Cardiovascular Benefits and Risks Across the Physical Activity Continuum

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ABSTRACT

Purpose of review: Habitual physical activity can reduce the risk of future cardiovascular morbidity and mortality. This review evaluates recent publications that have assessed the impact of the dose of physical (in)activity on cardiovascular outcomes.

Recent findings: Sedentary behavior, characterized by prolonged sitting, is increasingly prevalent across the globe and increases the risk for cardiovascular events in a dose-dependent fashion. Similarly, the number of individuals performing endurance exercise events has tripled over the last 2 decades, and some studies suggest that the high volumes of exercise training and competition may attenuate the health benefits of a physically active lifestyle.

Summary: Breaking-up sitting time or replacing sitting by (light) physical activity are effective strategies to attenuate its detrimental health effects. Low doses of physical activity, preferably at a high-intensity, significantly reduce the risk for cardiovascular and all-cause mortality. Larger doses of exercise yield larger health benefits. Extreme doses of exercise neither increase nor decrease the risk for adverse outcomes. Athletes demonstrate a transient cardiac dysfunction and biomarker release directly post-exercise. Chronic exercise training may increase the risk for atrial fibrillation, but is also associated with a superior life expectancy compared to the general population.

Keywords: sedentary behavior, sitting, endurance exercise, athletes, lifestyle

INTRODUCTION

Physical activity and the ability to perform endurance exercise played an essential role in human evolution [1]. Our early ancestors combined long-distance running and walking to track and hunt animals on the African savannah. During so-called 'persistence hunts', distances >30 km were regularly covered [2]. In contrast to this intermittent but substantial exertion, it is believed that hunters were predominantly physically inactive during the remainder of the day [1]. This inactive behavior reduced their energy expenditure and was essential to maintain a proper balance between energy intake and expenditure.

During the past century, our lifestyle has changed dramatically and the role of physical exertion is minimized in our contemporary lives. Machines have taken over the majority of our physical efforts at work, home and during transportation. Consequently, the prevalence of sitting time has increased, whereas the time performing exercise has decreased. These changes in habitual physical activity patterns greatly impact the energy intake/expenditure balance, which have contributed to an alarming increase in the incidence of obesity and other chronic diseases [3, 4]. Hence, physical inactivity was recently recognized as a major threat to global health [5].

The World Health Organization recommends that adults engage in at least 150 min/week of moderate-intensity exercise or 75 min/week of vigorous-intensity exercise [6]. Currently, only 61% of the European population [7] and 44% of the North American population [8] perform sufficient physical activity to meet the WHO guidelines, percentages that have changed only slightly over the past 20 years [9]. Incongruously, an increasing number of amateur athletes are participating in endurance exercise events. In fact, the number of US running race participants has tripled over the past two decades [10]. Although exercise training is believed to improve cardiovascular health [11], recent studies suggest that excessive volumes of physical activity may harm the heart [12].

The purpose of this review is to provide an overview of recent insights relating to the risks and benefits of physical activity. Given the increased prevalence of physical inactivity and the increasing popularity of endurance exercise activities, we will summarize the cardiovascular risks and benefits across the physical activity continuum: from sitting behavior to extreme volumes of exercise.

PHYSICAL INACTIVITY AND SITTING BEHAVIOR

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure. Hence, physical inactivity represents sedentary behavior that does not involve muscle contraction, which is most prevalent during sitting and lying. Recent studies revealed that accelerometer-measured mean daily sedentary time was 8.2 hrs/day among New York City adults [13], whereas Australian desk workers reported an average of 9.0 hrs/day of sitting time [14]. Physical inactivity is not restricted to the general population; it can be observed in (half-)marathon runners as they have reported sitting 10.75 hrs/day on workdays and 8 hrs/day on non-workdays [15].

