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CONTEMPORARY REVIEW

Challenges and Opportunities for the Prevention and Treatment of Cardiovascular Disease Among Young Adults: Report From a National Heart, Lung, and Blood Institute Working Group

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ABSTRACT: Improvements in cardiovascular disease (CVD) rates among young adults in the past 2 decades have been offset by increasing racial/ethnic and gender disparities, persistence of unhealthy lifestyle habits, overweight and obesity, and other CVD risk factors. To enhance the promotion of cardiovascular health among young adults 18 to 39 years old, the medical and broader public health community must understand the biological, interpersonal, and behavioral features of this life stage. Therefore, the National Heart, Lung, and Blood Institute, with support from the Office of Behavioral and Social Science Research, convened a 2-day workshop in Bethesda, Maryland, in September 2017 to identify research challenges and opportunities related to the cardiovascular health of young adults. The current generation of young adults live in an environment undergoing substantial economic, social, and technological transformations, differentiating them from prior research cohorts of young adults. Although the accumulation of clinical and behavioral risk factors for CVD begins early in life, and research suggests early risk is an important determinant of future events, few trials have studied prevention and treatment of CVD in participants <40 years old. Building an evidence base for CVD prevention in this population will require the engagement of young adults, who are often disconnected from the healthcare system and may not prioritize long-term health. These changes demand a repositioning of existing evidence-based treatments to accommodate new sociotechnical contexts. In this article, the authors review the recent literature and current research opportunities to advance the cardiovascular health of today's young adults.

Key Words: cardiovascular disease prevention ■ cardiovascular disease risk factors ■ primary prevention ■ young adults

Despite an overall population-wide decline in cardiovascular disease (CVD) mortality in the United States since 1968,¹ detailed analysis of age-specific rates reveals concerning trends within young adult populations. For example, the proportion of acute myocardial infarctions attributable to patients <55

years old has increased from 27% to 32% in the past 20 years.² and among women 35 to 44 years old, the mortality rate from CVD has increased ≈1.3% per year (95% CI, 0.2–2.5) since 1997.³ Acute ischemic stroke hospitalizations have also increased significantly for men and women 18 to 44 years old, with men 35 to

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Nonstandard Abbreviations and Acronyms

CARDIA	Coronary Artery Risk Development in Young Adults
CVH	cardiovascular health
DM	diabetes mellitus
EARLY	Early Adult Reduction of Weight through Lifestyle intervention
NHLBI	National Heart, Lung, and Blood Institute
PDAY	Pathological Determinants of Atherosclerosis in Youth study

44 years old demonstrating a doubling of acute ischemic stroke hospitalizations since 1996.⁴ Although improvements have been made in acute cardiovascular care, these gains have been offset by increasing racial/ethnic and gender disparities, persistence of unhealthy lifestyle habits, overweight and obesity, and other CVD risk factors such as diabetes mellitus (DM) and hypertension.^{2,4-7}

To enhance efforts promoting the cardiovascular health (CVH) of young adults, defined as 18 to 39 years old, the medical and broader public health community should understand the unique confluence of biological, interpersonal, and behavioral features of this life stage. The current generation of 21st century young adults live in an environment undergoing substantial economic, social, and technological transformations, differentiating them from young adults just 10 or 20 years ago. These changes demand a refashioning of existing evidence-based treatments to accommodate new sociotechnical contexts. Building an evidence base for CVD prevention in this population will require engagement of young adults, who are often disconnected from the healthcare system and may be unmotivated or unable to prioritize their long-term health. Although the accumulation of clinical and behavioral risk factors for CVD begins early in the life course, few trials have studied prevention and treatment of CVD in participants <40 years old.

The National Heart, Lung, and Blood Institute (NHLBI), with support from the Office of Behavioral and Social Science Research, convened a 2-day workshop in Bethesda, Maryland, in September 2017 to identify research challenges and opportunities related to the CVH of young adults. Further details of the meeting and deliberations of the working group can be found on the NHLBI website.⁸ A smaller writing group comprised of 5 members of the working group later convened to develop 2 conceptual frameworks summarizing the presentations of the independent experts. The first framework (Figure 1), inspired by the socioecological model⁹ and the

pathways linking socioeconomic status (SES) and health model,¹⁰ conceptualizes the CVH of young adults as influenced by individual, demographic, and community factors situated within a contemporary context. The second framework (Figure 2), inspired by the Life Course Health Development Framework,¹¹ posits how these various influences create enduring vulnerabilities that influence the trajectory of CVH during and after young adulthood. The writing group then worked with NHLBI staff and each member of the working group to update the recent literature in their respective domains. Consistent with the original goals of the workshop and funding priorities of the NHLBI, in this article we focus primarily on atherosclerotic coronary heart disease (CHD) and its risk factors, although related health conditions such as DM and stroke are discussed where relevant. We review the recent literature and conclude with suggestions for research to address the unique CVH needs of today's young adults.

CVH OF YOUNG ADULTS

Young adulthood encompasses the age range between 18 and 39 years old.¹² During this period, young adults may complete their education, enter the workforce, establish social networks and romantic relationships, create a family, and set financial goals.¹³ Critical health behaviors are either established or lost, helping to shape a life-long trajectory of CVH and well-being.^{14,15} Importantly, young adults often become parents, thereby initiating intergenerational CVH patterns and exposures.

In 2010, the American Heart Association set the bold goal of improving CVH of all Americans by 20% by 2020.¹⁶ To assess CVH, it chose 4 lifestyle factors (nonsmoking status, healthy diet, physical activity patterns, and healthy weight) and 3 clinical factors (optimal blood pressure, blood glucose, and blood lipid levels) consistently shown in epidemiologic studies to be associated with living longer, healthier lives. For the 7 metrics (with the exception of diet) and for the CVH construct overall, children and adolescents are much more likely to have ideal levels than adults. The "Heart Disease and Stroke Statistics—2020 Update" from the American Heart Association addresses these trends (see Figure 3 excerpted from the update) based on data from the National Health and Nutrition Examination Survey.¹⁷

The transition from the relatively ideal CVH of children to the poor CVH of older adults occurs in young adulthood. Considerably fewer young adults (35.2%) meet the criteria for ideal body mass index (BMI) compared with adolescents (60.1%). Young adults are also less likely than adolescents to meet ideal levels of total cholesterol, blood pressure, and

