime smoking behavior. *Health Econometrics and Data Group-University of York, Working Paper*. 2010;10:28.
46. Everyday Sexism: Survey on Girls' and Young Women's View on Gender Equality in Australia. Plan International and Our Watch Survey. 2016. https://www.ourwatch.org.au/getmedia/1ee3e574-ce66-4acb-b8ef-186640c9d018/Everyday-Sexism_version_03.pdf.aspx. Accessed March 1, 2017.
47. Deierlein AL, Wolff MS, Pajak A, Pinney SM, Windham GC, Galvez MP, Rybak M, Calafat AM, Kushi LH, Biro FM, Teitelbaum SL. Phenol concentrations during childhood and subsequent measures of adiposity among young girls. *Am J Epidemiol*. 2017;186:581–592. doi: 10.1093/aje/kwx136.
48. Volpe U, Tortorella A, Manchia M, Monteleone AM, Albert U, Monteleone P. Eating disorders: what age at onset? *Psychiatry Res*. 2016;238:225–227. doi: 10.1016/j.psychres.2016.02.048.
49. Stice E, Shaw H. Prospective relations of body image, eating, and affective disturbances to smoking onset in adolescent girls: how Virginia slims. *J Consult Clin Psychol*. 2003;71:129–135.
50. Cawley J, Markowitz S, Tauras J. Obesity, cigarette prices, youth access laws and adolescent smoking initiation. *Eastern Econ J*. 2006;32:149–170.
51. Hitchman SC, Fong GT. Gender empowerment and female-to-male smoking prevalence ratios. *Bull World Health Organ*. 2011;89:195–202. doi: 10.2471/BLT.10.079905.
52. Rich-Edwards JW, Mason S, Rexrode K, Spiegelman D, Hibert E, Kawachi I, Jun HJ, Wright RJ. Physical and sexual abuse in childhood as predictors of early-onset cardiovascular events in women. *Circulation*. 2012;126:920–927. doi: 10.1161/CIRCULATIONAHA.111.076877.
53. Hendrickson CM, Neylan TC, Na B, Regan M, Zhang Q, Cohen BE. Lifetime trauma exposure and prospective cardiovascular events and all-cause mortality: findings from the Heart and Soul Study. *Psychosom Med*. 2013;75:849–855. doi: 10.1097/PSY.0b013e3182a88846.
54. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, Anda RF. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. *Circulation*. 2004;110:1761–1766. doi: 10.1161/01.CIR.0000143074.54995.7F.
55. Slopen N, Non A, Williams DR, Roberts AL, Albert MA. Childhood adversity, adult neighborhood context, and cumulative biological risk for chronic diseases in adulthood. *Psychosom Med*. 2014;76:481–489. doi: 10.1097/PSY.0000000000000081.
56. U.S. Department of Health and Human Services, Administration for Children and Families. Children's Bureau. Child maltreatment 2015. http://www.acf.hhs.gov/programs/cb/research-data-technology/statistics-research/child-maltreatment. Accessed March 2, 2017.
57. Black MC, Basile KC, Breiding MJ, Smith SG, Walters ML, Merrick MT, Chen J,Stevens MR. The National Intimate Partner and Sexual Violence Survey (NISVS): 2010 Summary Report. Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; 2011.
58. Wegman HL, Stetler C. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. *Psychosom Med*. 2009;71:805–812. doi: 10.1097/PSY.0b013e3181bb2b46.
59. Stene LE, Jacobsen GW, Dyb G, Tverdal A, Schei B. Intimate partner violence and cardiovascular risk in women: a population-based cohort study. *J Womens Health (Larchmt)*. 2013;22:250–258. doi: 10.1089/jwh.2012.3920.
60. Clark CJ, Alonso A, Everson-Rose SA, Spencer RA, Brady SS, Resnick MD, Borowsky IW, Connett JE, Krueger RF, Nguyen-Feng VN, Feng SL, Suglia SF. Intimate partner violence in late adolescence and young adulthood and subsequent cardiovascular risk in adulthood. *Prev Med*. 2016;87:132–137. doi: 10.1016/j.ypmed.2016.02.031.
