Circulation Research

EARLY DETERMINANTS OF CARDIOVASCULAR DISEASE COMPENDIUM

# Physical Activity Over the Lifecourse and Cardiovascular Disease

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**ABSTRACT:** Despite improvements in cardiovascular care in recent decades, cardiovascular disease (CVD) remains a leading cause of death worldwide. At its core, CVD is a largely preventable disease with diligent risk factor management and early detection. As highlighted in the American Heart Association's Life's Essential 8, physical activity plays a central role in CVD prevention at an individual and population level. Despite pervasive knowledge of the numerous cardiovascular and noncardiovascular health benefits of physical activity, physical activity has steadily decreased over time and unfavorable changes in physical activity occur throughout people's lives. Here, we use a lifecourse framework to examine the evidence reporting on the association of physical activity with CVD. From in utero to older adults, we review and discuss the evidence detailing how physical activity may prevent incident CVD and mitigate CVD-related morbidity and death across all life stages.

**Key Words:** cardiovascular disease ■ coronary heart disease ■ exercise ■ myocardial infarction ■ physical activity

At the cornerstone of cardiovascular disease (CVD) prevention are modifiable, lifestyle health behaviors, including habitual physical activity.[1,2] There is strong scientific evidence supporting the association of physical activity with reduced risk of cardiometabolic risk factors and clinical end points.[3] For individuals with established CVD, physical activity attenuates progression, reduces the risk of developing another chronic condition, and improves quality of life and physical functioning.[3] Based on this evidence, physical activity is included as a component of the American Heart Association's Life's Essential 8 metric used to monitor cardiovascular health on the population level.[4]

Although the benefits of physical activity are well-understood, declines in physical activity across the lifecourse are well documented.[5] Biological, behavioral, or psychosocial factors have been shown to be associated with physical activity changes across the lifecourse.[6] These changes can also be triggered by major life events[7] that can temporarily interrupt or permanently change habitual behaviors.[7,8] Across the lifecourse, even short-term reductions in physical activity can accumulate and translate into increased susceptibility to cardiometabolic risk factor development, risk of subsequent nonfatal or fatal CVD events, related comorbid conditions, or premature death.[9] As defined in lifecourse epidemiology framework, the accumulation of risk concept posits that exposures, including inadequate physical activity, gradually accumulate and cause damage to biological systems as the duration or severity of the exposure accumulates over the lifecourse leading to long-term disease or disability.

However, this evidence and related interpretations are rarely contextualized using a lifecourse framework. In a recent editorial, Mielke[10] stated, "much assumed knowledge in this field is based on methods that empirically fail to consider that [...] physical activity and sedentary behavior constantly change across the lifespan". Specifically, conclusions are often drawn based on a single assessment of physical activity obtained during an arbitrary period (eg, midlife due to its proximity to median age of CVD onset) or repeated assessments obtained during a follow-up period that does not reflect a given life stage, a lifecourse transition, or the natural history of CVD progression. As a result, questions pertaining to the importance of timing and accumulation of the physical activity exposure across the lifecourse to optimize cardiometabolic health remain unresolved.

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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ARIC** | Atherosclerosis Risk in Communities Study |
| **CARDIA** | Coronary Artery Risk and Development in Young Adults |
| **CHD** | coronary heart disease |
| **CHS** | Cardiovascular Health Study |
| **CVD** | cardiovascular disease |
| **FHS** | Framingham Heart Study |
| **HDL** | high-density lipoprotein |
| **IMT** | intima-media thickness |
| **LDL** | low-density lipoprotein |
| **MI** | myocardial infarction |

Therefore, the primary objective of this review is to evaluate the evidence reporting on the associations of physical activity with CVD progression by applying a lifecourse framework. Based on the gaps in current evidence, opportunities for future research are highlighted and discussed.

## PRIMER ON THE NATURAL HISTORY OF CARDIOVASCULAR DISEASE

From birth, everyone is at risk for the development of CVD (Figure; Table 1). Most research on CVD development over the lifecourse has focused on atherosclerosis. Early stages of atherosclerotic disease are present in a substantial number of neonates, indicating the underlying processes may begin before birth.[11] As individuals progress through infancy and childhood, there is wide variation in the exposure to cardiovascular risk factors which results in varying trajectories of CVD. Related to this review, the association between sedentary behavior and atherosclerosis is mediated through NADPH oxidase activity and enhances reactive oxygen species in the vasculature.[12] Therefore, establishing a physically active lifestyle, and minimizing prolonged sedentary time, during childhood is increasingly seen as a powerful strategy for life-long CVD prevention.[13] During young adulthood, atherosclerosis may progress to fibrous plaques and the development of a necrotic core. Clinical manifestations of coronary atherosclerosis most commonly present in middle-aged adults as atherosclerotic lesions may calcify, hemorrhage, ulcerate, and thrombose, and in some cases result in ischemic events such as myocardial infarction (MI) or stroke. Middle-aged and older adults may suffer from the late stages of CVD with elevated risk of adverse events, reduced functional capacity, and death.

Although other cardiovascular and cardiometabolic diseases are also generally progressive through the lifecourse, they may present in any life stage and in some instances may fluctuate with behavioral modifications or therapeutic intervention. For example, a person may develop childhood obesity and subsequently develop diabetes in young adulthood. With weight loss (medical or surgical), hyperglycemia may resolve, and the person may return to a healthy weight.

## ROLE OF PHYSICAL ACTIVITY ON BIOLOGICAL PATHWAYS

The association of physical activity on CVD events is thought to be primarily mediated through impacts on CVD risk factors such as body weight, hypertension, diabetes, and lipids.[15] Overall, the cellular mechanisms by which these benefits are affected by physical activity are incompletely delineated. Hypertension appears to be prevented by physical activity via effects on sympathetic nervous system activity, renin-angiotensin system activity, sodium handling, and improved endothelial function[16] and does not appear to be driven by maintenance of a healthy weight.[17] Exercise improves insulin sensitivity and glucose uptake in skeletal muscle, helping reduce incidence of diabetes.[18] Aerobic physical activity decreases triglyceride and LDL (low-density lipoprotein) concentrations while increasing HDL (high-density lipoprotein) concentrations.[19] Further research is needed to better understand the mechanisms by which CVD prevention is achieved through physical activity.

