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The Uncharted Frontier: Preventive Cardiology Between the Ages of 15 and 35 Years

Holly Gooding¹ and Heather M. Johnson²

¹Departments of Medicine and Pediatrics at Harvard Medical School, Division of Adolescent/Young Adult Medicine at Boston Children's Hospital, and Division of General Internal Medicine at Brigham and Women's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA

²Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health, H4/512 CSC, MC 3248, 600 Highland Avenue, Madison, WI 53792, USA

Abstract

It is well established that atherosclerosis, the pathological basis of cardiovascular disease (CVD), begins in childhood and progresses steadily between the ages of 15 to 35 years. These adolescent and young adult years are also marked by significant physiological, psychological, and sociodemographic changes that impact both CVD risk factor development and CVD prevention and treatment strategies. In this review, we highlight the importance of the *primordial* prevention of CVD risk factors before they ever occur and the *primary* prevention of CVD by treating CVD risk factors in this age group. Although the long time to first CVD event for most young people precludes the availability of clinical trials with hard end-points, findings from epidemiology, health psychology, health services research, and clinical trials with surrogate endpoints are discussed to inform an evidence-based approach to CVD prevention in adolescents and young adults.

Keywords

Adolescents; Young adults; Primordial prevention; Primary prevention; Risk factors

Introduction

Cardiovascular disease (CVD) remains the number one cause of death worldwide [1, 2•] despite decades of improvements in awareness and treatment. While prompt treatment of CVD events and secondary prevention of their recurrence remain important, to truly reduce the burden of CVD, we must improve the *primary* prevention of CVD by treating established CVD risk factors as well as the *primordial* prevention of those risk factors before they ever

Correspondence to: Holly Gooding.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

Conflict of Interest

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occur. In concordance with this view, the American Heart Association established the concept of *ideal cardiovascular health* in 2010 [3] based on the consistent epidemiologic finding that middle-age adults without any CVD risk factors demonstrate remarkably low risk of developing CVD later in life [4–7]. Unfortunately, it is exceedingly rare for middle-aged adults in the US have all seven ideal cardiovascular health factors, which include nonsmoking status, a normal body mass index (BMI), healthy dietary and physical activity patterns, and normal blood pressure, blood cholesterol, and blood glucose in the absence of drug treatment [2••]. While children, adolescents, and young adults fare better than older Americans in that they are more likely to have the physiologic factors that comprise ideal cardiovascular health, two important observations should give us pause. First, young people are even less likely than older adults to have ideal dietary habits (0.5 vs. 2.2 %) and about as likely to have ideal physical activity patterns (36.5 vs. 35.2 %) [2••]. This lack of ideal health behaviors will almost certainly translate into lower levels of physiologic cardiovascular health in the future. Second, a sharp decline is seen in the prevalence of ideal BMI and ideal blood pressure from the adolescent (ages 12–19) to the young adult (ages 20–39) years, with more steady declines seen in the prevalence of ideal blood cholesterol and blood glucose levels [2••]. In this report, we argue that for these epidemiologic reasons as well as for physiologic and psychological ones, the years between ages 15 and 35 hold great potential for the prevention of CVD and yet remain a largely uncharted frontier.

Adolescent and Young Adulthood as a Critical Window for CVD Prevention

Early Origins of Atherosclerosis

Early autopsy studies of young war veterans [8] and youth who died of accidental causes [9] established that atherosclerosis, the pathological process underlying CVD events, begins as early as 10 years of age. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, an autopsy study of 2876 individuals who died of accidental causes between the ages of 15 and 34 years, confirmed that early atherosclerotic lesions were present in the majority of 15-year olds and that the prevalence and extent of atherosclerosis increased steadily with advancing age [10]. Further, PDAY studies found that essentially, the same physiologic factors that comprise ideal cardiovascular health—BMI, non-HDL cholesterol, blood pressure, and blood glucose, along with smoking status—can be used to predict the likelihood of atherosclerosis in the coronary arteries and abdominal aorta in this age group [11]. In addition, a risk score comprised of these factors developed from the PDAY data predicts coronary artery calcium scores [12] and carotid intima-media thickness [13] in middle-aged adults in living cohorts. Similarly, the Bogalusa Heart study demonstrated that as the number of cardiovascular risk factors increases, so does the pathological evidence for atherosclerosis in the aorta and coronary arteries, even beginning in early childhood [14, 15]. Serial evaluations of subclinical atherosclerosis from childhood to young adulthood demonstrated that significant predictors for abnormal coronary artery calcium and increased carotid intima-media thickness were elevated BMI and blood pressure in childhood and increased BMI and lipid disorders in young adulthood [14].