61. Suglia SF, Sapra KJ, Koenen KC. Violence and cardiovascular health: a systematic review. *Am J Prev Med*. 2015;48:205–212. doi: 10.1016/j.amepre.2014.09.013.
62. Baron CE, Smith TW, Uchino BN, Baucom BR, Birmingham WC. Getting along and getting ahead: Affiliation and dominance predict ambulatory blood pressure. *Health Psychol*. 2016;35:253–261. doi: 10.1037/hea0000290.
63. Jacobson NS, Gottman JM. *When Men Batter Women: New Insights Into Ending Abusive Relationships*. New York, NY: Simon and Schuster; 1998.

64. Brondolo E, Libby DJ, Denton EG, Thompson S, Beatty DL, Schwartz J, Sweeney M, Tobin JN, Cassells A, Pickering TG, Gerin W. Racism and ambulatory blood pressure in a community sample. *Psychosom Med*. 2008;70:49–56. doi: 10.1097/PSY.0b013e31815ff3bd.
65. Steffen PR, McNeilly M, Anderson N, Sherwood A. Effects of perceived racism and anger inhibition on ambulatory blood pressure in African Americans. *Psychosom Med*. 2003;65:746–750.
66. Australian Human Rights Commission. Working Without Fear: Results of the National Sexual Harassment Survey 2012. https://www.humanrights.gov.au/sites/default/files/content/sexualharassment/survey/SHSR_2012%20Web%20Version%20Final.pdf. ISBN 978-1-921449-37-6. Accessed March 2, 2017.
67. Nielsen MB, Einarsen S. Prospective relationships between workplace sexual harassment and psychological distress. *Occup Med (Lond)*. 2012;62:226–228. doi: 10.1093/occmed/kqs010.
68. Smart Richman L, Pek J, Pascoe E, Bauer DJ. The effects of perceived discrimination on ambulatory blood pressure and affective responses to interpersonal stress modeled over 24 hours. *Health Psychol*. 2010;29:403–411. doi: 10.1037/a0019045.
69. Kuper H, Marmot M. Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. *J Epidemiol Community Health*. 2003;57:147–153.
70. Munsch CL. Her support, his support: money, masculinity, and marital infidelity. *Am Sociol Rev*. 2015;80:469–495.
71. Liu H, Waite L. Bad marriage, broken heart? Age and gender differences in the link between marital quality and cardiovascular risks among older adults. *J Health Soc Behav*. 2014;55:403–423. doi: 10.1177/0022146514556893.
72. Orth-Gomér K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study. *JAMA*. 2000;284:3008–3014.
73. Gallo LC, Troxel WM, Matthews KA, Kuller LH. Marital status and quality in middle-aged women: associations with levels and trajectories of cardiovascular risk factors. *Health Psychol*. 2003;22:453–463. doi: 10.1037/0278-6133.22.5.453.
74. Revenson TA, Griva K, Luszczynska A, Morrison V, Panagopoulou E, Vilchinsky N, Hagedoorn M. Gender and caregiving: the costs of caregiving for women. In: *Caregiving in the Illness Context*. London, United Kingdom:Springer; 2016:48–63.
75. Lyons JG, Cauley JA, Fredman L. The effect of transitions in caregiving status and intensity on perceived stress among 992 female caregivers and noncaregivers. *J Gerontol A Biol Sci Med Sci*. 2015;70:1018–1023. doi: 10.1093/gerona/glv001.
76. O'Neil A, Fisher AJ, Kibbey KJ, Jacka FN, Kotowicz MA, Williams LJ, Stuart AL, Berk M, Lewandowski PA, Taylor CB, Pasco JA. Depression is a risk factor for incident coronary heart disease in women: an 18-year longitudinal study. *J Affect Disord*. 2016;196:117–124. doi: 10.1016/j.jad.2016.02.029.
77. Australian Institute of Health and Welfare 2010. Cardiovascular disease mortality: trends at different ages. Cardiovascular series no. 31. Cat. no.47. Canberra: AIHW.
78. Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, Ganiats TG, Gomes AS, Gornik HL, Gracia C, Gulati M, Haan CK, Judelson DR, Keenan N, Kelepouris E, Michos ED, Newby LK, Oparil S, Ouyang P, Oz MC, Petitti D, Pinn VW, Redberg RF, Scott R, Sherif K, Smith SC Jr, Sopko G, Steinhorn RH, Stone NJ, Taubert KA, Todd BA, Urbina E, Wenger NK; Expert Panel/Writing Group; American Heart Association; American Academy of Family Physicians; American College of Obstetricians and Gynecologists; American College of Cardiology Foundation; Society of Thoracic Surgeons; American Medical Women's Association; Centers for Disease Control and Prevention; Office of Research on Women's Health; Association of Black Cardiologists; American College of Physicians; World Heart Federation; National Heart, Lung, and Blood Institute; American College of Nurse Practitioners. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481–1501. doi: 10.1161/CIRCULATIONAHA.107.181546.
79. Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fabunmi RP, Grady D, Haan CK, Hayes SN, Judelson DR, Keenan NL, McBride P, Oparil S, Ouyang P, Oz MC, Mendelsohn ME, Pasternak RC, Pinn VW, Robertson RM, Schenck-Gustafsson K, Sila CA, Smith SC Jr, Sopko G, Taylor AL, Walsh BW, Wenger NK, Williams CL; American Heart Association. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*. 2004;109:672–693. doi: 10.1161/01.CIR.0000114834.85476.81.
80. Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, Krumholz HM, Lichtman JH. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO Study. *J Am Coll Cardiol*. 2015;66:1949–1957. doi: 10.1016/j.jacc.2015.08.859.
81. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med*. 2013;11:200. doi: 10.1186/1741-7015-11-200.
82. Pinheiro Ade O, Pereira VL Jr, Baltatu OC, Campos LA. Cardiac autonomic dysfunction in elderly women with myocardial infarction. *Curr Med Res Opin*. 2015;31:1849–1854. doi: 10.1185/03007995.2015.1074065.
83. Mäkikallio TH, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP, Schmidt G, Huikuri HV. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J*. 2005;26:762–769. doi: 10.1093/eurheartj/ehi188.
84. Longin E, Gerstner T, Schaible T, Lenz T, König S. Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. *J Perinat Med*. 2006;34:303–308. doi: 10.1515/JPM.2006.058.
85. Valentini M, Parati G. Variables influencing heart rate. *Prog Cardiovasc Dis*. 2009;52:11–19. doi: 10.1016/j.pcad.2009.05.004.
86. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol*. 1998;31:593–601.
87. Raphael D. *Social Determinants of Health: Canadian Perspectives*. 2nd ed. Toronto, Canada: Canadian Scholars' Press; 2009.
88. Aspelund T, Gudnason V, Magnusdottir BT, Andersen K, Sigurdsson G, Thorsson B, Steingrimsdottir L, Critchley J, Bennett K, O'Flaherty M, Capewell S. Analysing the large decline in coronary heart disease mortality in the Icelandic population aged 25-74 between the years 1981 and 2006. *PLoS One*. 2010;5:e13957. doi: 10.1371/journal.pone.0013957.
89. Gauthier AH, Hatzius J. Family benefits and fertility: an econometric analysis. *Population Studies*. 1997;51:295–306.
90. Eydal GB, Gíslason IV, Rostgaard T, Brandth B, Duvander A-Z, Lammi-Taskula J. Trends in parental leave in the Nordic countries: has the forward march of gender equality halted? *Community Work Fam*. 2015;18:1–15.
91. Häikiö L, Hvinden B. Finding the way between universalism and diversity: a challenge to the Nordic model. In: Anttonen A, Haikio L, Stefansson K, eds. *Welfare State, Universalism and Diversity.* Cheltenham, United Kingdom: Edward Elgar Publishing; 2012.
92. Gracia E, Merlo J. Intimate partner violence against women and the Nordic paradox. *Soc Sci Med*. 2016;157:27–30. doi: 10.1016/j.socscimed.2016.03.040.
93. Rudman LA, Glick P. Prescriptive gender stereotypes and backlash toward agentic women. *J Soc Issues*. 2001;57:743–762.