## HISTORICAL AND CONTEMPORARY METHODS TO ESTIMATE PHYSICAL ACTIVITY

### Occupational Classifications or Job Types

Research related to the role of physical activity on CVD, specifically coronary heart disease (CHD), began in the late 1940s with the seminal work of Dr Jeremy Morris,[20] when little was known about the etiology of CHD. To explore the potential causes of CHD, the London Transport Study was conducted that compared the incidence of fatal CHD between 2 job categories among men aged 35 to 64 years; the conductors (active; walked up and down the bus aisles and stairs selling tickets and collecting passenger fares) and the drivers (nonactive) of London's double-decker buses.[21] The age-standardized rates of sudden death and death within the first 3 months that resulted from the first MI per 1000 men per year was lower among the more active conductors when compared with the drivers. Findings from studies relying on job classification to estimate physical activity were replicated in a second set of government workers representing high and low active occupations (postmen versus telephonists)[20] and among US railroad workers in the early 1960s[22] and longshoremen in the early 1970s.[24]

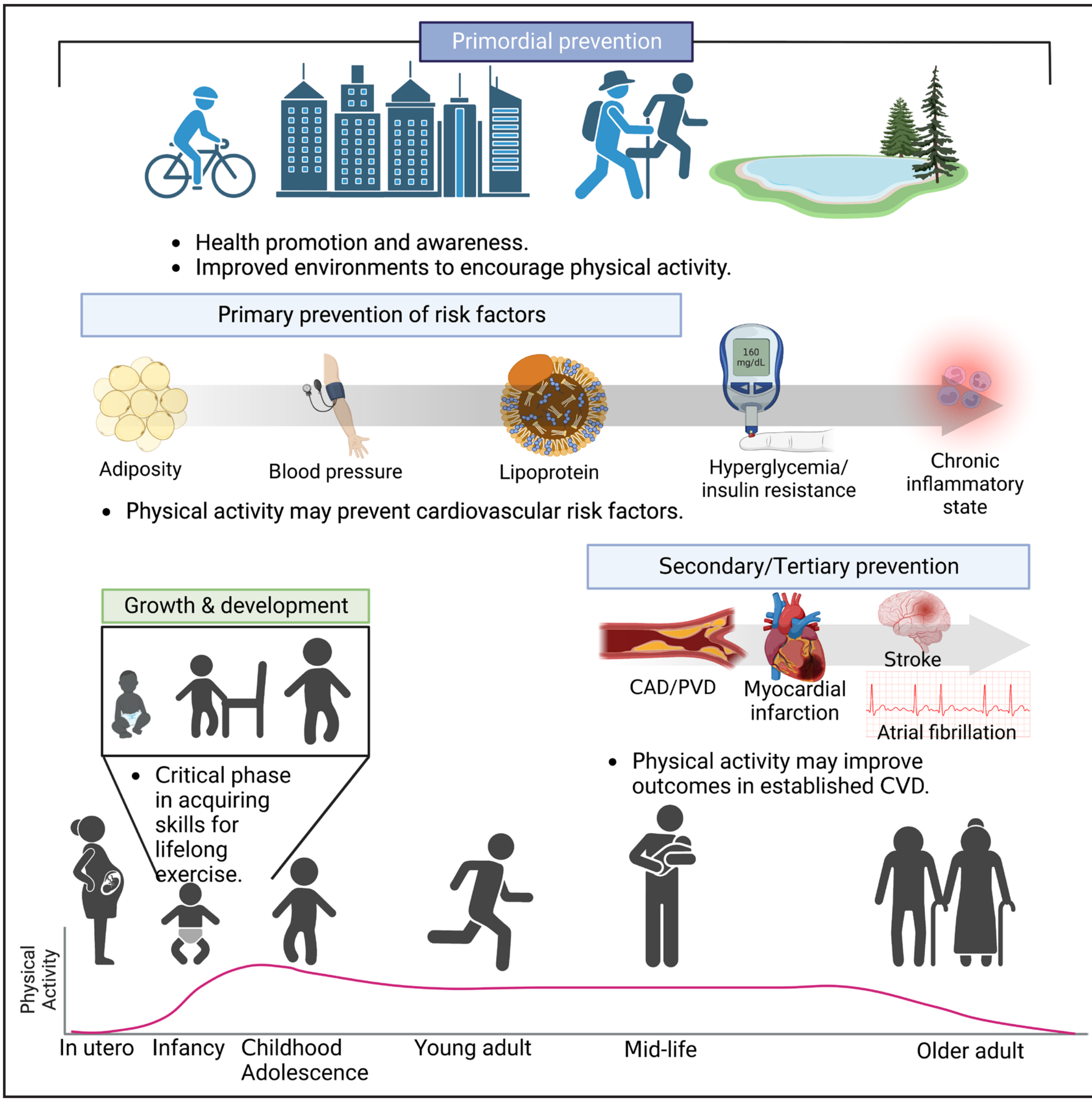


**Figure. Physical activity and prevention of cardiovascular disease (CVD) over the lifecourse.**
Physical activity plays central roles in the primordial, primary, secondary, and tertiary prevention of CVD throughout the lifecourse. CAD indicates coronary artery disease; and PVD, peripheral vascular disease.