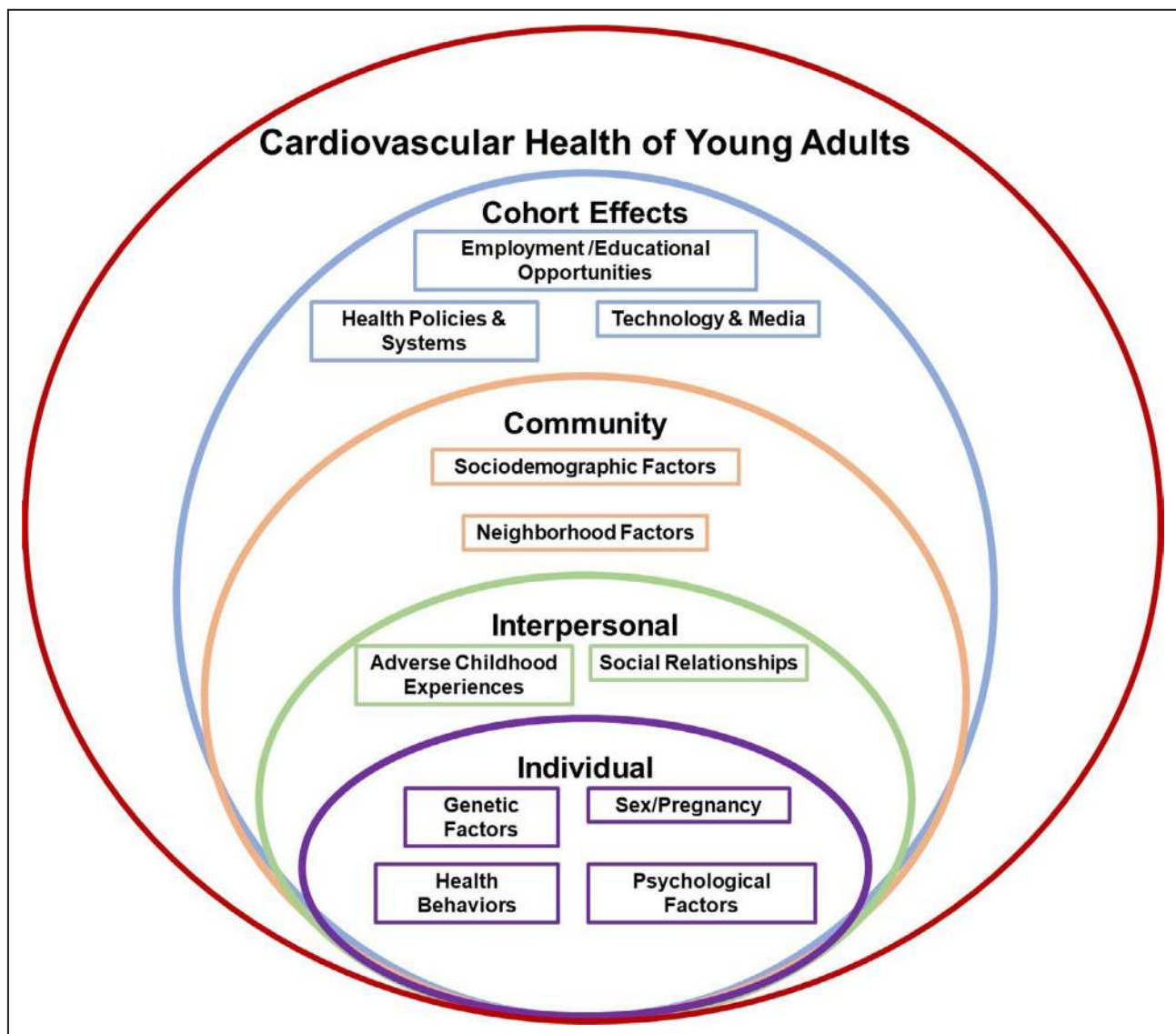


Figure 1. Multilevel influences on young adult cardiovascular health.

The multilevel factors influencing young adult cardiovascular health are depicted here as concentric circles including individual, interpersonal, and community factors situated within a contemporary context referred to as cohort effects. Similar to the socioecological model,⁷ this framework supposes that outer rings influence the rings within them. Similar to the pathways linking SES and health model,⁸ there are bidirectional relationships and interactions among many of the factors. SES indicates socioeconomic status.

fasting glucose (Figure 3). Importantly, in both children and adults, the proportion of the US population meeting ideal criteria for blood pressure and total cholesterol has risen over the past decade, while the prevalence of ideal BMI and glucose levels has declined.¹⁷ There is robust evidence that type 2 DM is increasing in younger individuals worldwide as well.¹⁸ Although use of traditional cigarettes has declined for young adults, they are increasingly using e-cigarette products that appear to pose cardiovascular risk.^{19–21} E-cigarette use by young adults is also associated with subsequent adoption of traditional tobacco products²² thus, this may portend a worsening of the smoking metric in future years.

Although not 1 of the original 7 ideal CVH metrics, sleep health is also critical to CVH and is insufficient among young adults, with 38% reporting an inadequate sleep duration (<7 hours per night).²³ Adolescents with inadequate sleep are more likely to be obese and have elevated glucose and insulin levels, higher blood pressure, greater fat mass, and more behavioral risk factors such as physical inactivity and an unhealthy diet.^{24,25} Adults with inadequate sleep duration are more likely to be obese and physically inactive, report substance use including use of tobacco products, experience depressed mood and anxiety symptoms, and develop chronic diseases such as hypertension and DM.^{23,26}

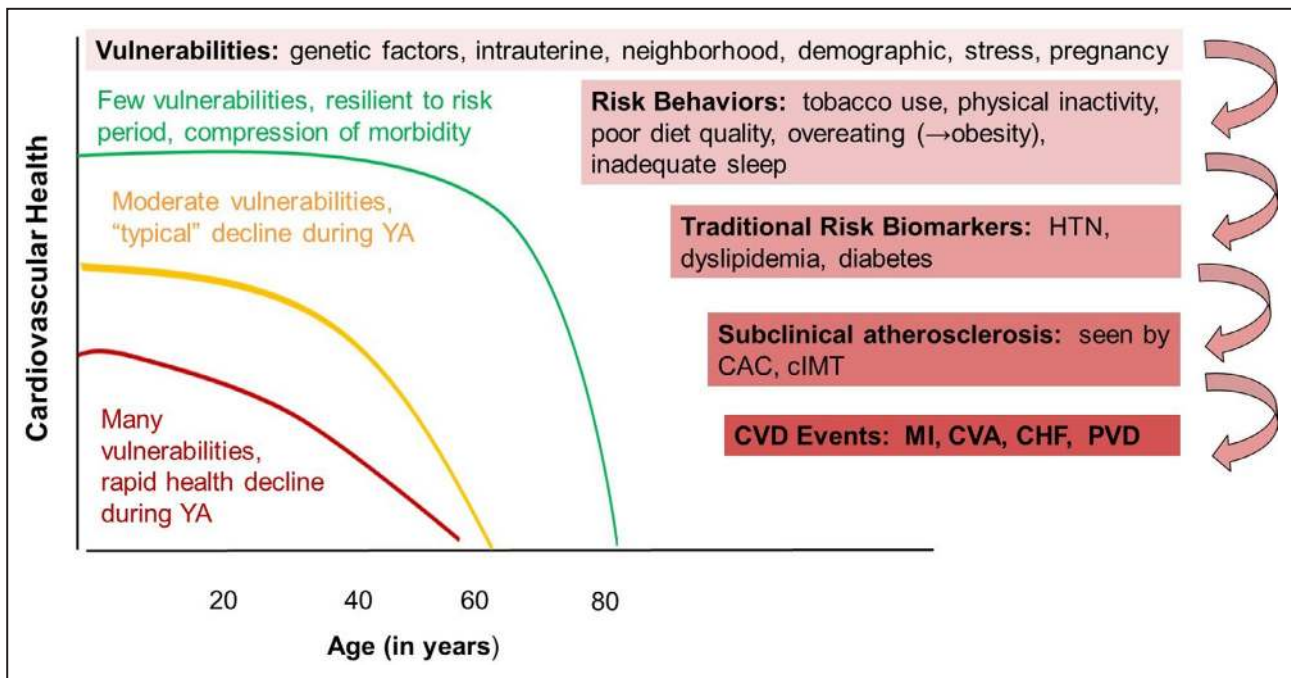


Figure 2. Causes of variation in trajectories of cardiovascular health.

