

# Medicine & Science IN Sports & Exercise

The Official Journal of the American College of Sports Medicine  
www.acsm-msse.org

*. . . Published ahead of Print*

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Accepted for Publication: 28 July 2014

*Medicine & Science in Sports & Exercise*® **Published ahead of Print** contains articles in unedited manuscript form that have been peer reviewed and accepted for publication. This manuscript will undergo copyediting, page composition, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered that could affect the content.

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**Running title:** Sedentary Physiology and Health

## **Acknowledgments:**

The workshop was sponsored by the National Heart, Lung and Blood Institute, the National Institute on Aging and the Office of Disease Prevention of the National Institute of Health. In addition to the listed authors, additional investigators took part as discussants. These discussants included Dr. Benjamin Levine (Univ. of Texas- Southwestern), Dr. Mark Tarnopolsky (McMaster University - Canada), Dr. Marc Hamilton (Pennington Biomedical Research Center - LSU), Dr. David Dunstan (Baker IDI Heart and Diabetes Institute & Deakin University, - Australia), Dr. Konstantin Khrapko (Harvard Medical School)

The views expressed in this document reflect the collective ideas and opinions of the authors and does not necessarily represent the official views of the National Institutes of Health , or the U.S. department of health and Human Services and the other workshop participants. JPT supported by NIH (R01DK088940); JAL supported by NIH (R01DK 72479-4, R015R01DK085516-04-1), and the Mayo Clinic Foundation, Arizona State University; MD supported by NIH/NCI (R25CA094880).

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## ABSTRACT

**Purpose:** This paper reports on the findings and recommendations of the “Physiology of Sedentary Behavior and its Relationship to Health Outcomes” group, a part of a larger workshop entitled *Sedentary Behavior: Identifying Research Priorities* sponsored by the National Heart, and Lung and Blood Institute and the National Institute on Aging, which aimed to establish sedentary behavior research priorities. **Methods:** The discussion within our workshop led to the formation of critical physiological research objectives related to sedentary behaviors, that if appropriately researched would greatly impact our overall understanding of human health and longevity. **Results and Conclusions:** Primary questions are related to physiological “health outcomes” including the influence of physical activity vs. sedentary behavior on function of a number of critical physiological systems (aerobic capacity, skeletal muscle metabolism and function, telomeres/genetic stability, and cognitive function). The group also derived important recommendations related to the “central and peripheral mechanisms” that govern sedentary behavior and how energy balance has a role in mediating these processes. General recommendations for future sedentary physiology research efforts include that studies of sedentary behavior, including that of sitting time only, should focus on the physiological impact of a “lack of human movement” in contradistinction to the effects of physical movement and that new models or strategies for studying sedentary behavior induced adaptations and links to disease development are needed to elucidate underlying mechanism(s).

**Keywords:** physical activity, inactivity, exercise, chronic disease

This paper reports on the findings from the second of four sessions of a workshop entitled *Sedentary Behavior: Identifying Research Priorities* workshop organized by the National Heart, Lung, and Blood Institute, and the National Institute of Aging of the National Institute of Health. The second session entitled “*Physiology of Sedentary Behavior and its Relationship to Health Outcomes*” was led by a group of investigators with expertise in physiology and human relevant health outcomes. The group discussed the current state of scientific knowledge regarding the relations between sedentary behavior, physiology, and health outcomes culminating in a list of recommendations for future sedentary physiology research.

A large body of scientific evidence indicates that higher levels of physical activity and/or regular exercise provide benefit for a variety of health outcomes measures. Indeed, aerobic capacity, or cardiorespiratory fitness is a primary predictor of early mortality and disease risk (4, 19). Although mechanisms are not completely known, it is clear that regular physical exercise and greater cardiorespiratory fitness are related to better health at the molecular, cellular, and systems levels. Also, an increasing body of epidemiological evidence suggests that sedentary behavior (loosely defined as sitting, television viewing, couch time) is associated with increased risk for at least 35 chronic diseases/clinical conditions (8) and increased mortality rates (40). Epidemiological reports also suggest that regular defined bouts of exercise may not protect against early mortality in certain populations if excessive sedentary behavior occurs over time. Following this logic, we might speculate that the continuously sitting office worker who performs endurance training on a daily basis may still be at increased risk, despite meeting governmental guidelines for weekly physical activity levels. To be clear, the epidemiological data upon which such declarations are based are fraught with potential problems including the

possibility of reverse causation (i.e., does sedentary behavior cause disease or *vice versa*), reliance on self-reported estimates instead of objective measures of sedentary behavior, lack of a widely accepted and consistently applied operational definition of sedentary behavior, and a general lack of physiologically based studies. Overall, we believe that an improved body of knowledge of the physiological alterations that occur with increased sedentary behavior would aid in addressing issues related to what behaviors (avoiding sedentary, obtaining a certain level of physical activity, or both) are needed for optimal health. The following sections list recommendations and supportive rationale generated by the workshop. Each rationale falls under categories related to 1). Aerobic capacity, muscle strength and aging; 2). Central neural effects; and 3). General recommendations for sedentary physiology research.