## Sports Participation and Exercise During Leisure Time

However in the 1960s, as jobs became increasingly more sedentary, it became apparent that relying on occupational categories or job types to assess physical activity to examine associations with cardiovascular risk factors and disease would no longer be appropriate[23,24] because the assessment strategy should elicit information on the largest contributors of energy expenditure for a given population.[25] Researchers transitioned to report-based methods to estimate physical activity during discretionary periods of the day. For example, Harvard Alumni Study investigators developed a questionnaire that assessed (1) flights of stairs climbed each day, (2) city blocks walked each day, and (3) sports (or recreational activity types) played in the past week.[26] From this information, a physical activity summary estimate, expressed in kilocalories per week (kcal $wk^{-1}$), was derived. With this questionnaire, they found that those who expended less than 2000 kcal $wk^{-1}$ had a 64% higher risk of first MI when compared to the more active group (≥2000 kcal $wk^{-1}$).[26] The investigators extended these findings by demonstrating an inverse dose-response association with risk of death up to a dose of 3500 kcal $wk^{-1}$ (22% to 54% risk reduction) when compared to participants extending <500 kcal $wk^{-1}$.[27]

Since then, the evidence has greatly expanded to document similar inverse associations of physical activity with cardiovascular risk factors, events, and disease in younger (children) or older age groups, women, and under-represented minority groups with many studies

**Table 1. A Primer on the Natural History of Cardiovascular Disease**

| Stages of CVD progression | Underlying | Susceptible | Subclinical | Clinical | Recovery, disability, or death |
|---|---|---|---|---|---|
| Stages of prevention | Primordial: Risk factor reduction targeted towards the entire population through a focus on social and environmental conditions. | Primary: Risk factor reduction aimed at a susceptible population or individual. | Secondary: Early disease detection (screening) | Tertiary: Disease management, reduction of disability, and comorbidities | |
| | Goal: Reduce population prevalence of risk factors. | Goal: Prevent development of subclinical disease. | Goal: Diagnose disease in subclinical phase to improve prognosis. | Goal: Reduce severity of disease and any adverse sequelae. | |
| Examples | Sidewalks to promote activity | Exercise programs for overweight individuals | Cardiopulmonary exercise testing | Cardiac rehabilitation | |
| | Health promotion campaigns | | FitnessGram | | |
| | | | Physical activity readiness screeners | | |
| Life stage | In utero | | | | |
| | Infancy | | | | |
| | Early childhood | | | | |
| | Childhood and adolescence | | | | |
| | Young adults | | | | |
| | Midlife | | | | |
| | Older adults | | | | |

Using a disease progression framework alongside a lifecourse framework demonstrates the applicable prevention stages for each life stage.[14] Here we classify stages of prevention using epidemiology terminology, recognizing these are different from what is used in clinical guidelines.

developing their own physical activity questionnaires (eg, Physical Activity Questionnaire for Older Children,[28] Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire,[29] Women's Health Initiative Physical Activity Questionnaire,[30] and Modifiable Activity Questionnaire[31]). Most of these questionnaires are structured to elicit information on the frequency and duration of physical activity, either by using broad intensity categories or specific activity types, within a specified recall time frame. With information on frequency, duration, and intensity, summary estimates can be derived that are expressed as either kcal $wk^{-1}$ or metabolic equivalents of task minutes (or hours) per week (metabolic equivalents of task min $wk^{-1}$), or min $wk^{-1}$ within broad intensity categories (eg, moderate-intensity min $wk^{-1}$). These are common summary estimates reported in the literature; however, there are deviations that do not represent the direct product of these physical activity characteristics (eg, ARIC [Atherosclerosis Risk in Communities Study] Baecke Physical Activity Questionnaire,[32] CARDIA [Coronary Artery Risk and Development in Young Adults] Physical Activity History,[33] Physical Activity Questionnaire for Older Children[28])

## Daily Accumulated Movement

Self-report methods are prone to error because of inaccurate recall, incomplete ascertainment (eg, higher intensity, leisure-time physical activity), and prevarication bias,[34] which has led researchers to explore alternative assessment methods. In 1965, the Japanese Yamax company designed the 10 000 steps meter as 10 000 steps were thought to be related to a reduced risk of CHD.[35] The step-counting technology improved in accuracy over time, and in the 1990s the Digi-walker (DW-500) pedometer was released. Since then, step metrics, including steps per day and stepping rate (peak 30 minutes or the highest number of steps accumulated over 30 minutes) have become acceptable estimates of physical activity volume and intensity.

As the step-counting technology in pedometers improved, researchers developed a type of wearable device that leveraged the acceleration and deceleration of the trunk to characterize human movement[36]; the characteristic of physical activity behavior.[37] In 1979, the Large-Scale Integrated Motor Activity Monitor was developed to estimate physical activity in epidemiological research.[38] The subsequent advancements in technology not only improved the accuracy of accelerometers but also made this assessment method more feasible to implement in population-based studies.[39] This transition was perhaps stimulated by the implementation of the ActiGraph 7164 accelerometer into the 2003 to 2004 and 2005 to 2006 National Health and Nutrition Examination Survey cycles.[40] Since then, several large cardiovascular disease cohort studies including CARDIA (2005–2006, 2015–2016, and 2020–2022) have supplemented report-based estimates of physical activity with accelerometry measures, including both research grade and consumer-based devices (eg, Fitbit). The continuous data sampling capabilities of accelerometers allow for derivation of more traditional estimates (eg, moderate to vigorous intensity physical activity min $wk^{-1}$ using established threshold values applied to count data[41]) or novel estimates (eg, activity fragmentation[42]).

Over 7 decades of research, measurement methods have improved far beyond use of occupational categories to provide crude estimates of physical activity within a single domain (Table 2). Modern assessment strategies provide researchers with endless opportunities to derive more granular phenotypes of physical activity behavior to examine cardiovascular risk and disease outcomes across the lifespan. In many instances, the selected assessment strategy is also used to elicit information on the prevalence of meeting (or not meeting) physical activity recommendations pertinent to each life stage (Table 3).