A recent meta-analysis combining the outcomes of 41 studies (n=829,917 participants) found that sedentary time was associated with cardiovascular mortality (HR: 1.18, 95%CI: 1.11-1.26), but also with cardiovascular disease incidence (HR: 1.14, 95%CI: 1.0011.73), cancer mortality (HR: 1.17, 95%CI: 1.11-1.24), cancer incidence (HR: 1.13, 95%CI 1.05-1.21), and the incidence of type 2 diabetes (HR: 1.91, 95%CI: 1.64-2.22) [16]. The authors emphasized that the detrimental health effects of sitting were independent of the physical activity patterns of study participants [16]. The population-attributable fraction for all-cause mortality associated with sitting time was explored in another paper and included data from 54 countries. Sitting time was responsible for 3.8% of all-cause mortality, but large differences were observed across countries (0.6-11.6%) [17]. The sitting- related mortality risk was the highest in Western Pacific countries (5.7%), followed by European (4.4%), Eastern Mediterranean (3.3%), American (3.2%), and Southeast Asian (2.0%) countries [17].

A potential strategy to reduce the harmful effects of prolonged sitting, is to limit the duration of sitting sessions [18]. Breaking-up prolonged sitting time with 2 minute bouts of walking reduced postprandial glucose and insulin levels [19] and lowered systolic and diastolic blood pressure [20]. A different strategy is to replace sitting time with exercise or non-exercise activities (i.e. household chores, lawn and garden work, and daily walking). In a cross-sectional analysis, less active individuals (<2 hrs/day, n=69,606) demonstrated a reduced risk for cardiovascular mortality when 1 hr/day of sitting was replaced by exercise (HR: 0.47, 95%CI: 0.40-0.56) or non-exercise activities (HR: 0.64, 95%CI: 0.57-0.71) [21]. Active individuals (≥2 hrs/day, n=85,008) also demonstrated a reduced risk for cardiovascular mortality when 1 hr/day of sitting was replaced by exercise (HR: 0.84, 95%CI 0.78-0.90) but no benefit was observed for non-exercise activities (HR: 1.00, 95%CI: 0.96-1.04) [21].

An observational study modeled the health benefits of replacing 2 hrs/day of sitting by standing or stepping. Sitting-to-standing reallocation was associated with lower levels of fasting glucose (~2%), total/HDL-cholesterol ratio (~6%), triglycerides (~11%), and a higher HDL-cholesterol (~0.06 mmol/L) [22]. Sitting-to-stepping reallocation was associated with a lower BMI (~11%) and waist circumference (~7.5 cm), and lower levels of post-load glucose (~12%), triglycerides (~14%) and a higher

HDL-cholesterol (~0.10 mmol/L) [22]. The benefits of low-intensity activities to reduce the detrimental effects of sitting were reinforced by a recent study in the UK Women's Cohort Study (n=12,778) [23]. Sitting ≥7 hrs/day significantly increased the risk for all-cause mortality compared to sitting <5 hrs/day. However, fidgeting behavior (small movements of hands and feet) appeared to modify the association between sitting time and all-cause mortality. The increased mortality risk associated with sitting was only observed in women reporting no fidgeting, whereas women reporting regular to frequent fidgeting demonstrated comparable mortality risks between high and low volumes of sitting [23].

Importantly, these observations demonstrate that small changes in sitting behavior can improve (cardiovascular) health. Consequently, policy documents from the United Kingdom and Australia already include statements about sitting behavior [24, 25]. Experts from the United Kingdom recommend including specific guidelines on sedentary behavior in future physical activity guidelines [24]. In Australia, minimizing time spent in prolonged sitting and breaking up long periods of sitting as often as possible are already included in the national physical activity guidelines [25]. These initiatives are likely to contribute to increased awareness of the detrimental health effects of sitting. Indeed, the time spent in sedentary behavior has not increased in European adults over the past decade [26]. More importantly, the prevalence of prolonged sitting (7.5 hrs/day) decreased from 23.1% in 2002 to 17.8 in 2013 [26]. Further reductions in sitting times may be achieved via workplace interventions such as sit-stand desks, but high quality intervention trials are needed to provide evidence for the cost-effectiveness and health benefits of such interventions [27].

THE OPTIMAL EXERCISE DOSE

Exercise is associated with risk reductions in at least 26 different diseases, including the metabolic syndrome, polycystic ovarian syndrome, type 1 and 2 diabetes, cancer, musculo-skeletal disorders and psychiatric, neurological, cardiovascular, pulmonary and metabolic diseases [28]. Furthermore, physically active individuals have a lower risk for all-cause and cardiovascular mortality and morbidity compared to sedentary peers [29, 30].