## **AEROBIC CAPACITY, MUSCLE STRENGTH, AND AGING**

**Recommendation 1:** Determine the molecular basis by which sedentary behavior accelerates the loss of maximal aerobic capacity and muscle strength.

**Rationale:** A long history of bed rest studies (3, 31) and more recent studies in which active individuals are transitioned to physical inactivity for a defined period (36) provide hints regarding the systemic physiological events that are likely evoked by prolonged sedentary behavior. Overall, these studies suggest that chronic sedentary behavior contributes to reduced aerobic capacity, muscle strength, mass, and metabolic function. However, these models may not accurately reflect the effects of limited daily episodes of sedentary behavior in humans, and the molecular mechanisms of these effects remain unexplored.

Aging is associated with reduced cardiovascular, cardiorespiratory and skeletal muscle function, but evidence suggests that a portion of these changes may be due to an increase in sedentary behavior throughout the lifespan (30, 37). For example, it is well known that sedentary behavior impacts metabolic function such as reducing glycemic control (26) and increasing risk for type 2 diabetes (16). Therefore, we believe it is imperative that future studies determine the molecular basis by which sedentary behavior accelerates the loss of maximal aerobic capacity and muscle strength. Recent literature also suggests that other important factors may be impacted by sedentary behavior. For example, telomeres are protective regions of repetitive DNA at the ends of chromosomes that serve to maintain genetic stability (5). Telomeres undergo erosion as a consequence of cell division, oxidative stress, and inflammation—serving as a potential indicator of cellular aging (1). Telomere shortening may play a role in the disease development of many aging-associated diseases (10). Regular achievement of physical activity thresholds have been associated with reduced oxidative stress and inflammation (25) and several large population based studies have reported a positive association between the amount of physical activity and telomere length (13, 32). This suggests that sedentary behavior might contribute to telomere shortening. In a study of 7,813 women, those who exercised a moderate or high amount (at least 9 MET-hours/week) showed a 0.07 standard deviation increase in leukocyte telomere length, which corresponded on average to 4.4 years of aging (13). For sedentary behavior, however, time spent sitting was not associated with telomere length. Because sitting was self-reported in this study, measurement error may have led to attenuated associations and accounted for these null findings. However, it could also be possible that a threshold of daily physical activity or regular exercise is needed to inhibit telomere shortening. This is the only study to date to examine the role of sedentary behavior in telomeres and thus this hypothesis

warrants further study. In addition, recent evidence suggests that sedentary behavior may influence cognitive function by increasing brain volume and neurogenesis and angiogenesis within the brain (22, 41) .

Additional questions related to the relationships between exercise, aerobic capacity, and sedentary behavior remain. We must determine if traditional vigorous exercise training (one bout per day) impacts detrimental effects of excessive sedentary behavior and determine if reducing sedentary behavior and increasing non-exercise physical activity is enough, or if elevating or maintaining aerobic capacity is needed for maximal health. Recent epidemiological evidence suggests that sedentary behavior may increase risk for early mortality even if individuals perform regular defined exercise (40). These data are difficult to reconcile. Does this mean that an elite endurance athlete with very high aerobic capacity who spends 1-2 hours a day performing exercise training is at an increased risk for disease if they spend the rest of their day in sedentary pursuits (office job and sleeping)? Thus, the beneficial effects of healthy rest and sleep patterns for those performing high levels of physical activity were not considered. For example the beneficial effects of sedentary behavior and sleep in recovery and tissue healing from repeated high exertion were not considered. Such considerations may also be applicable for non-athletes who could regularly perform relatively intense endurance exercise and thus actively maintain or protect aging induced reductions in aerobic capacity.