Despite continuous advances in strategies to assess physical activity and related constructs, there is not a perfect, "one-size fits all" method. Report-based assessments, including recall questionnaires, are widely available with minimal cost but have associated limitations.[34] Furthermore, although questionnaires have been developed, evaluated, and used to estimate physical activity behavior in individuals of all ages, they have limited utility in young children (≈8 years of age[28]) and those living with intellectual disabilities and cognitive impairment. Among these population subgroups, proxy reports of physical activity are often obtained by parents or caregivers. Similar to report-based methods, device-based strategies also have limitations. For example, pedometers appear to be less accurate at slower gait speeds,[45] which is of particular relevance to children[46] and older adults.[47] Commercial wearable accelerometers provide generally reliable estimates of step counts, yet are prone to undercounting steps in free-living settings,[48] particularly among older adults.[49] Wearables are also less reliable in estimates of energy expenditure[48] raising concerns about determining activity intensity. Research grade accelerometers more accurately estimate physical activity-related energy expenditure[50] or daily accumulated time spent on intensity categories but are least accurate in detecting nonambulatory physical activities (eg, free-play in young children or tai chi in older adults) and are reliant on prediction equations or threshold-based approaches, for example.

## PHYSICAL ACTIVITY AND PREVENTION OF CVD ACROSS THE LIFECOURSE

Throughout this review we have chosen to discuss levels of prevention using terminology from epidemiology (Table 1).[14] Effective physical activity promotion at the population level requires use of an ecologically-based multilevel framework incorporating aspects of land use, transportation, recreational, school, worksite, and home environments.[51] Thus, primordial prevention strategies require a strong partnership between communities, academia, government, nonprofit, healthcare organizations, and for-profit organizations. In addition, strong partnerships with media and legislation (federal, state, and local) can also help facilitate these population-level strategies. For example, the US Department of Health and Human Services Move Your Way[52,53] campaign provides free tools and resources to promote the U.S. Physical Activity

**Table 2. Evolution of Physical Activity Measures in Research**

| | Occupation | Leisure | Transport | Household/self-care | Assessment method | Physical activity estimates |
|---|---|---|---|---|---|---|
| 1940–1950s |  | | | | Job type | Low, moderate, high active |
| 1960–1980s |  |  |  | | Questionnaire | kcal $wk^{-1}$ |
| | | | | | | MET min $wk^{-1}$ |
| | | | | | | min $wk^{-1}$ |
| 1990s |  |  |  |  | Questionnaire (sample specific) | kcal $wk^{-1}$ |
| | | | | | | MET min $wk^{-1}$ |
| | | | | | | min $wk^{-1}$ |
| 1990s |  |  |  |  | Pedometer | steps $day^{-1}$ |
| 2000s |  |  |  |  | Accelerometer | counts min $wk^{-1}$ |
| | | | | | | min $wk^{-1}$ |
| | | | | | | steps $day^{-1}$ |
| | | | | | | Novel metrics |

Representation of how physical activity research has progressed from quantifying an individual's amount of physical activity by job type to wearable monitors. MET indicates metabolic equivalents of task.

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**Table 3. Summary of Physical Activity Guidelines Across the Lifecourse**

| Life stage | Recommendation | Source |
|---|---|---|
| In utero | 150 min wk$^{-1}$ of moderate-intensity physical activity for pregnant women | *Physical Activity Guidelines for Americans*, Second Edition[3]<br>American College of Obstetricians and Gynecologists[43] |
| Infancy (<1 y) | 30 min d$^{-1}$ of prone position tummy time | World Health Organization[44] |
| Early childhood (1–2 y) | 180 min d$^{-1}$ of any intensity physical activity | World Health Organization[44] |
| Early childhood (3–4 y) | 180 min d$^{-1}$ of any intensity physical activity of which 60 min is moderate-vigorous intensity | World Health Organization[44] |
| School-age children and adolescents (6–17 y) | 60 min d$^{-1}$ of moderate-vigorous intensity physical activity | *Physical Activity Guidelines for Americans*, Second Edition[3] |
| Young adults (18–44 y) | 150–300 min wk$^{-1}$ of moderate-intensity physical activity odds ratio<br>75–150 min wk$^{-1}$ of vigorous-intensity physical activity | *Physical Activity Guidelines for Americans*, Second Edition[3] |
| Midlife (45–64 y) | | |
| Older adults (≥65 y) | | |

Guidelines for all people across all life stages and for health professionals to share with their patients, students, and communities. In 2020, the American Heart Association released a policy statement summarizing initiatives across federal, state, and local agencies to encourage creation of built environments to promote active transportation to encourage physical activity.[54,55] As such, primordial prevention strategies aimed to increase physical activity are relevant to all individuals, regardless of age, and should be at the forefront of CVD prevention efforts.

## IN UTERO

The prevention of CVD may begin as early as during fetal development. In addition to being preprogrammed by genetics, fetal development is reliant on the pregnant person's health status, environment, and behaviors. Those with uncomplicated pregnancies can engage in aerobic and resistance exercise but may need some modification, with a reduction in high exercise volumes and weight-bearing exercise in late pregnancy. During any period of pregnancy, resistance exercise in the supine condition may not be recommended on the basis of low-quality evidence from observational studies which suggested a potential increased risk of adverse events for the fetus.[56]

### Primary Prevention

During fetal development, the circulatory system begins to take shape. Exercise during pregnancy has been shown to increase fetal heart rate variability and other favorable measures of autonomic function.[57] These benefits may persist after birth as infants born to persons who exercised had higher heart rate variability at one month of age.[58] Few studies have assessed these outcomes and, therefore, there is limited evidence supporting the role of prenatal exercise on development of the fetal cardiovascular system. Exercise during pregnancy also reduces the risk of gestational diabetes, excess weight gain, preeclampsia, and preterm labor.[56] The fetal origins of disease hypothesis suggests that offspring exposed to exercise throughout gestation may have lower risk of developing diseases later in life, such as obesity and diabetes. But evidence supporting this hypothesis is lacking and confined to few observational studies.[59] We will need randomized controlled trials of exercise during pregnancy with long-term follow-up of the offspring to provide strong evidence for these suggested benefits.

## INFANCY AND EARLY CHILDHOOD (BIRTH TO 5 YEARS)

Infancy, encompassing birth to 12 months, is a period of rapid growth and development. By one year of age, birthweight has tripled. Major gross motor development milestones include rolling over around 6 months, crawling around 9 months, and pulling up to stand and first steps around 12 months. By the toddler period, 1 to 2 years of age, a child begins independently walking, jumping, and playing. Continued physical and motor skill development during early childhood, ages 3 to 5 years, or the preschool years, has many health implications.[60] Infants and young children are entirely reliant on care providers; thus, the home and childcare environment play important roles in physical activity levels at this life stage.