Several recent papers have explored the dose-response relationship between physical activity and adverse health outcomes [31-33]. A pooled analysis including 661,137 men and women from 6 large prospective American and European population studies found a 20% risk reduction for all-cause mortality in individuals performing moderate-intensity physical activity <100 min/week during 14 years of follow-up [34]. Increasing volumes of physical activity gradually decreased the mortality risk. The maximal benefit of an active lifestyle was found at an exercise dose representing 3 to 5 times the WHO physical activity recommendation (HR: 0.61, 95%CI: 0.59-0.62) [34]. Larger doses of exercise did not further decrease mortality risks, but did not increase it either. These findings align with a recent perspective document from the American College of Cardiology's (ACC's) Sports and Exercise Cardiology Leadership Council. They reported that the 'optimal' exercise dose to reduce the risk for cardiovascular events was established at 41 MET-hrs/week: i.e. 9.1 hrs/week of moderate-intensity exercise [35].

Interestingly, the dose-response relationship appears to be different for moderate *versus* vigorous intensity activities. Whereas a progressive decrease in the risk for cardiovascular mortality is observed for increasing volumes of moderate intensity physical activity, no further risk reduction is observed beyond a vigorous intensity exercise dose of 1.3 hrs/week (11 MET-hrs/week) [35]. These findings were reinforced by an Australian prospective cohort study (n=204,542) that investigated the role of vigorous activities on all-cause mortality during 6.5 years of follow-up. Individuals performing <30% of their total exercise dose at a vigorous intensity had a significantly lower mortality risk (HR: 0.91, 95%CI 0.84-0.98) compared to the reference group that performed a similar exercise dose but refrained from vigorous activities [36]. Individuals reporting ≥30% of their exercise dose to be vigorous demonstrated a comparable mortality risk reduction (HR: 0.87, 95%CI: 0.81-0.93) [36]. Thus, low doses of vigorous intensity physical activities seem to be extremely efficient at reducing the risk for adverse (cardiovascular) events.

Despite the undeniable health benefits of exercise, a substantial proportion of the population does not perform enough physical activity to derive a health benefit [37]. Therefore, novel strategies to improve active behavior are needed [38]. Activity trackers are available globally and these devices provide real-time quantification and insight into one's activity pattern. Hence, these trackers can assist an individual in reaching activity goals and adopting a physically active lifestyle. A randomized clinical trial found an increase of 970 steps/day in individuals receiving a wireless activity tracker, regardless of their initial activity level [39]. Personalized encouragement, social competition and effective feedback loops are other key factors needed to pursue a behavioral change towards an active lifestyle [40]. The 'setting' to stimulate individuals to become physically active is important. A randomized clinical trial compared 3 methods to frame financial incentives to increase physical activity among overweight and obese adults [41]. Participants were instructed to cover 7000 steps/day and were randomly allocated to a 1) control, 2) gain incentive ($1.40/day if goal was achieved), 3) lottery incentive (daily eligibility for $1.40 if goal was achieved), or 4) loss incentive ($42 allocated monthly upfront and $1.40/day was removed if goal was not achieved) study groups. Only the loss incentive group demonstrated a larger proportion (0.45, 95%CI: 0.38-0.52) of participant-days achieving the 7000 steps/day goal compared to the control group (0.30, 95%CI: 0.22-0.37) [41]. These findings emphasize the difficulty in changing behavior, but also that a tailored intervention can increase activity patterns in a group at risk. Personalized exercise prescriptions are therefore warranted in the era of precision medicine.

TOO MUCH EXERCISE?

The volume of exercise performed during training and competition by amateur and professional athletes to improve cardiorespiratory fitness often exceeds the dose needed to optimize cardiovascular health. High volumes of exercise training improve cardiovascular risk factors [42], and cause an initial increase in left ventricular chamber size followed by an increase in wall thickness during chronic exercise training [43]. Remodeling also occurs in the right heart, allowing the right ventricle to tolerate the increased pulmonary artery pressures during exercise [44]. These adaptations are part of the 'athlete's heart' and are believed to represent physiological remodeling.

Some studies suggest that performance of prolonged vigorous exercise (such as marathon running) may harm the heart acutely or chronically. For example, cardiac dysfunction of the left and right ventricles was observed immediately post-exercise in endurance athletes [45, 46]. Similarly, increased cardiac troponin levels have been reported following marathon running, with 69% of the population exceeding the upper limit of the normal threshold [47]. Both phenomena are transient, however, as cardiac function and biomarker levels typically recover within 24-48 hours post exercise [12]. The risk for acute adverse cardiac events during endurance exercise is therefore considered low, and data from a French registry demonstrated a prevalence of life threatening events of only 0.75 per 100 000 athletes [48].