A Time of Transition

As noted in the introduction, there appears to be a precipitous drop in cardiovascular health during the transition from adolescence to adulthood. In cross-sectional NHANES data, 45 % of adolescents ages 12–19 years have at least five ideal cardiovascular health components compared to just 33 % of young adults ages 20–39 years and only 10 % of adults ages 40–59 years [2••]. Similar declines are seen in longitudinal cohorts including the Cardiovascular Risk in Young Finns Study (CARDIA) and the Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) [16–18]. While some of this drop may be due to the physiology of aging, the fact that a small proportion of older adults are able to maintain full cardiovascular health argues against biological aging as the singular source of the decline. Rather, the behavioral choices made by youth as they transition to independent living play a key role in cardiovascular health persistence or desistence. There is growing evidence that these behavioral “choices” are well-established by adolescence, track strongly into adulthood, and differ greatly based on one’s socioeconomic resources in early life [19].

Referred to in social psychology as “emerging adulthood,” the twenties and thirties are the time when most people complete their primary schooling, secure employment, and begin childrearing [20]. These activities, understood by many to mark the transition to adulthood, may limit the financial, temporal, and psychological resources necessary for adherence to healthy diet and physical activity recommendations. While policy makers and researchers often refer to people in this age group as “young invincibles” [21], there is actually little data to support the notion that adolescents and young adults are any more likely than older adults to discount the impact of their current behaviors on future disease risk [22].

Young adults are also in a period of transition between pediatric and adult-centered models of care [23]. Their rates of health insurance and adherence to preventive health guidelines are the lowest of any age group [24]. These gaps in preventive care may make early recognition of elevated blood pressure [25], cholesterol [26], or glucose [27] less likely. Even when they are connected to regular primary care, their cardiovascular risk factors often remain undiagnosed due to a confluence of both patient and provider biases. Young adults with documented hypertension experience significant delays receiving this diagnosis [28], receiving counseling on lifestyle changes proven to reduce blood pressure [29], and starting pharmacologic treatment [30•]. Finally, conflicting pediatric and adult guidelines for the treatment of cardiovascular risk factors such as elevated cholesterol [31•] may lead to unnecessary confusion about when to initiate pharmacologic treatment in youth.

One additional consideration for this age group is the impact of their cardiovascular risk factor accumulation on future generations, as ages 15 to 35 are the prime reproductive years for women. Elevated body mass index at conception [32–34], excessive gestational weight gain [32, 33], and pregnancy complications such as preeclampsia [35•, 36] and gestational diabetes [37, 38] are all associated with elevated cardiovascular risk in the offspring of those pregnancies. Pregnant women may be particularly motivated to address cardiovascular risk factors that affect the health of their children [39]. Thus, investment in young women’s cardiovascular disease prevention in particular has the potential to lead to double the return.

Primordial Prevention of Cardiovascular Disease Risk Factors in Adolescents and Young Adults

Successful approaches for primordial prevention in adolescents and young adults require a focus on diet, exercise, lifelong tobacco cessation, and weight management [40]. Dietary intake is a major modifiable determinant of cardiovascular disease risk factors such as dyslipidemia, hypertension, and obesity [41, 42]. Unfortunately, sustained changes following dietary interventions have shown modest results and long-term follow-up (>12 months), and detailed adherence data is lacking [43].

Health benefits of exercise in adolescence include weight control, lower blood pressure, improved psychological wellbeing, and a predisposition to maintenance and/or increased physical activity into adulthood [44]. Physical fitness is consistent participation (four to five times per week) in activities that generate energy expenditures significantly above the resting level, and ideally, at least 50 to 60 % of maximal exertion [44]. While several cohort studies have documented a decline in physical activity during the transition to adulthood [45, 46], cross-sectional data from the National Health Interview Survey show encouraging increases in recent years in the proportion of young adults meeting physical activity recommendations [47]. The contribution of work-related physical activity to cardiovascular health, an important source of exercise as youth leave the world of organized or competitive sporting activities, remains a complex area in need of further study [48]. Nearly all tobacco use begins in adolescence and young adulthood [49], and this is a common time for transition from experimentation to daily smoking [50]. Fortunately, tobacco cigarette use has declined precipitously in the past decade [47], but other forms of tobacco use such as electronic cigarettes have greatly increased [51]. Whether this will translate into lower or higher rates of tobacco addiction is unknown. Ongoing education and counseling during routine clinical encounters with familial and social support decreases the probability that youth will start smoking behaviors [52].