Congenital cardiovascular defects are estimated to affect 1% of U.S. infants each year,[61] increasing their risk for CVD. In addition to structural defects present at birth, birth weight can be associated with future CVD progression. A recent meta-analysis found birth weight has a U-shaped association with adulthood CVD. Infants of low birth weight (<2500 g) and high birth weight (>4000 g) have increased risk for CVD in adulthood.[62] Birth weight between 3000 and 4000 g had the lowest risk of future

CVD. During infancy and early childhood, the development of fatty streaks (earliest visible stage of atherosclerosis characterized by lipid-engorged macrophages and T lymphocytes in the intima) and the obesity trajectory begins.[63] Rapid weight gain during the first 2 years is associated with later obesity.[64] The prevalence of US children under 2 years that have high weight for length (a measure of obesity) is ≈9%.[65] By preschool years, the prevalence of obesity is ≈14%.[65] The incidence rate for obesity is higher during early childhood than at any other time in the lifecourse, and preschool-aged children living with overweight by age 5 years have 4× the odds of obesity by adolescence than those with healthy weight.[66] Similarly, low birth weight, having a rising obesity trajectory through early childhood, and having obesity throughout early-to-late childhood increases odds of having hypertension in adolescence and young adulthood compared to a stable normal weight trajectory.[67] Preschool children living with overweight/obesity and low physical activity had 3.8 (95% CI, 1.6–8.6) higher odds of elevated blood pressure compared to healthy weight, physically active preschool-aged children.[68] There were no significant differences in blood pressure among physically active preschool-aged children living with overweight/obesity or healthy weight preschool-aged children with low physical activity compared to healthy weight, physically active children.[68]

### Primary Prevention

At this life stage, physical activity is paramount to combat pediatric obesity to decrease cardiometabolic risk factors and subsequent health outcomes. The direct association between physical activity and other CVD risk factors remains limited with evidence inconsistent.[69]

More research is needed to understand how early childhood physical activity may impact subclinical development of CVD. Birth cohorts should consider adding measurement of physical activity during infancy and early childhood, particularly device-based tools. Inflammatory markers for CVD are understudied in this life stage.

## CHILDHOOD AND ADOLESCENCE (6–17 YEARS)

Childhood and adolescence are distinguished as the school-age period. Children continue to develop fine motor skills and by early adolescence may begin to play organized sports.[70] Increases in muscle mass, strength, and cardiorespiratory fitness continue during adolescent development.[70] For those living with congenital defects, there are guidelines in place for participation in competitive sports or high-intensity training[71]; however with physician guidance, all ages should maintain active lifestyles.[72] At this age, home, school, and extracurricular activities are significant locations for physical activity, and behavior is influenced by adults and their peers.

Among US children and adolescents, the prevalence of elevated blood pressure is ≈15%.[73] Obesity is also a strong predictor of carotid intima-media thickness (IMT), which is concerning, considering 1 in 5 US children and adolescents have obesity.[65] Similarly, a large proportion of children and adolescents have elevated concentrations of lipids with ≈15% of children and ≈22% of adolescents having at least 1 adverse level of cholesterol (HDL, non-HDL, or total).[74] Furthermore, these risk factors can have an additive effect as the presence of 2 or more risk factors negatively impacts carotid IMT; however, the combination of obesity and HDL was found to have the greatest influence on carotid IMT in children.[75] Prevention of obesity during this life stage is important given evidence that those experiencing obesity throughout this period had 5.2 times (95% CI, 4.5–6.0) greater risk of having obesity into adulthood.[76] A systematic review of cardiorespiratory fitness in childhood found higher fitness is associated with favorable adiposity and cardiometabolic biomarkers.[77] However, the results were mixed, and the quality of the evidence was low. One explanation is the direct association of physical activity and cardiorespiratory fitness on carotid IMT has been found to be attenuated when controlling for regional adiposity[78]; therefore, physical activity at this age is important to reduce risk of obesity and other cardiometabolic risk factors (eg, blood pressure, lipid profile).[13] Despite the benefits of physical activity, only 21% to 28% of children and adolescents meet the *Physical Activity Guidelines* recommendations.[79] Prevalence of activity varies by age, sex, disability status, weight status, and race and ethnicity. Adolescents, girls, youth with disabilities, youth with obesity, and Hispanic youth are less likely to meet guideline recommendations.

### Primary Prevention

Childhood and adolescence are critical stages to prevent or delay risk factors that can accelerate development of CVD, including obesity, dyslipidemia, and hypertension. For example, several blood pressure measurement indicators, including systolic blood pressure, mean arterial pressure, and pulse pressure, during childhood and adolescence, are associated with adulthood carotid IMT,[80] a subclinical measure for early atherosclerosis and predictor of future MI and stroke.[81]

### Secondary Prevention

FitnessGram, a fitness assessment for youth implemented in US schools,[82] measures aerobic capacity (cardiorespiratory fitness; $VO^2$ max), muscular strength, endurance, flexibility, and body composition (body mass index). Using established age-gender cut points, youth are categorized into 3 categories: Healthy Fitness Zone, Needs Improvement, and Health Risk. Student reports and personalized feedback can help youth understand their health and future health risks if their fitness does not improve. Similar programs include the Presidential Youth Fitness Program,[83] which includes FitnessGram assessments.

Much of the evidence base has been established using report-based methods, thus large-scale, device-based monitoring in this age group is still needed. More research on the benefits of muscle- and bone-strengthening activities for CVD progression is needed as well as longitudinal changes in physical activity and cardiorespiratory fitness. More work is needed to reduce the overall decline in activity throughout this period of life.