Other physiological evidence counters the epidemiological evidence that sedentary behavior dictates adverse outcomes. Bed rest studies combined with exercise as a counter-measure show that daily bouts of exercise (<1 hour/day) protect against continuous (>23 hours/day) bed rest-induced diminishments in stroke volume, cardiac atrophy, overall cardiovascular remodeling, and muscle strength (12, 33, 38). Moreover comparison of insulin

sensitivity levels to physical activity and sedentary behavior found that indeed, those who were most sedentary had the lowest insulin sensitivity (2). However, a subset of individuals maintained higher insulin sensitivity through a small volume of high intensity movement despite being more sedentary (2). Because of the clear and reproduced evidence that maximal aerobic capacity is a powerful predictor of disease and mortality risk during aging (4, 19), it appears that simply reducing sedentary behavior would not result in more favorable outcomes, but rather that regular physical activity in order to improve aerobic capacity might be required to provide beneficial effects on morbidity and mortality. In summary, clinical trials are clearly needed to determine if traditional exercise training impacts the detrimental effects of excessive sedentary behavior and if reducing sedentary behavior and increasing physical activity is enough or if elevating or maintaining aerobic capacity is needed for maximal health. It is very likely that the answer to these recommendations may be outcome specific.

Therefore, we extended our first recommendation to include the following: *“Determine the molecular basis by which sedentary behavior accelerates the loss of maximal aerobic capacity, muscle strength, cognitive function, telomere length/genomic stability, and metabolic function that occurs with aging.”*

**Recommendation 2:** Determine if negative physiological consequences of increased sedentary behavior can be counteracted by reduced energy intake, or if increased energy cycling through avoiding sedentary behavior is obligatory for healthy aging.

**Rationale:** In invertebrate and vertebrae models caloric restriction increases longevity. Recent evidence in *Drosophila* suggests that the effects of caloric restriction may be dependent on a threshold level of daily activity or alternatively, an avoidance of sedentary behavior (18). Also, a threshold level of activity is needed to maintain proper control of dietary intake (23). However, energy restriction may be accompanied by decreases in energy expenditure by physical activity. Further, maintaining aerobic capacity throughout the lifespan is associated with reduced early mortality and disease risk and maintenance of aerobic capacity would be dependent on avoiding a totally sedentary lifestyle (7, 8). New data provide evidence that periods of relative energy deprivation followed by repletion, or energy cycling, are more advantageous for stem cell function than constant periods of excess caloric availability or deprivation (fasting or caloric restriction) (9, 34). Thus, avoiding chronic sedentary behavior and subsequently increasing physical activity may provide advantages of improved stem cell health, repair and immune surveillance in addition to overall improved caloric balance. Evolutionary reasoning suggests that our genes and metabolic pathways evolved and were selected during conditions in which avoidance of chronic sedentary behavior and obtainment of high daily activity (energy cycling) would have been required for survival (6). Thus, our genes and metabolic pathways would be optimized under said conditions. Together these concepts led the group to question if maintaining a normal body weight through pairing sedentary behavior with caloric restriction versus maintaining body weight through avoiding sedentary behavior and thus having higher “energy cycling” provides the best metabolic, cardiovascular, and overall health outcomes.

## CENTRAL NEURAL EFFECTS

**Recommendation 3:** Determine the molecular and physiological mechanisms underlying central and peripheral control of sedentary behavior and if they are impacted by energy balance.”

**Rationale:** Our technological gains have afforded us an environment in which survival does not depend on activity. In fact, our living built environments make it difficult to avoid a sedentary lifestyle. Nonetheless, there is no doubt that some individuals have a greater motivation and drive to be physically active and/or to avoid sedentary behavior. The drive for spontaneous activity is important for healthy aging. To wit, obese humans are less active and have greater volumes of sedentary behavior than normal weight humans suggesting that reduced activity may be causative for obesity (21). Epidemiological evidence suggests that excessive sedentary behavior increases risk for obesity (17). Interestingly, a hypercaloric diet (+1,000 kcals a day) reduced physical activity and increased sedentary behavior in free living humans (21), suggesting that energy balance has an impact on voluntary human movement. Avoidance of overfeeding-induced weight gain in humans is correlated with greater physical activity [also defined as non-exercise activity thermogenesis (NEAT)] (20). Rats who display resistance to dietary induced obesity partially accomplish this through enhanced spontaneous physical activity levels (movement within cages) (29). Thus, the central regulatory factors that dictate volume of sedentary behavior and physical activity have profound importance. Moreover, we should also examine if signals from peripheral tissues impact central control of voluntary movement as has been suggested by previous studies (14). Therefore, we concluded that studies by basic scientists are needed to determine the molecular and physiological mechanisms underlying central and peripheral control of physical activity and how are these impacted by energy balance.