The 3 cases illustrated in the figure vary from having a low early vulnerability burden that allows CVH to develop maximally (green curve) to having a high vulnerability burden that constrains the development of CVH (red curve). The case illustrated by the green curve shows high resilience to the young adult period of risk (ie, maintaining the high starting level of CVH until late in life). Both the yellow and the red curves show loss of CVH during the young adult risk period, illustrating a lack of resilience to the challenges imposed by this life period. Both the green and the yellow curves illustrate a steep slope, where CVH is lost rapidly. The comparison of the green and yellow curves illustrates that the clinical impact of such a rapid loss of CVH varies depending upon its timing in the life course. These 3 simplified curves are shown for illustrative purposes; dynamic changes to CVH trajectories across the life course are likely caused by alterations in the enduring vulnerabilities and risk behaviors through changes in life circumstances, individual, or public health interventions. CAC indicates coronary artery calcium; CHF, congestive heart failure; CIMT, carotid intima media thickness; CVA, cerebral vascular accident; CVD, cardiovascular disease; CVH, cardiovascular health; HTN, hypertension; MI, myocardial infarction; PVD, peripheral vascular disease; and YA, young adulthood.

MULTILEVEL INFLUENCES ON THE CVH OF YOUNG ADULTS

As depicted in Figures 1 and 2, many factors influence the CVH trajectory of young adults by contributing to either the slowing or the acceleration of the development of CVD. A selection of these factors is presented below, beginning with those unique to individuals, followed by interpersonal and community factors, and cohort effects. Similar to the socioecological model,⁷ this framework supposes that outer levels influence the levels within them. Similar to the pathways linking SES and health model,⁸ there are bidirectional relationships and interactions among many of the factors.

Genetic Factors

Genetic conditions cause premature heart disease, including familial hypercholesterolemia (prevalence 1:250). Emerging data suggest the addition of a genetic risk score to conventional risk factors may improve the prediction of accelerated subclinical

atherosclerosis in younger adults and premature onset of CHD events.^{27–31} For example, a 182-variant polygenic risk score predicted a 2-fold increase in risk of premature coronary artery disease (≤ 40 years old for men and ≤ 45 years old for women), a rate similar to that observed in individuals with heterozygous familial hypercholesterolemia.²⁸

Gender

The young adult years hold important CVD prevention implications for women. CVD remains the leading cause of mortality among women in the United States and developed countries.³² Women experience a higher fatality rate following a first myocardial infarction, and despite an overall decline in the CVD death rate in the United States, the rate of decline has been slower for women compared with men. In addition, the death rate is 70% higher in Black women compared with White women.³³ Two-thirds of CHD sudden deaths occur in women with no previous symptoms compared with half of CHD sudden deaths in men. It is now evident that this excess mortality

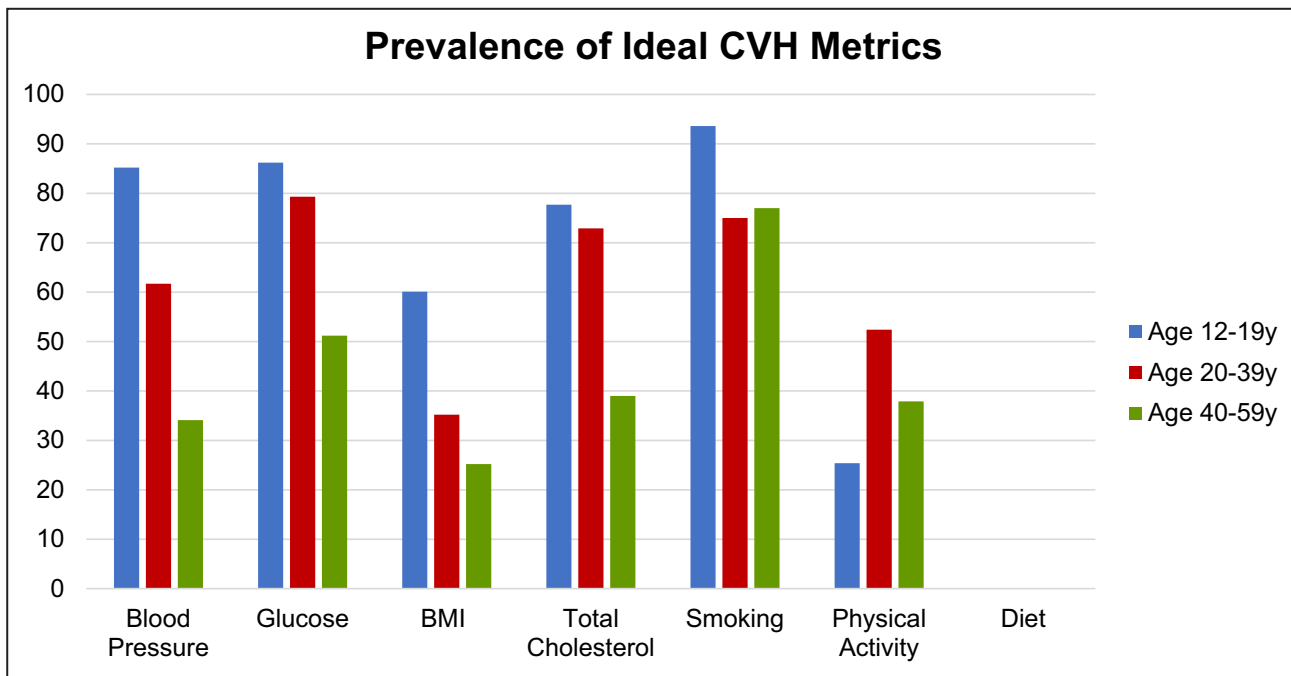


Figure 3. Prevalence of adolescents (ages 12–19 years), young adults (ages 20–39 years), and middle-aged adults (ages 40–59 years) meeting ideal status for each of the 7 cardiovascular health metrics.

Prevalence (unadjusted) estimates of US adults across 3 age strata meeting ideal status for each of the 7 metrics of cardiovascular health as reported in “Heart Disease and Stroke Statistics—2020 Update” from the American Heart Association.¹⁷ BMI indicates body mass index; and CVH, cardiovascular health. *Healthy diet score reflects 2013 to 2014 NHANES (National Health and Nutrition Examination Survey). *Source:* National Center for Health Statistics, NHANES, 2015 to 2016 (healthy diet score, 2013 to 2014).

is based in part on the increased death rate among premenopausal women, although less is known regarding coronary artery disease among this group.³⁴ Recent data on 20-year trends in acute myocardial infarction demonstrate that the proportion attributable to patients >55 years old has increased from 27% to 32%, with the largest increases observed in young women.² Additionally, women 18 to 44 years old have a higher incidence rate of ischemic and nonischemic stroke compared with men of the same age.³⁵ Thus, the detection of elevated risk in young women and a greater understanding of gender-related differences may provide a critical opportunity to delay or prevent onset of CVD in women.

Pregnancy

More than 80% of American women bear a child during their young adult years³⁶; pregnancy can be viewed as a “stress test,” with adverse pregnancy outcomes associated with increased future CVD. Hypertensive disorders of pregnancy (eg, preeclampsia, gestational hypertension) affect up to 7% of births. A firmly established link exists between the development of hypertension during pregnancy and a 2- to 8-fold higher risk of hypertension, CVD, and renal disease later in life.³⁷ Rates of chronic hypertension 2 to 5 years after

affected pregnancies are as high as 50% following early-onset preeclampsia, 39% after gestational hypertension, and 25% following late-onset preeclampsia.³⁸ By comparison, hypertension rates in women with normotensive, term births are very low (3.8%) 2 to 7 years after delivery.³⁹ Diastolic dysfunction and asymptomatic heart failure have been detected 4 years postpregnancy in 25% of women with preeclampsia.⁴⁰ Women with preeclampsia have a higher risk of CVD within 5 years after delivery, suggesting that the short- and long-term cardiovascular sequelae are high.^{41,42} Thrombotic events are more likely in the period immediately following pregnancy.⁴³

Gestational DM, which affects up to 10% of pregnancies, is associated with a 50% to 85% higher CVD risk in women.^{42,44–46} Nearly half of women who experience gestational DM will develop type 2 DM within 10 years after pregnancy.^{47,48} Gestational DM is also related to risk of atherosclerosis, even in women who do not progress to DM.⁴⁹ Lactation may mitigate some of these adverse maternal consequences of gestational DM, suggesting that the reproductive years also present opportunities for risk reduction.⁵⁰ Other complications such as preterm birth are also linked to CVD risk.^{51–54} Further, there is an alarming increase in severe maternal morbidity and mortality in the United States, the dominant cause of which

is cardiovascular in nature.⁵⁵ There are also profound racial disparities, with Black women carrying the highest risk for these severe events compared with White women.⁵⁶ Evidence-based strategies to increase CVD risk evaluation during preconception, prenatal, and postnatal care are needed, as are interventions to mitigate CVD risk during this critical time for young adult women.