## YOUNG ADULTHOOD (18–44 YEARS)

Young adulthood is characterized by many major life events, which may include moving away from home, school-to-work transition, partnerships (including marriage/cohabitation and dissolution/divorce), and becoming a parent.[84]

Although the prevalence of diabetes remains relatively low in young adults (3% to 5% of Americans), the Centers for Disease Control and Prevention recently reported that prediabetes rates have reached 27.8% of young adults.[85] Studies in individuals with prediabetes, like the Diabetes Prevention Program, have shown that physical activity interventions (with and without a dietary component) improved glycemic control and reduced the risk of developing type 2 diabetes.[86] Long-term adherence to lifestyle change is often more challenging, so further research should focus on improving the long-term effectiveness of intervention programs, especially in under-represented and underserved communities. Qualitative and community-engaged research may be important to understand the barriers to achieving physical activity recommendations and how to overcome these barriers.

Another risk factor with high prevalence in young adults is hypertension, affecting ≈25% of 20- to 40-year-olds.[61] Meta-analyses of clinical trials including normotensive and hypertensive individuals suggest that aerobic exercise or a combination of aerobic and resistance training is expected to have an average effect of lowering systolic and diastolic blood pressure by 3 to 4 mm Hg.[87] There is also strong observational evidence of a dose-response association of leisure time physical activity with a 6% to 33% lower risk of developing hypertension, depending on the level of physical activity.[3] Clinical trials consistently demonstrate the favorable effect of physical activity on lowering triglyceride levels and increasing HDL cholesterol, but evidence supporting a beneficial effect of physical activity on LDL cholesterol is less consistent.[3,87]

### Primary Prevention

The major focus during young adulthood is the primary prevention of CVD risk factors.[87–89] Evidence supporting the association of physical activity with lower risk factors has come from both observational studies and clinical trials, as summarized in the Physical Activity Guidelines.[3] The evidence supporting physical activity in the prevention of weight gain is strongest in young adults, compared to middle and older ages. Finally, recent evidence in CARDIA highlights the importance of young adulthood physical activity and cardiorespiratory fitness levels to reduce long-term risk of premature death and fatal and nonfatal cardiovascular events.[90,91]

### Tertiary Prevention

By the time most people enter adulthood, the early stages of CVD development, atherosclerosis, have already begun. One striking example comes from an autopsy study from the Korean war, which reported that >77% of soldiers (mean age 22 years) had atherosclerosis in their coronary arteries.[92,93] The prevalence of risk factors of CVD also begins to accumulate, especially as individuals near middle age. The first line treatment for many of these conditions is improving diet and physical activity, as an adjunct to pharmacotherapy.[87] Because the prevalence of primary risk factors for CVD is much higher in middle age, tertiary prevention strategies will be detailed in the next section, but its relevance first begins in the growing number of young adults already diagnosed with a chronic disease.

Longer follow-up will be necessary to establish the volume and intensities of physical activity that are required in young adulthood for optimal prevention of CVD that may not manifest clinically until older adulthood. This type of research may require follow-up periods lasting 40-50 years. We also look forward to future insights into precision physical activity and exercise prescription that may identify certain subgroups of the population (eg, through genetics, subclinical biomarkers, environmental/lifestyle exposures, or responses to interventions) that may stand to benefit the most from certain types of training approaches.[94]

## MIDDLE ADULTHOOD (45–64 YEARS)

Middle adulthood can be a dynamic stage of life. Persons in this stage may experience several life events including residence related (eg, relocation), employment-related (eg, loss of job, change of job), family related (eg, change of partner, loss of partner, or other family), and health-related events (eg, menopause, diagnosis of chronic illness, etc).[7]

Cardiovascular and cardiometabolic diseases are increasingly prevalent in this life stage (coronary artery disease >40%; diabetes ≈20%; hypertension ≈60%; severe obesity ≈10%).[61,95–97] Atherosclerotic lesions become complex with calcifications, hemorrhage, and ulceration earlier in men whereas these developments are more common in postmenopausal women. These lesions may rupture and thrombose, leading to adverse events such as MI or stroke. Despite prevalent subclinical atherosclerotic disease, cardiovascular events resulting in hospitalization or death occur in just 0.7% of middle-aged women and just over 1% of middle-aged men.[98] Physical activity may slow disease progression and improve outcomes in the transition to older adulthood. In a study of masters age athletes (mean age 54±9 years) with an average of >30 years participation in endurance sports, almost half of the athletes had a coronary artery calcium score of 0.[99]

However, there is concern that excessive exercise may accelerate the atherosclerotic process[100] or result in malignant cardiac remodeling.[101] A dose-dependent relationship appears to exist in exercise-induced cardiac remodeling, with no apparent exercise-induced cardiac remodeling observed in individuals who exercise within the *Physical Activity Guidelines*.[102] Endurance athletes may also be at increased risk for atrial fibrillation, data from a study of >52 000 participants (10% women) of a long-distance cross-country ski race showed greater risk of incident atrial fibrillation among those participants with ≥5 race finishes.[103] Further research is needed to determine whether excessive exercise is associated with long-term CVD morbidity and CVD-related death.

Whether the association between physical activity and CVD is modified by race or sex has been of particular interest. Analyses from ARIC and CARDIA observed no interaction by race (Black and White) on the association between physical activity and lower incidence of CVD, with a similar association seen in both races.[90,104] Regarding differences by sex, physical activity was associated with reduced all-cause and CVD-attributable death in the FHS (Framingham Heart Study), but a reduction in incident CVD was only observed in men raising the question of whether there are sex-specific differences in risk factor modification and development of disease.[105] A later study from FHS utilizing a commercial wearable monitor (Apple watch) reported an association between greater physical activity and lower 10-year ASCVD (atherosclerotic cardiovascular disease) risk in a sample of mostly women.[106] A report from the CARDIA study did not demonstrate differences between physical activity and premature CVD events across sex.[90] A large meta-analysis including 33 studies on >500 000 individuals, demonstrated sex-specific differences between physical activity and the risk of CHD, with women having greater benefits than men.[107] Overall, while the magnitude of benefit may vary by race or sex, the directionality of benefit is likely consistent across race and sex.