Cardiac remodeling associated with chronic exercise exposure may also increase the risk for arrhythmias in athletes [49]. A previous athletic population study [50] and a systematic review [51] have demonstrated an increased risk for atrial fibrillation (AF) in endurance athletes. However, contrasting findings were reported in 2 recent studies. Data from the Henry Ford Exercise Testing (FIT) Project found a 7% risk reduction for AF with every increase of 1 MET in cardiorespiratory fitness [52]. Fit individuals had a substantially lower risk (HR: 0.44, 95%CI: 0.39-0.50) for incident AF compared to unfit individuals [52]. Similarly, data from the CARDIO-FIT Study found a 20% reduction in the risk of AF recurrence for each MET increase in cardiorespiratory fitness among overweight and obese individuals with symptomatic AF [53]. Differences in maximum exercise capacity and cardiorespiratory fitness between the FIT/CARDIO-FIT studies and previous observations in athletes may explain the conflicting outcomes [54]. It may well be that initial increases in cardiorespiratory fitness decrease the risk for AF, but that excessive exercise training and associated fitness increase the AF risk.

Finally, recent epidemiological studies have assessed the long-term outcomes of high volumes of exercise training. Data from the Million Women Study [55] and Copenhagen City Heart study [56] report a U-shaped curve for the relationship between exercise exposure and risk for morbidity and mortality. Thus, inactive individuals had the highest risks and physically active individuals demonstrated a reduced risk, but the benefits of exercise were attenuated in vigorous exercisers. These observations contradict pooled data from 6 European and American cohorts that noted that individuals performing exercise at a dose 5 – 10 times the international recommendations, had a 31% reduction in all-cause mortality risk (HR=0.69, 95%CI 0.59-0.78) compared to inactive peers [34]. Furthermore, a 50-year follow-up study among Finnish elite athletes demonstrated that endurance athletes (HR: 0.70, 95%CI:

0.61-0.79) and team sport athletes (HR: 0.80, 95%CI: 0.72-0.89) had lower mortality risks compared to controls [57]. Explanations for the different outcomes in the Million Women Study and Copenhagen City Heart study may relate to the characteristics of the most active individuals (high smoking prevalence and low socioeconomic status [31]) and definition of the control group (allowed to exercise <2h/week [58]). Therefore, we believe that there is currently no solid evidence for an increased risk for adverse outcomes in the most active individuals.

CONCLUSIONS

The priority for reducing cardiovascular burden should be mainly focused on the lower end of the physical activity continuum. Physical inactivity, characterized by too much sitting, is a serious health problem as it independently increases the risk for cardiovascular morbidity and mortality. Future physical activity guidelines should incorporate specific recommendations on strategies to reduce sedentary behavior. Habitual physical activity and exercise training are powerful strategies to reduce the risk for adverse cardiovascular outcomes and mortality in a dose dependent way. High intensity exercise produces larger health benefits compared to moderate intensity exercise. Personalized exercise programs and wireless devices with real-time feedback may help individuals meet the international guidelines for physical activity. Currently, there is no strong evidence that supports the ‘too much exercise hypothesis’. Individuals performing exercise at a multiple of the recommended dose live longer and have a comparable risk for cardiovascular morbidity and mortality as moderately active peers.

Key points

- Prolonged sitting is highly prevalent in the general population and increases the risk for cardiovascular mortality. Breaking-up of prolonged sitting time or replacement of sitting time by (light) physical activity can effectively reduce the detrimental effects of sitting.
- A curvilinear dose-response relationship between exercise and cardiovascular health is found. Low doses of exercise improve health, but higher doses give larger benefits. Also, high-intensity activities induce larger risk reductions compared to moderate-intensity activities of a similar volume.
- Exercise-induced cardiac remodeling of all cardiac chambers is present in athletes. Acute exercise can lead to transient cardiac dysfunction and cardiac biomarker release. Chronic exercise may increase the risk for atrial fibrillation. Nevertheless, there is strong evidence that athletes live longer compared to individuals from the general population.

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