Psychological Factors

Psychological stressors are associated with CVD risk behaviors and CVD.⁵⁷ Acute mental stress is associated with alterations in myocardial blood flow, and chronic exposure to stress is associated with alterations in inflammation signaling pathways.^{58,59} Young adults commonly face a variety of psychological stressors, including neighborhood factors and sequelae of adverse childhood experiences, as well as financial hardships, relationship changes, and discrimination based on race, gender, sexual orientation, or other societally disadvantaged situations. The cumulative effects of an increasing number of stressors, as well as the protective effects of individual and collective resilience factors, are active areas of investigation.

Three-fourths of mental health disorders are present by 24 years old.⁶⁰ Compelling evidence suggests that major depression and depressive symptoms predict premature heart disease morbidity and mortality. Putative mechanisms include standard biological and lifestyle factors, inflammation, oxidative stress, and endothelial dysfunction.⁶¹ An analysis of data from the National Survey on Drug Use and Health for the years 2005 to 2015 found an increasing prevalence of depression in the United States, with adolescents and young adults showing the largest increases, to 13% and 10%, respectively.⁶² A substantial decline in CVH among young adults may be caused by mental health disorders and related obesity, physical inactivity, smoking, and disturbed sleep,⁶¹ although this remains an area for investigation.

Adverse Childhood Experiences

Adverse early life experiences may be particularly damaging to CVH in young adults. Typically, these include physical and sexual abuse, neglect, a family member with mental health problems, incarceration of a parent, and sometimes poverty. In a sample of 29 229 adult men and women, more than 50% reported at least 1 form of childhood adversity; 17% reported 4 or more adverse experiences.⁶³ Not only do adverse early life experiences predict depression, but they are also related to behavioral and physiologic cardiovascular risk factors.^{64–67} The accumulation of adverse early life experiences is predictive of clinical CVD in adulthood.⁶⁸ A meta-analysis of 9 studies (15 effects) that reported

hazard ratios (HRs) and 29 studies that reported odds ratios (ORs; 62 effects) found significant associations between cumulative childhood adversity and adult cardiometabolic disease (HR, 1.42, 95% CI, 1.20–1.67; OR, 1.36, 95% CI, 1.27–1.46). We know of no evidence to suggest that the prevalence of adverse child experiences is declining. Interventions to decrease exposure to childhood adversities and mitigate their downstream effects are needed.

Social Relationships

In adults, lower social support, less integration into social networks, and greater social isolation are associated with increased risk of morbidity and mortality.⁶⁹ Less evidence regarding the cardiovascular risk of social relationships is available in adolescents and young adults. The Dunedin Multidisciplinary Health and Development study showed that social isolation in childhood (5–11 years old) based on parent and teacher ratings predicted the age 26 summary index of lipids, blood pressure, BMI, waist circumference, glycated hemoglobin, and maximum oxygen consumption.⁷⁰ These effects were independent of childhood family SES and overweight. Peer social integration based on parental reports of time their sons spent with friends from ages 7 to 16 was related to blood pressure and BMI when men were in their thirties.⁷¹ These relationships were also independent of family SES, childhood BMI, and social integration in adulthood. Data from the Add Health (National Longitudinal Study of Adolescent to Adult Health) study indicated that greater social integration within peer networks, school, family, and community during adolescence was associated with lower levels of inflammation, blood pressure, BMI, and waist circumference in young adulthood.⁷² Several studies have reported that being a victim of bullying was associated with inflammation, obesity, and psychosocial risk factors, in addition to its mental health consequences.^{73,74} The long-term impact of early social relationships and social relationships in young adulthood are an important area for future research.

Sociodemographic Factors

SES has a profound influence on adult CVD risk, regardless of whether SES is based on the education, the income, or the occupation of the individual or of family members, or whether these factors apply to the neighborhood.¹⁰ Many explanations of SES and CVD risk association have focused on poverty, but it appears that the relationship of SES and health is monotonic, such that each increasing level of SES is associated with better health. Studies examining the influence of SES across the life course have found that low SES in childhood is related to adult CVD morbidity and mortality, even

when statistical adjustments are made for adult SES.^{75,76} Extensive reviews of the literature show that lower SES in youth is associated with CVD risk factors, including greater exposure to passive and active smoking, physical inactivity (eg, more hours watching television), obesity, poor sleep health, and central adiposity.^{77–79} In the Add Health study, lower SES during adolescence was related to a higher Framingham risk score 14 years later.⁸⁰ Mediation analyses showed that educational attainment, financial stress, and lack of medical/dental care were key pathways to high-risk scores. In the same study, lower family income was related to higher systolic blood pressure.⁸¹

Black and Hispanic youth are more likely to grow up in lower SES families and live in lower SES neighborhoods than their White and Asian counterparts. Further, although there is evidence from studies that Black adults receive less of a health benefit from higher SES status than White adults,^{82,83} only a few studies among youth simultaneously consider SES and minority status and whether the effects are independent or synergistic.⁸⁴ In an analysis of National Health Interview Survey data for US children 0 to 18 years old, lower parental education was associated with higher rates of “circulatory conditions” in Black and White children and were null or reversed in Asian and Hispanic children.⁸⁵ In the Add Health study, the influence of SES on obesity differed by race and gender.⁸⁶ In several studies of healthy children, low SES was related to higher ambulatory blood pressure throughout the school day in Black and White children, and family income was related to high nighttime pressure in Black children only.^{87,88} Taken together, the stage is set by adolescence for a long-lasting effect of family SES on CVH into adulthood, with more adverse among Black and Hispanic young adults, with some gender-specific differences.