Physical activity can reduce the development of CVD risk factors in middle-aged adults. The highest rates of incident diabetes are in middle-age adults.[85] An analysis from the *All of Us* Research Program utilizing longitudinal measures of physical activity from commercial wearable devices reported an association between higher levels of physical activity and a lower risk of incident diabetes.[108] Analyses from CARDIA have suggested that physical activity in young adulthood with maintenance into middle adulthood may reduce incident hypertension and prevent premature cardiovascular events in middle-aged adults.[109] Reduction in heart failure risk with physical activity may be most effective in persons without established atherosclerotic disease.[110] Physical activity can reduce the development of CVD risk factors in middle-aged adults.

Several investigations have sought to unravel the importance of accumulated versus intensity-specific physical activity volume and their respective relations with CVD. In a study of >90 000 participants in the UK Biobank who wore a 7-day accelerometer, there were no observed differences in moderate versus vigorous intensity activity, and importantly, no threshold for the association with incident CVD.[111] This is in line with other reports[112] indicating that any amount of physical activity has associative benefits and sedentary individuals may derive benefit from any increased amount of physical activity. However, other analyses from UK Biobank observed fewer CVD events among participants with greater proportions of moderate to vigorous intensity physical activity (20% versus 10% of total energy expenditure)[113] and a maximal reduction in CVD risk when vigorous activity accounted for 30% of total moderate to vigorous intensity physical activity.[114] There may be differences across types of physical activities (eg, aerobic versus resistance) in their associations with reduced incidence of CVD.[115] Physical activity does not need to be accumulated all at once, with findings suggesting intermittent physical activity throughout the day is associated with reduced all-cause and CVD-related death.[116] This can be important for those employed in primarily sedentary occupations.

The majority of studies have leveraged either self-reported questionnaire or device monitoring over a brief period (mostly 7 days). More research is needed to observe the associations of changes in physical activity over time on subsequent disease burden. Looking at physical activity patterns over time provides an opportunity to account for seasonal, environmental, or behavioral variation. A recent study using data from the *All of Us* Research Program found that daily step counts over a median 4 years of monitoring period had a significant inverse and nonlinear relation with essential hypertension risk, with no further risk reduction beyond 8000 steps per day.[117] However, this analytical cohort was relatively young (median age, 57 years), educated, and owned Fitbit devices, indicating the need for further studies to examine relation of physical activity over time with CVD in older, socioeconomically, and clinically diverse populations. Long-term physical activity is certainly associated with lower CVD risk, but initiation of physical activity in middle age may provide similar benefits and should be a goal for all individuals at this life stage.[118–120]

While higher levels of physical activity are associated with slower disease progression (and potentially regression of atherosclerosis[121]), it is important to recognize the "physical activity paradox" wherein leisure time physical activity is associated with clinical benefit, but occupational physical activity (ie, manual labor) is not.[122,123] Holtermann et al[124] postulated the reasons why this paradox exists. They provide 6 hypotheses: (1) occupational physical activity may not be of sufficient duration or intensity; (2) it raises 24-hour heart rate; (3) heavy lifting and static positions elevate blood pressure; (4) there is no recovery time; (5) workers cannot control their environment and may be subjected to detrimental climate extremes and dehydration; (6) sustained activity increases inflammation.[124] Socioeconomic status potentially confounds the relationship between occupational physical activity and CVD, with greater amounts of occupational physical activity observed among low socioeconomic groups[125] who experience healthcare disparities and higher rates of unhealthy risk behaviors (smoking, diet, stress) which. may further attenuate the benefit of physical activity.[126] This may account, in part, for the discrepant findings of early studies of occupational physical activity (eg, longshoreman,[22] bus drivers/conductors[21]) demonstrating a benefit of occupation-related physical activity and contemporary studies.

### Secondary Prevention

Highly prevalent subclinical CVD places many middle-aged adults as targets for secondary and tertiary prevention efforts. Exercise stress testing is a mainstay for screening and diagnosis of CVD.[127] Using exercise as a physiological stressor, ECG and blood pressure monitoring provide evaluation of cardiac response to exercise with modern implementations frequently employing additional cardiac imaging (echocardiography or nuclear scintigraphy) to enhance sensitivity and specificity. Although submaximal stress tests may be used to guide an exercise prescription,[128] maximal stress tests are generally preferred for diagnostic and prognostic purposes.[127,129]

### Tertiary Prevention

For those with established CVD, lifestyle modifications including diet, physical activity, weight management, and smoking cessation are foundational and often complemented by pharmacological therapy. The 2012 Stable Ischemic Heart Disease Guidelines recommend 30 to 60 min $d^{-1}$ of moderate-intensity activity.[130] Importantly, the safety of physical exercise in the presence of coronary artery calcification was examined and observed to not increase risk of CVD events (with a caveat that the study included no women).[131] For those with advanced CVD, cardiac rehabilitation may be considered given its relation with improved functional capacity and death.[132–134] More information on cardiac rehabilitation is reported in the next section on older adulthood.

Significant research on physical activity associations with CVD has focused on middle-aged adults. This lends strength to the reported associations as they are replicated in multiple, distinct cohorts. These studies have relied primarily on self-reported measures of physical activity or time-limited assessments with a wearable device. Correlations between questionnaire-based assessments of physical activity and accelerometer-based assessments are modest,[135,136] and short-term accelerometer use may misclassify individuals' degree of physical activity.[137] Further research may focus on using longitudinal, continuous measures of physical activity to further characterize patterns of physical activity. In addition, increased uptake of commercial, wearable devices in the population will allow for "real world" data, but may not be representative of the entire population.[138] Investigation into the interaction between physical activity and sleep patterns may yield meaningful insights into lifestyle.