Finally, the Coronary Artery Risk Development in Young Adults Study (CARDIA), which included white and black young adults (18–30 years old), demonstrated that participants who maintained a stable body mass index over time had minimal progression of cardiovascular risk factors and lower incidence of metabolic syndrome by middle-adult age, regardless of baseline BMI [53]. Unfortunately, in this same study, only 16.3 % of participants maintained consistently stable or decreased BMI over 15 years of follow-up [53]. In a separate analysis in the CARDIA cohort, young adults who had more cardiovascular health factors at ages 18–30 years or who improved their health factors with age were less likely to have coronary artery calcium in mid-adulthood [54•]. Ongoing focus on weight control and weight maintenance, combined with the other areas of primordial prevention during the transition to adulthood, could significantly impact population prevalence of cardiovascular risk factors.

Primary Prevention of Cardiovascular Disease in Adolescents and Young Adults

The goal of primary prevention of cardiovascular disease in any population is to impact the atherosclerotic disease process by treating established CVD risk factors, with a dedicated focus on preventing future cardiovascular morbidity and mortality [55]. Recent studies in older adults with intermediate risk for CVD have confirmed that treating elevated lipids and blood pressure leads to lower CVD event rates and lower mortality [56, 57]. The association of these same cardiovascular risk factors with atherosclerotic disease development in youth, as highlighted earlier, has now shifted the focus of primary prevention guidelines from solely older adults to younger populations. Unfortunately, randomized clinical trials of cholesterol or blood pressure treatment in youth with sufficient follow-up time to demonstrate a reduction in clinical cardiovascular events are unlikely given current funding cycles. This creates a major gap in evidence-based guidelines for CVD risk reduction, leading clinicians who treat younger populations to infer benefit from studies of older adults or of subclinical endpoints.

The data do show that rates of hypertension in the USA have increased over the last several decades among adolescents and young adults [58]. Even among this younger population, elevated blood pressure accelerates the development of atherosclerosis and contributes significantly to the pathogenesis of premature cerebrovascular accidents, heart failure, and renal failure [44, 59]. Among all the risk factors cited by the Framingham Heart Study, hypertension has been identified as one of the most potent antecedents of cardiovascular events [44].

The level of severity and duration of blood pressure elevation that causes target-organ damage has not been established. Clinical studies demonstrate that elevated blood pressure in adolescence is associated with abnormal carotid intima-media thickening [60, 61] and reduced large artery compliance in young adults [62]. The prevalence of left ventricular hypertrophy is greater than 30 % among adolescents with mild but untreated elevated blood pressures [63, 64]. Furthermore, longitudinal cohort studies demonstrate that participants treated to goal blood pressure with antihypertensive agents still have a higher prevalence of end-organ damage compared to those at goal blood pressure without the use of medications [65]. While prevention of hypertension or resolution with lifestyle changes is thus clearly the goal, indications to initiate pharmacotherapy and reduce known sequelae of subclinical cardiovascular disease include symptomatic hypertension, secondary hypertension, established hypertensive target-organ damage, and failure of non-pharmacologic measures [59].

Unfortunately, the incidence of obesity and diabetes mellitus is increasing in younger populations, thus increasing the risk of macro- and microvascular complications earlier in life [66, 67]. A cross-sectional study evaluated vascular health among youth, comparing individuals with a lean BMI (<85th percentile), obese BMI (>95th percentile), or with type 2 diabetes mellitus (T2DM) [66, 68]. Those with T2DM had significantly greater carotid intima-media thickness and stiffer carotid arteries than lean individuals. The presence of

either T2DM or obesity contributed independently to adverse changes in carotid structure and function [66, 68].

The increased prevalence of obesity over the past 30 years has also been associated with an increased prevalence of lipid disorders among young people [69]. Most predominantly are higher levels of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (HDL-c) [69]. Although lifestyle modifications are recommended across age groups, the current US treatment paradigm focuses on using pharmacologic therapy primarily in middle-aged and older adults, except in children with genetic dyslipidemias (e.g., familial hypercholesterolemia [FH], familial combined hyperlipidemia) [70]. The recent 2013 American College of Cardiology/American Heart Association *Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults* [71] provided recommendations for statin initiation in patients 40 to 75 years of age, leaving treatment of younger populations up to clinician judgment. However, youth with nongenetic dyslipidemias are at higher risk of premature atherosclerosis, especially with comorbid risk factors of diabetes mellitus and/or obesity [12, 72]. Randomized clinical trials with statin therapy in children and adolescents with FH demonstrated significant findings of slowed atherosclerosis progression [73], even into young adulthood [74], without significant adverse events [73, 74]. These findings have begun to shift the focus of primary cardiovascular disease prevention to all adolescents and young adults.