Neighborhood Factors

Findings from the Add Health study also indicate that the prevalence of obesity, as well as high systolic and diastolic blood pressures and metabolic syndrome,⁸⁹ is lower in young adults who never lived in poor neighborhoods, compared with those who later or consistently lived in poor neighborhoods as adolescents.^{90,91} Independent of neighborhood poverty, aspects of the neighborhood physical environment, including access to healthy foods, walkability, and transportation have been consistently linked to behaviors such as smoking, physical activity, and dietary intake, as well as a range of CVD risk factors including BMI, hypertension, and DM.^{92–97} Aspects of the neighborhood social environment including crime, perceptions of safety, and reports of neighborhood social

cohesion have also been associated with a range of indices of CVD risk, including smoking, physical inactivity, dietary quality, insomnia, hypertension, and increased BMI.^{93,98–101}

Cohort Effects

Regardless of treatment modality or preventive strategy, trials of any intervention to improve CVH during young adulthood will need to understand and navigate the unique socioeconomic characteristics exhibited by 21st century young adults. Young adults living in the United States today are less likely than previous generations to marry, have children, and own their own home.¹⁰² The modal living arrangement is with their parents (33%), and 1 in 4 young adults who live at home are neither working nor in school.¹⁰² Furthermore, though young adults living in the United States today are more educated than previous generations, they have taken on much more debt related to their education. Each of these shifts has implications for the likelihood and ability of young adults to engage in preventive behaviors and pay for health care. These contextual factors require consideration for both initiating and sustaining lifestyle modifications,^{103,104} and, if indicated, starting and maintaining adherence to antihypertensive, lipid-lowering, or glucose-regulating medication.¹⁰⁵ These demographic trends are seen most often in highly industrial or postindustrial societies. In other societies and in more rural communities in the United States and elsewhere, the phenomenon known as “emerging adulthood,” a delayed transition to typical adult roles, is less common.¹²

Technological advances have changed the nature of work and leisure time for young adults around the world, and in both rural and urban settings. Young adults are the most likely age group to own a smartphone (92% in 2017), use social media (86%), and be dependent on their smartphone for accessing the internet.¹⁰⁶ Thirty-nine percent of young adults report they are “constantly online” and 49% report they are online “multiple times per day.”¹⁰⁷ The beneficial and harmful effects of young adults being connected to these electronic devices for much of their waking, and even their sleeping hours, are unclear. Electronic media usage has been associated with insufficient sleep,¹⁰⁸ physical inactivity,¹⁰⁹ increased caloric intake,¹¹⁰ and elevated BMI¹¹¹ in young adults, although some studies find improved nutrition and physical activity among young adults who use health-related apps.¹¹²

Early young adulthood, between 18 and 21 years old, is when individuals transition from pediatric-oriented to adult-oriented healthcare systems in the United States.¹¹³ Consistent engagement with medical care is essential for young adults with higher CVD risk. Even among insured young adults, a longer time

between physician visits is associated with worse hypertension control.¹¹⁴ Yet, many young adults have a prolonged gap in care when transferring across healthcare systems. A recent national retrospective study of insured young adults found a gap of 20.5 months for office visits and 41.7 months for preventive visits when transitioning from an adolescent to adult medical practice.¹¹⁵ Males and young adults from lower-income neighborhoods experienced even longer gaps in care.¹¹⁵ Young adults also have relatively low rates of preventive care service utilization as compared with other age groups. The 2014 to 2016 Medical Expenditure Panel Surveys, which reflect implementation of the Affordable Care Act, found that only 23% of young adult men and 42% of young adult women received a routine primary care examination. Of those who attended any healthcare visit in a 3-year period, 86% received blood pressure screening, but only 42% received cholesterol screening. Rates of preventive care were higher in females, young adults with higher reported income, and those with health insurance.¹¹⁶

CAUSES OF VARIATION IN TRAJECTORIES OF CVH

Optimal preventive interventions should consider not only who is at greatest risk of adverse CVD outcomes based on exposures and individual susceptibility, but also when risk develops and when intervention would be most beneficial. The schematic in Figure 2 illustrates different trajectories of loss of CVH over the lifespan in relation to enduring vulnerabilities from the influences described above, individual risk behaviors, and traditional risk biomarkers. CVD risk factors vary in their temporal trajectories across the life course.^{117,118} The first parameter in the model is maximal capacity for CVH, represented by the y-axis intercept. Various genetic, intrauterine, sociodemographic and life event factors, operating from conception throughout childhood, function as vulnerabilities to impact the maximum capacity for CVH.^{119,120} The second parameter reflects the degree of resilience against loss of CVH present during young adulthood. The third parameter is the slope of the trajectory of loss of CVH; steeper slopes represent more rapid loss. Each curve in Figure 2 illustrates how these parameters may influence the timing and rate of loss of CVH. Optimal is decline after age 70 to 80 years based on lifelong stably high CVH level (green curve in Figure 2). This illustrates the advantageous compression of morbidity until achieving old age based on maximal capacity and healthy lifestyle.¹²¹ Most typical is rapid decline from the presence of prior moderate CVH during young adulthood; this presages reaching suboptimal CVH during late adulthood (yellow

curve in Figure 2). Unfavorable levels of cardiometabolic and biochemical markers (eg, increased systolic blood pressure, increased waist circumference, and decline of glomerular filtration rate) are evident at least 15 to 20 years before CVD diagnosis, indicating that risk is partly determined by or during young adulthood.¹²² Those with limited maximal capacity, adverse circumstances, and severe or multiple risk will experience CVD in young adulthood (red curve in Figure 2).

PATHOPHYSIOLOGIC PROGRESSION AND RISK PREDICTION: FROM SUBCLINICAL CARDIOVASCULAR MARKERS TO CVD

Subclinical Atherosclerosis and CVD Risk Prediction

Epidemiologic and clinical studies have established that atherosclerosis can start during the childhood years and progress through young adulthood, leading to CHD by middle age.^{123,124} The PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study confirmed that advanced atherosclerosis can start in late adolescence, with progression of atherosclerotic plaque in relation to CVD risk factors occurring in the third and fourth decades of life.¹²³ The advanced atherosclerotic lesions seen in some young adults are of the type that can rupture and produce acute events.¹²⁵ Preliminary analyses, using CARDIA (Coronary Artery Risk Development in Young Adults) study data, support a relationship of these high-grade lesions with atherosclerotic events.¹²⁶ The major traditional risk factor predictors of advanced atherosclerosis in the PDAY study were DM, dyslipidemia, smoking (particularly for atherosclerosis in the abdominal aorta), hypertension, and obesity (in men). Effects on traditional risk factors, oxidative stress, and endothelial dysfunction have been described as pathways whereby lifestyle risk factors convert to cardiometabolic risk factors and further the progression to atherosclerosis and CVD.^{127,128} However, lifestyle risk factors also occur against a background of variable inherited and acquired individual vulnerability to atherosclerosis and cardiovascular events^{28,29} and in a context that offers more or less socioenvironmental support.¹²⁹

Current risk prediction equations for atherosclerotic cardiovascular disease (ASCVD; defined as a nonfatal myocardial infarction [heart attack], CHD death, or stroke)^{130,131} use the traditional risk factors of age, sex, DM, smoking, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, antihypertensive therapy, as well as race/ethnicity. These equations perform well in non-Hispanic White and Black women and men 40 to 79 years

old.¹³² Insufficient data have been available to develop ASCVD risk prediction equations for adults <40 years old, or for other racial/ethnic groups.¹³⁰

A PDAY risk score was developed to predict the presence of subclinical atherosclerosis in young adults; this score is based on age, sex, HDL-C and non-HDL-C, smoking, blood pressure, and glycosylated hemoglobin. The usefulness of this score was confirmed in both the CARDIA study¹³³ and the Young Finns Study.¹³⁴ A critical finding was that the PDAY score calculated in adolescents (Young Finns Study) or at age 18 to 30 years (CARDIA study) was more predictive than risk factors measured later in adulthood for higher carotid intima media thickness or presence/intensity of coronary artery calcium measured 15 to 25 years later. Between 40% and 60% of those with a high PDAY score will have advanced atherosclerosis. These observations suggest that atherosclerosis present in young adulthood is the result of chronic risk exposure over a lifetime; early prevention efforts can reduce the atherosclerotic burden in middle age.^{135,136} Longitudinal studies with childhood and adult measures of subclinical atherosclerosis consistently show independent relationships of youth risk factors to adult outcomes.¹³⁷