## OLDER ADULTHOOD (≥65 YEARS)

Older adulthood is a period where there are health-related events and transitions (eg, increased risk of comorbidities such diabetes, cancer, osteoarthritis) and family and employment-related transitions (eg, loss of partner and retirement). These life events may have an impact on an individual's ability to be active. If preexisting chronic conditions limit activity, older adults can personalize the goal of being active as their ability and condition permit.[84]

As age advances, there are numerous functional cardiac changes, such as dysfunction related to systolic and diastolic blood pressure and electrical activity of the heart (arrhythmias), which in turn increases the cardiovascular risk. Within the older adult population, CVD and its primary risk factors are highly prevalent. Nearly, >65% have hypertension, ≈65% have clinical or subclinical CVD, ≈5% to 10% have atrial fibrillation, ≈10% have moderate-severe valve disease, and ≈5% to 10% have heart failure.[61,139] Engaging in any intensity of physical activity have been related to lower CVD risk.[140] Higher physical activity index score, which was a composite measure of participant-reported time spent in different physical activities either at work or leisure and a weight based on the oxygen consumption at each activity type, was related to lower incidence of heart failure over average 10-year follow-up in 1142 elderly FHS participants who did not have prior MI at baseline.[141] Similarly, in a 40-year follow-up of 4729 participants in the FHS who were aged 30 to 60 years old at baseline, those who were active, which was assessed using surveys over 3 follow-up visits that were 14 to 16 years apart, were associated with 17% to 19% lower CVD-attributable and all-cause mortality risk compared to those who were inactive.[105] In addition, a recent harmonized meta-analysis found older adults (≥60 years) who walked 6000 to 9000 steps per day had a 40% to 50% lower CVD risk, including heart attack, compared to those who walked <2000 steps per day.[142] Similar findings are seen in the CHS (Cardiovascular Health Study), which found among 4207 older adults (mean age, 73 years) those who walked at least 49 blocks per week had a 36% to 47% lower risk of CHD, stroke, and CVD compared with those who walked <5 blocks per week.[143] These cohort studies highlight that engaging in any intensity of physical activity or taking more steps is related to better cardiovascular health in older adults. Furthermore, it is known as adults age, they may have functional limitations[144] such as slow gait speed, which might limit their ability to engage in physical activity. Particularly relevant to this challenge is the observation that in older women, shorter bouts of sedentary time are associated with reduced risk of CVD events.[145] In turn, it is important to assess adults' functionality and evaluate their physical and mental ability to engage in physical activity. Walking is considered low risk and a preferred physical activity among older adults.[143,146,147] Evidence suggest that leveraging wearable devices, consultation with healthcare professionals, and incorporating behavioral change components such as positive reinforcement messaging have been shown to improve physical activity in adults with cardiovascular diseases.[148–150] However, further research is warranted in implementing interventions in sociodemographically diverse adults who may not have access to care or technology as well as limited health literacy.

### Tertiary Prevention

Cardiac rehabilitation is multifaceted intervention, which includes exercise, lifestyle modification, diet, risk factor education, and psychological support. The goal of cardiac rehabilitation is to optimize the recovery and prevent future cardiac events. A study on 601 099 U.S. Medicare beneficiaries who were hospitalized for coronary conditions or cardiac revascularization has shown that mortality rates were 21% to 34% lower in socioeconomically and clinically diverse older adults who utilized cardiac rehabilitation versus those who did not.[151] Regardless of where cardiac rehabilitation is delivered (home versus center), it has shown to be equally effective in improving clinical and functional outcomes among patients with heart failure, MI, atrial fibrillation, and cardiac surgery.[132–134] Despite these health benefits and coverage provided by Medicare, cardiac rehabilitation is under-utilized in older adults.[151] Thus, there is a need for future research to focus on identifying effective strategies to increase the utilization of cardiac rehabilitation among older adults.

## SUMMARY

Incorporating a lifecourse framework into the study of physical activity and its relation to CVD can provide meaningful insights. Certainly, physical activity has benefits, regardless of age. Yet, as we have shown, the goals and target levels of physical activity vary across life stages and findings are rarely contextualized using a lifecourse framework. A key knowledge gap, in this regard, is the relation of different trajectories of physical activity over the lifecourse (eg, maintenance of physical activity from childhood to older adulthood versus an undulating pattern) with CVD. While it is likely not feasible to establish a birth cohort with repeated assessments through death, harmonizing data across several cohorts at different life stages may be a more realistic approach.

For example, based on the expert recommendations from the 1978 Bethesda Conference, CARDIA, ARIC, and CHS were initiated with each cohort reflecting an adult lifecourse stage (young, middle, and older adulthood, respectively). However, given inconsistencies in physical activity assessment tools used by these studies, additional methodological work is needed to harmonize and pool data to fully reflect physical activity changes across the adult lifecourse, such as the Steps for Health Collaborative.[142,152] Another data harmonization example is the International Children's Accelerometry Database which has pooled and harmonized over 37 000 raw accelerometer data files of children and adolescents aged 3 to 18 years from 20 studies worldwide (Europe, United States, Brazil, Australia).[153] However, there is a paucity of CVD cohort studies that integrate earlier lifecourse stages (eg, infancy to adolescence) with the adult studies. Cohort studies should consider adding offspring ancillary studies to examine physical activity across lifecourse stages, such as the Avon Longitudinal Study of Parents and Children[154] and the Framingham Offspring Study.[155] With the advent of the quantified self, an exponential growth in the amount of quantified, longitudinal physical activity data opens opportunities to resolve several unanswered questions.[156] A central question revolves around 24-hour patterns of physical activity (eg, sleep, sedentary behavior) and how they may modify the association of physical activity with CVD. Separately, what role do genetic variants play in determining an individual's ideal amount and intensity of physical activity?Finally, the pivotal role of individual choice cannot be understated. Although it is generally well-established that physical activity improves cardiovascular health and longevity, there is prevalent cognitive dissonance manifested by the almost universal disparities between the *Physical Activity Guidelines* and reported physical activity. For many, the delay between physical inactivity and incident CVD reduces the motivation to exercise. For others with established CVD, a feeling of futility may prohibit engagement. At the same time, we acknowledge systemic factors heavily influence individual choice. Significant barriers to physical activity exist for large portions of the population, including social and environmental factors. Given the impact of early exposure and training, we are excited to see efforts aimed to increase physical activity in children and youth.[157] Further investigation into how to increase physical activity at an individual and population level are urgently needed to optimize cardiovascular health across the lifecourse.

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