## GENERAL RECOMMENDATIONS FOR SEDENTARY PHYSIOLOGY RESEARCH

**Recommendation 4:** Studies of sedentary behavior, including that of sitting time only, should focus on the physiological impact of a “lack of human movement” in contradistinction to the effects of physical movement.

**Rationale:** As it currently stands, researchers have concluded that sedentary behavior is distinct or independent from time spent in light, moderate, or vigorous intensity physical activity (28). For example, recent evidence shows that there is no difference in daily sitting time between women who achieve sufficient (>30 min/day) or insufficient (<30 min/day) levels of moderate vigorous physical activity (11). It is not clear how the spectrum of movement from sleep through bed rest, sitting, standing, low level physical activity to moderate and vigorous physical activity differ physiologically. Defining a behavior based upon a strict semantic definition of “sedentary behavior”, without understanding the continuum of physiology underlying human physical activity may be problematic. For example, is the “lack of movement” the converse of physical activity with respect to physiologic effects on health and the development of chronic diseases? We posit that physiological studies should include groups that may not only be “sedentary” by any strict definition, but also individuals who do not meet U.S. governmental physical activity recommendations. Thus, sedentary behavior should not be studied in isolation but rather in addition to the effects of low, moderate, and vigorous physical activity. This is important for the overall field, as most adults in the US and in other developed countries have limited daily physical activity, including a lack of programmed exercise (only ~3% achieve guidelines), low daily living physical activity (39), and high volumes of sitting time (28) in combination. It will be challenging but important to attempt to separate the physiological impact of increased sitting time from those of standing while performing light activity. We propose that future

physiological research endeavors recognize that both sedentary behavior and physical inactivity play a role in disease development.

**Recommendation 5:** Appropriate models or strategies are needed in both animal models and human subjects to study the links between sedentary behavior and the development of disease.

**Rationale 7:** One of the major challenges in studying the links between sedentary behavior and disease is the time course at which pathologies occur. Imposing bed rest or transitioning a highly active individual to a period of low activity will quickly lead to a change in function. Perfect examples are the reduced insulin sensitivity that occurs within hours after there is a transition to sedentary pursuits (15), and a decrease in skeletal muscle myofibrillar protein synthesis rates following the first 5 hours of unloading (35). This matching of reduced substrate uptake with reduced energy demand is a physiological and not a pathological alteration. If the sedentary behavior continues over a prolonged period current evidence suggests it could transition to a pathological condition that leads to disease (8), but the time course over which this occurs is unknown. Moreover, because chronic diseases can take years to develop it will be extremely difficult to mechanistically link a transition of reduced activity to actual chronic disease risk. This is further complicated by the fact that chronic diseases are polygenetic and are the result of interactions of various tissues. Given the large volume of biomedical research studying development of chronic diseases, a very small proportion has examined the physiological role of sedentary behavior as a cause of disease (24, 27). We are confident that new, unique and pertinent animal and human models can be developed to mechanistically link sedentary behavior to disease development. This will justify the monitoring and subsequent development of countermeasures for sedentary behavior. This also may provide therapeutic targets for those who are bound to a sedentary life due to disabilities.

## **FUTURE DIRECTIONS**

Future studies are needed to understand the underlying physiological processes by which sedentary behavior negatively impacts health. Studies are particularly needed that determine the molecular mechanisms by which sedentary behavior accelerates aging processes (e.g., reduced aerobic capacity and muscle strength). Studies to examine the central and peripheral regulatory features that control daily sedentary behavior also are needed.

ACCEPTED

## **Acknowledgments**

The workshop was sponsored by the National Heart, Lung and Blood Institute, the National Institute on Aging and the Office of Disease Prevention of the National Institute of Health. In addition to the listed authors, additional investigators took part as discussants. These discussants included Dr. Benjamin Levine (Univ. of Texas- Southwestern), Dr. Mark Tarnopolsky (McMaster University - Canada), Dr. Marc Hamilton (Pennington Biomedical Research Center - LSU), Dr. David Dunstan (Baker IDI Heart and Diabetes Institute & Deakin University, - Australia), Dr. Konstantin Khrapko (Harvard Medical School)

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## **Conflict of interest**

JAL has the following conflicts of interest: Conflicts of interest: Kersh medical Solutions, Amway International, Gruve Technologies Inc., Lumoback Inc., Gentag Inc.

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