CVD Risk Based on Hypertension and DM

There is a high prevalence of uncontrolled hypertension among young adults.^{105,138–141} Up to 38% of hypertension goes undetected before age 40.¹⁴² Hypertension in young adulthood has been associated with adverse cardiovascular outcomes later in life, with many of these events occurring before age 50 years.^{143–145} Multiple studies have demonstrated that Black young adult men and women have an earlier onset and more severe hypertension compared with young adult White men and women.^{141,146} Analysis of 24-hour ambulatory blood pressure data found a higher mean 24-hour blood pressure, higher prevalence of nocturnal hypertension, and higher rates of masked hypertension among young Black men and women compared with White men and women of similar age.^{141,147} Historical cohort studies also have found more severe baseline hypertension (>160/95 mm Hg) among Black young adults and its association with higher rates of hypertension-related mortality.¹⁴¹

More concerning is that the severity of hypertension among Black young adults is often underestimated using blood pressure measurements taken in a clinic.^{141,147} Analyses of blood pressure trajectories highlight the emergence of age, gender, and racial/ethnic hypertension disparities beginning at least as early as 8 years old.¹⁴⁶ Using 2007 to 2012 data from the National Health and Nutrition Examination Survey, there were earlier transitions from ideal blood pressure (<120/80 mm Hg) to prehypertension, and ultimately

sustained hypertension among boys (compared with girls) and Black compared with White youth.¹⁴⁶ With the updated 2017 American College of Cardiology and American Heart Association high blood pressure guidelines defining hypertension as a blood pressure $\geq 130/80$ mm Hg, there is now a greater prevalence of elevated blood pressure (120–129/<80 mm Hg, previously “prehypertension”) and hypertension among young adults.¹⁴⁸ Disparities in the incidence and severity of hypertension also contribute to similar disparities noted in the prevalence of heart failure among young adults.¹⁴⁹ In the CARDIA study, 20-year follow-up of 18- to 30-year-olds found higher rates of incident heart failure among Black males and females compared with White men and women. Of note, Black young adults in the United States carry a disproportionate burden of many psychosocial contributors to poor CVH including poverty and stress noted above. Thus, the accrual of CVD risk for Black young adults can be profound.

The prevalence of DM in adolescents and young adults is increasing.^{150,151} Both type 1 and type 2 DM have been related to early vascular dysfunction, and share risk factors similar to those for CVD including hypertension, dyslipidemia, microalbuminuria, inflammation, and hyperglycemia.¹⁵² However, young-onset type 2 DM appears to be associated with manifestation of the vascular abnormalities earlier and at lower glycosylated hemoglobin levels, despite shorter duration of diagnosed DM.^{153,154}

PRIMORDIAL AND PRIMARY PREVENTIVE INTERVENTIONS IN YOUNG ADULTS

Two main intervention strategies are available to curb longitudinal loss of CVH (Figure 4). Primordial prevention intervenes to deter the development of risk factors by focusing on the outer level of influences (Figure 1).¹⁵⁵ Examples targeting the entire population include media health education campaigns and policy interventions (eg, Clean Indoor Air Act, sugar-sweetened beverage tax, fruit and vegetable subsidies, and zoning ordinances to make neighborhoods more walkable). Primary prevention treats individuals who already have risk factors to reduce their odds or slow their trajectory of progression toward CVD events. This is typically focused on the innermost level of individual influences (Figure 1).

Role of Healthcare Engagement by Young Adults for CVH Promotion and Disease Prevention

For primary prevention to reach young adults with risk, barriers to young adults' engagement in health

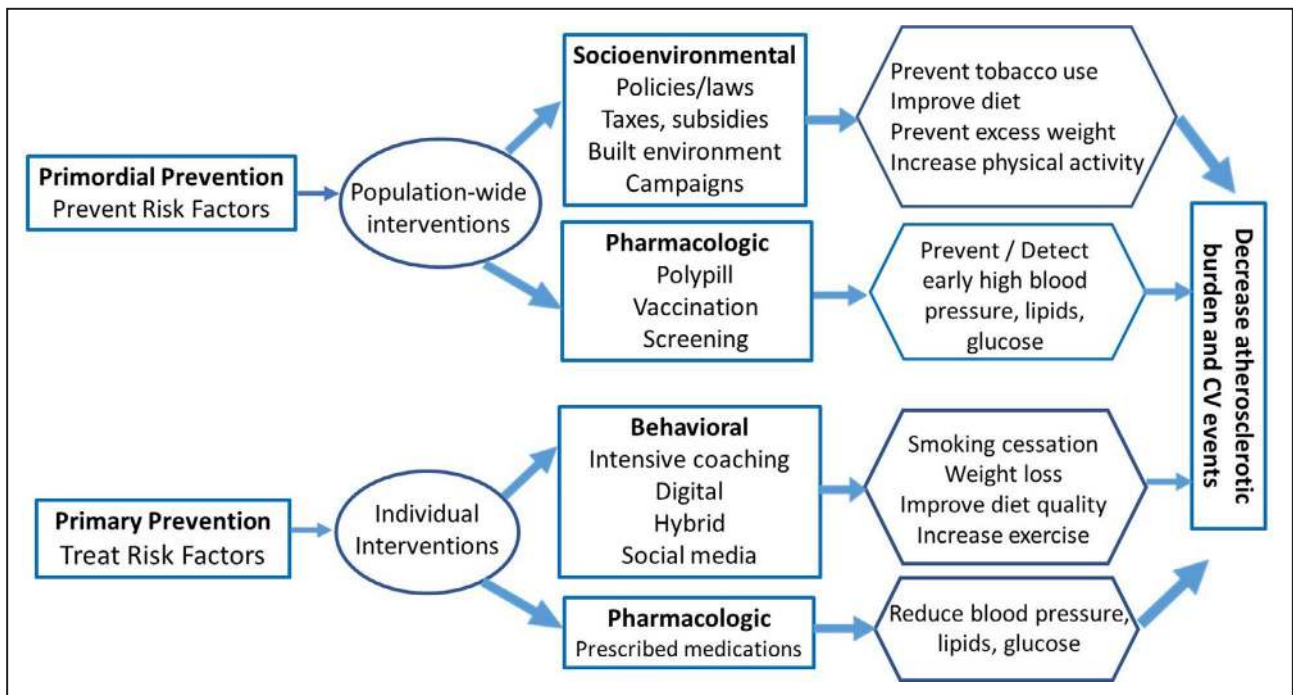


Figure 4. Risk factor intervention.

Two main intervention approaches to preventing the development of (primordial prevention) or treating already developed cardiovascular risk factors (primary prevention). Either intervention approach can deploy behavioral-socioenvironmental or pharmacologic treatment modalities. The intervention targets depicted (in hexagons) are the established cardiovascular risk factors included in the American Heart Association’s Simple 7 metric, but might also include developing markers: insufficient sleep, stress/depression, or inflammation.

care must be overcome. Policies are critically needed to offer young adults continuous, affordable health insurance and consistent care access without racial and socioeconomic disparities. At a healthcare systems level, it is important that primary and specialty care practices recognize the transitions that occur throughout young adulthood. To maintain young adults’ continued engagement, traditional outpatient clinics may need to accommodate their preferences for convenient, integrated, and flexible care, by offering services during evening or weekend hours or via telemedicine.¹⁵⁶ Similarly, young adults may prefer using technology to schedule health appointments, access health records, and monitor engagement in health-related behaviors by using their own mobile/wearable devices. By incorporating data from mobile devices and wearable devices, the healthcare provider can potentially partner with patients to provide tailored assessments and behavior-change advice.^{157,158} Although integration of patients’ digital data into the electronic health record to support connected care remains in its infancy, such infrastructure has already become a reality at some institutions.¹⁵⁹ Expansion of training programs with a young adult focus, such as joint pediatric and adult medicine training, can increase developmentally tailored programs for young adults.¹⁶⁰

Community-Based CVH Promotion and Disease Prevention

Given low overall rates of engagement with traditional medical settings, novel programs may be needed to promote healthy behaviors among young adults. Because young adults are highly represented in the workforce, health promotion programs delivered in occupational settings may be particularly beneficial to promote heart-healthy behaviors.¹⁶¹ Also, linking preventive health care to concern for the environment (eg, lower environmental impact of wholly plant-based or reduced animal protein diets, walking, or biking) and to other motivational factors may appeal to young adult values. Similarly, social media may be harnessed to promote health knowledge and motivation among difficult-to-reach or disengaged young adults.¹⁶² It is important to respect young adults’ need for privacy on social media and provide resources for how to find and identify credible health information.¹⁶³ Provision of high-quality, coordinated care for young adults will require improved communication across healthcare systems and providers who may work in student health, retail-based, and urgent-care clinics. By incorporating these care delivery entities outside of traditional health settings, coordinated care may be able to catch young adults where they are receiving care.