Cardiovascular Disease Risk Assessment in Younger Populations

Individual treatment of cardiovascular risk factors requires understanding important differences between a patient's *biological* age vs. their *vascular* age when evaluating the risks and benefits of adding pharmacologic therapy to ongoing lifestyle modification in younger populations [72]. Unfortunately, cardiovascular disease event risk in young adults is underestimated despite the high prevalence of cardiovascular risk factors [75]. In 2013, the American College of Cardiology and the American Heart Association released new guidelines for global cardiovascular risk assessment in asymptomatic adults 40 to 70 years old, with a class I indication to perform a 10-year risk assessment [76]. However, validation of the Framingham Risk Score demonstrated an inability to perform accurate 10-year risk assessments in younger adults (<40 years old) despite a high-risk factor burden [77]. Therefore, the ACC/AHA risk assessment guidelines also provided a class IIb indication to perform a 30-year or lifetime risk assessment starting at 20 years old, using traditional cardiovascular risk factors (age, sex, total cholesterol, HDL-c, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, and current smoking) [76] for patients without a high short-term (10-year) risk. These guidelines build on evidence that even with a lower 10-year risk, young adults with multiple risk factors can have a high lifetime risk of cardiovascular events and greater incidence of atherosclerotic disease progression compared to young adults of the same age with a low lifetime risk [78]. The National Longitudinal Study of Adolescent Health demonstrated that the average 30-year risk for hard events (coronary death, myocardial infarction, fatal and nonfatal stroke) was 10.4% (95 % confidence interval (CI): 10.1–10.7) among 14,333 participants (mean age 28.9; 95 % CI 28.6–29.1) [79]. Unfortunately, the majority of young adults are not aware of their short- or long-term cardiovascular disease risk [75], or may be misled by a low 10-year risk

decreasing motivation and adherence to cardiovascular disease prevention recommendations [77]. Assessment of lifetime risk among young adults can guide patient-provider communication and assist with informed decision making that may include more aggressive pharmacologic treatment for cardiovascular risk factors [77, 78].

Emerging Methods to Deliver Cardiovascular Prevention to Adolescents and Young Adults

Despite the urgent need to alter healthcare delivery to support primordial and primary prevention of CVD, questions remain about identifying, implementing, and disseminating effective interventions in this age group. Effective interventions must address the multiple influences on health-related attitudes, beliefs, and behaviors, including individual, educational, socioeconomic, and environmental factors. Current evidence supports the need to tailor lifestyle education and prescriptions for behavior change [42]. This can be achieved by delivering education and counseling at appropriate health literacy levels, tailoring topics to adolescents' and young adults' knowledge gaps, needs, and interests [42, 80], addressing health behavior at every healthcare encounter, identifying and assisting with necessary resources, and involving significant others, family, and peers as partners in behavior change [42].

As noted earlier, these are major times of transition in the life course and efforts must be made to meet young people in their evolving contexts. Family and school-based programs are important for younger teens. While data on school-based programs to mitigate CVD risk behaviors are mixed [81, 82], recent studies utilizing a positive youth development framework [83] to promote cardiovascular health in the school context have shown some promise [84]. For college-bound youth, campus efforts to combat the emergence of sedentary behaviors [85, 86], suboptimal nutrition patterns [87, 88], weight gain [85, 89], and tobacco dependence [90] may be particularly important. Finally, for youth transitioning to employment, workplace wellness programs [91] aimed specifically at the developmental needs of young adults [92] will be needed.

One promising method for reaching this population with prevention efforts is social media, a widely popular means of interaction that allows the sharing and exchange of information with nearly instant responses [93]. Research and implementation of social media interventions to engage, educate, and provide self-management support is growing. Ideally, social media can be used to supplement preventive education and counteract healthcare system, staff, and patient barriers to timely, recurrent education [29, 93]. Despite the promise of social media and other novel interventions, critical healthcare delivery and policy challenges remain. Current reimbursement models do not support healthcare system and provider investment in social media; however, this may change as incentives shift for patient engagement and value-based outcomes [93]. Additionally, the integration of social media platforms with electronic health records is lacking and/or insufficient [93]. Privacy and confidentiality are concerns for both healthcare systems and patients. Previous social media research among young adults has highlighted concerns about using social media for healthcare interactions due to fear of victimization by peers and cyber bullies [80, 94, 95].

Conclusion

Prevention of CVD risk factor development and progression in 15- to 35-year olds holds a great promise and is truly an uncharted frontier. Data from randomized controlled trials of CVD prevention strategies with sufficient follow-up from adolescence and young adulthood to demonstrate a reduction in CVD events is unlikely in the current funding climate. However, we believe the preponderance of data from pathobiological studies, epidemiologic cohorts, and trials with surrogate end-points demonstrates the time is now to invest in CVD prevention during this critical time in the life course.

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