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Population-Wide Health Interventions

Population-wide interventions have the potential to reach those of low SES, smokers, and consumers of low-cost, unhealthy diets who are often not linked to medical care. Population-based interventions may be especially relevant to young adults, who may be disengaged from the formal healthcare sector and may choose to prioritize immediate concerns over long-term health risks. Some of the best-supported population-wide interventions involve laws and policies.

Two particularly impactful tobacco control policies legislated at the state or municipal level have been tobacco product taxation, passed on to the consumers at the point of purchase, and tobacco bans, which outlaw smoking in workplaces, public transit, restaurants, and bars. The National Longitudinal Survey of Youth found that a \$1 increase in tobacco excise taxes lowers the odds of daily heavy smoking in young adults (1 or more packs per day) by 17.9%.¹⁶⁴ Young adults living in cities with comprehensive smoking bans were 21.1% less likely to smoke. Electronic cigarettes share the same addictive properties as traditional tobacco products, but have only recently become popular among adolescents and young adults. The health effects of electronic cigarettes have not been well-described, but early evidence shows that young adults who start as never-smokers and start using electronic cigarettes are 3.6 times more likely to become regular tobacco smokers than those who avoid electronic cigarettes.¹⁶⁵ This suggests that stronger electronic cigarette regulation in young adults could limit the population of young adult and longer-term tobacco smokers.

Recently, population-wide interventions have been applied to the risk factors of poor-quality diet and physical inactivity with the rationale that powerful environmental contexts make individual behavior changes difficult to sustain. Examples include food sources dominated by packaged, processed, and high-calorie foods with low nutritional value and built and workplace environments that encourage sedentary habits. New York City 2006 government regulation of trans-fatty acid use in restaurant cooking led to a 62% reduction in mean serum trans fatty acid levels in adults between 2004 and 2014.¹⁶⁶ In the United Kingdom, food companies were encouraged by the government to make voluntary agreements to lower sodium content in packaged foods starting in 2006. Young adults in the United Kingdom (16–34 years old) had the highest sodium consumption at baseline of any age group (6.6 g/d in 2003) and experienced a 9.5% decrease in daily sodium intake by 2007.¹⁶⁷ An excise tax on sugar-sweetened beverages introduced in Berkeley, California, led to

reduced consumption of sugar-sweetened beverages and increased consumption of untaxed beverages (eg, water).^{168,169} Not all public health interventions need be punitive. For example, the US Supplemental Nutrition Assistance Program, introducing incentive subsidies to encourage consumption of fruits and vegetables combined with a sugar-sweetened beverage ban, could lead to substantial lifetime health gains and be cost-effective.¹⁷⁰

Individual Behavioral Interventions

Systematic evidence reviews of behavioral interventions for the general adult population suggest their benefit on intermediate CVD risk factors, diet, and exercise behaviors,¹⁷¹ as well as tobacco cessation.¹⁷² Less evidence exists for young adults specifically. Traditionally, young adults have been underrepresented in behavioral intervention trials. For example, in a pooled analysis of lifestyle interventions for weight loss, young adults represented <10% of the sample, attended 25% fewer sessions than older adults, and were less likely to be retained at follow-up.^{173,174}

The EARLY (Early Adult Reduction of Weight through Lifestyle Intervention) trial, a consortium of 7 randomized controlled trials funded by the National Institutes of Health, sought to address this gap by enrolling only individuals 18 to 35 years old in 2-year behavioral weight control interventions.¹⁷⁵ The EARLY trial enrolled over 4000 young adults, and had an average retention of 83% at 2 years across all 7 studies, demonstrating that young adults are interested in and can be successfully retained in long-term behavioral trials designed specifically for them.^{175–181} Retention was variable across populations and follow-up methods; whereas 97% of weights were obtained using electronic medical records, fewer (68%) were obtained when directly measured in the clinic. Results across EARLY studies were variable, with some studies showing significant weight loss¹⁷⁸ or weight gain prevention at 2 years¹⁸¹ and others showing only short-term weight loss or effects on secondary outcomes.^{175,177,180}

In an effort to appeal to young adults, each of the EARLY studies used digital tools, either alone or in combination with face-to-face methods. Systematic reviews and meta-analyses provide evidence that using digital health tools can produce positive short-term effects on smoking cessation¹⁸² and weight control.¹⁸³ Digital and hybrid treatments that combine digital with phone or face-to-face care can vary significantly with respect to content and intensity.¹⁸⁴ Generally, interventions with greater dose, tailoring, and inclusion of a human coach or counselor have been more effective. The outcomes across the 7 EARLY trials in young adults are consistent with this interpretation.

Moving forward, behavioral research should focus on optimizing interventions such that more potent, efficient, and scalable interventions are developed and tested. The multiphase optimization strategy, an engineering-inspired framework, encourages experimental approaches to the selection and configuration of intervention components. The multiphase optimization strategy offers a suite of research designs that test how to optimize interventions so that they achieve the maximum effect possible given resource constraints.^{185,186} Adaptive interventions (those that deliver sequential treatments or intensities based on progress) address heterogeneity of outcomes in behavioral interventions and may be particularly important for young adults who face different life events and circumstances that pose challenges for behavior change.^{185,187} Just-in-time-adaptive interventions capitalize on real-time data from young adults' ubiquitous mobile technologies to adapt the timing and content of interventions day to day and even moment to moment.¹⁸⁸ Emerging genomic, metabolomic, and microbiome data may also help to understand the heterogeneity of behavioral treatment outcomes and expand the set of predictors and treatment-matching variables available to personalize intervention selection.

Individual Pharmacologic Interventions

Current clinical practice guidelines for the primary prevention of ASCVD have been based on evidence from cardiovascular outcomes trials that have enrolled individuals ≥ 40 years old for the end points of ASCVD events, heart failure, cardiovascular or total mortality, or atherosclerosis progression.^{131,189} Few trials targeting the exclusively primary prevention population included participants who were < 50 years old: Ages ranged from a mean of 57 to 66 years old.^{190–193} An ongoing 10-year primary prevention statin trial is enrolling men 35 to 50 years old and women 45 to 59 years old.¹⁹⁴ Although randomized trial data suggest that greater reductions in the relative risk of ASCVD occurred when statins were used in lower-risk (eg, younger) individuals,¹⁹⁵ the absolute risk of ASCVD events is low before age 50 years, especially in women, who have a lower absolute risk of premature CHD.^{196,197} Clinical trials with cardiovascular outcomes as end points in younger adults would require either a very large sample size and duration > 5 years, identification of very effective interventions with large reductions in relative risk of ASCVD, or more precise identification of the most susceptible populations with the highest risk of nearer-term ASCVD events.

On the other hand, trials focused on preventing the development or progression of atherosclerosis, early predictors of heart failure, or progression of hypertension are feasible in younger adults. Populations

at higher risk in young adulthood include those with hypertension, early-onset DM (type 1 or type 2), familial hypercholesterolemia, or multiple risk factors associated with obesity. It could be expected that prevention of atherosclerosis or stabilization of early atherosclerotic plaque would largely prevent the subsequent manifestation of clinical ASCVD later in life. Because apolipoprotein-B containing lipoproteins appear to play a key causal role in the development and progression of atherosclerosis, interventions to lower LDL-C or non-HDL-C may hold promise for influencing atherosclerosis progression.¹⁹⁸ Clinical trials of high-intensity statins and proprotein convertase subtilisin-like/kexin type 9 monoclonal antibodies have shown that atherosclerotic plaque volume can be reduced in middle-aged adults with more advanced stages of atherosclerosis.¹⁹⁹ However, animal data suggest that intensive LDL-C lowering in younger high-risk adults may have an even greater impact on plaque regression and the potential to normalize arterial function.^{198,200} Validation of this approach in cardiovascular outcomes trials would also lay the groundwork for an early-intervention approach to lifetime ASCVD prevention. Notably, proprotein convertase subtilisin-like/kexin type 9 inhibition provides a promising target for such interventions because it is the key regulator of LDL-C receptor expression, though available drugs are costly.²⁰¹

Some evidence suggests regression of early atherosclerosis, reduction in arterial stiffness, and normalization of endothelial function could also prevent or delay the later development of hypertension.^{202–205} The urgency to reduce premature heart failure, stroke, and chronic kidney disease among young adults is increasingly recognized; multiple young adult hypertension trials are in progress.^{206–208} Several statin trials have found reductions in blood pressure and hypertension incidence in statin-treated patients.²⁰⁹ Proprotein convertase subtilisin-like/kexin type 9 inhibitors have also recently been shown to improve endothelial function in proportion to the magnitude of LDL-C lowering.²¹⁰ Similar approaches have been taken to prevent progression of hypertension or improve subclinical markers of future heart failure.²¹¹ The new blood pressure guidelines present new opportunities to discuss and launch trials to improve blood pressure management in young adults, including studies of interventions to improve treatment adherence that have the potential to prevent millions of CVD events.²¹² In individuals with DM, ongoing trials seem reassuring with respect to cardiovascular safety of newer agents such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. These agents may prove to be significant adjunct therapies in the prevention of CVD in young adults with obesity and DM.

Imaging data, coupled with risk factor, genetic, and metabolomics characteristics, could potentially be used to characterize the phenotypes of the young adults most responsive to intensive LDL-C-lowering therapies, antihypertensive therapy, or for planning future definitive trials with cardiovascular outcomes,¹⁹⁸ particularly if the markers have strong associations with future events. Imaging data are available to understand the factors influencing progression of atherosclerosis throughout the lifespan. No data are available regarding the impact of earlier treatment of atherosclerosis. Intimal medial thickness has been assessed in European ancestry children and younger adults, with limited long-term follow-up or treatment response data. Coronary artery calcification measured by computed tomography is associated with the presence of advanced plaque and increased risk of cardiovascular events, but cannot be used to assess response to therapy.^{213–215} Moreover, coronary artery calcium occurs later in the course of atherosclerosis progression and may be absent in high-risk younger adults with a substantial burden of noncalcified plaque.¹⁹⁷ Computed angiographic tomography has emerged as the preferred choice for evaluating and characterizing composition of coronary plaque, and strongly predicts ASCVD events and response to therapy.^{216–223} The latest generation of scanners has less radiation exposure than a mammogram. Newer noninvasive technologies such as positron emission tomography can assess inflammation and are promising for understanding earlier stages of plaque development.¹⁹⁷ A similar process could be followed to examine cardiac function markers, as assessed by echocardiography and magnetic resonance imaging, in relation to future heart failure risk.^{224,225}

RESEARCH OPPORTUNITIES

Given the demonstrated necessity of improving the CVH of young adults, prioritizing research areas will be critical. Future research should focus on identifying effective strategies that improve control of risk biomarkers via evidence-based strategies and promote healthy lifestyle behaviors. Emphasis should be placed on young adults who experience health disparities and are at highest risk for early cardiovascular events, as they often experience inadequate education, lower SES, exposure to psychosocial stress, and identification as part of a racial/ethnic minority population.²²⁶ Given the unique characteristics of today's contemporary young adults, future research should integrate cutting-edge digital approaches into all aspects of study design. This could include leveraging innovative assessment methods that easily integrate patient self-entry of data, transmit home blood pressure measurements, and automatically capture dense

digital data from wearable devices (eg, physical activity sensors, sleep trackers, continuous glucose monitors). The use of population management tools to capitalize on the wealth of information available from electronic health records has the potential to improve reach and recruitment of high-risk young adults. Next steps in leveraging technology include exploring how digital tools can extend traditional retention strategies (eg, use of reminders, financial incentives) and can inform emerging strategies that build participant trust.^{227–229}

Here, we prioritize 3 critical research areas: primordial prevention, primary prevention, and implementation science. First, research on primordial prevention—the improvement in population-based metrics such as tobacco use, obesity prevalence, dietary choices, physical activity, and sleep habits—could identify new ways to lower the prevalence of cardiovascular risk factors in the population. Tobacco control provides many examples of strategies to lower population risk exposure, as does the decades-long success in lowering cholesterol levels in the population via awareness of excess saturated fat intake and elimination of trans fats from the food chain. Public health intervention strategies to curb the obesity epidemic and improve engagement of young adults with preventive health care are promising opportunities.

Second, clinical trials of promising primary prevention strategies could identify new approaches to prevention of CVD in young adults, especially those with significant behavioral risk factors, genetic factors, and presence of subclinical cardiovascular dysfunction or vascular abnormalities. For example, these trials could target women with high-risk pregnancies or individuals with multiple risk behaviors or psychosocial stressors, such as exposure to childhood adversity. Potential outcomes include improvements in end-organ injury (eg, slowed atherosclerosis progression, improved vascular function, improved cardiac function, prevention of incident hypertension, prevention of renal injury) as well as reduction of early ASCVD events.

Third, implementation science studies could inform approaches to increase the uptake of effective primary prevention and risk factor control strategies for young adults with established risks (hypertension, dyslipidemia, DM) for whom evidence-based treatment guidelines exist. Gaps exist in recognition of risk, initiation of treatment, and adherence to treatment, some of which may be created by disparities based on race, ethnicity, gender, education, and lack of health insurance coverage. In young adults, an important question is whether it may be more useful to set implementation trials in community settings (eg, workplaces, pharmacies, beauty and barbershops, churches) rather than in medical clinics.

SUMMARY

This review summarizes discussions from a 2-day workshop in Bethesda, Maryland, in September 2017 to identify research challenges and opportunities related to the CVH of young adults (18–39 years old). There are substantial observational data documenting lack of progress in CVD prevention in this group, as evidenced by the significant prevalence of risk factors attributable to multiple contributors. Significant knowledge gaps remain concerning the ability of public health agencies and/or healthcare delivery systems to act on this information. Future research opportunities include understanding the influence of the substantial change in the lifestyles of young adults over the past few decades, addressing the lack of engagement of young adults in the healthcare system, developing interventions to mitigate health disparities, and addressing the paucity of clinical trials for both behavioral and pharmacologic interventions. Given strong evidence that the origins of chronic CVD begin at a young age, the greatest opportunity to eradicate heart disease in the future is likely primordial and primary prevention beginning in young adulthood, if not earlier.

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