Linking performance and chronic disease risk: indices of physical performance are surrogates for health

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ABSTRACT

Recent studies have identified a remarkable association between indices of athletic performance and optimal health of the general public. Both high aerobic capacity and high skeletal muscle strength are associated with lower mortality. Furthermore, higher aerobic capacity and often higher skeletal muscle strength are associated with a lower prevalence of most chronic diseases. Also, maintenance of aerobic capacity and skeletal muscle strength by lifelong physical activity delays the biological ageing in most organ systems, therefore delaying premature death. These facts raise the question whether associations between high aerobic capacity and muscle strength are causally or associatively related to either metabolic health or elite performance. If a causal relationship was noted at the molecular level, it would have major public health implications. In this review, evidence is presented for the assertion that research on elite athletes and chronic disease prevention by exercise is actually addressing the same biochemical, physiological and genomic phenomena.

It is well established that elite exercise performance, depending on sport, may be determined largely by the magnitude of aerobic capacity, muscle strength, or both.¹ More recently a remarkable association has become evident between indices of the potential of elite athletic performance and optimal health of the general public. Using mortality risk as an index of health, both high aerobic capacity² and high skeletal muscle strength³ are associated with lower mortality. Furthermore, higher aerobic capacity and often higher skeletal muscle strength are associated with a lower prevalence of most chronic diseases. Convincing epidemiological evidence exists that physical activity decreases coronary artery disease, type 2 diabetes, hypertension, stroke, breast cancer, colon cancer, sarcopenia, osteoporosis and loss of cognitive function⁴ or a clustering of risk factors such as the metabolic syndrome.⁵ In addition, maintenance of aerobic capacity and skeletal muscle strength by lifelong physical activity delays the biological ageing in most organ systems, therefore delaying premature death.⁶ ⁷

A major pending question is whether associations between high aerobic capacity and muscle strength are causally or associatively related to either metabolic health or elite performance. The answer to this question could have a significant impact if a causal relationship was noted at the molecular level. We can imagine the significance if those studying limiting molecular factors for elite athletic performance were in essence investigating the same biochemical, physiological and genomic mechanisms as those studying how physical activity prevents most common chronic diseases. Such an outcome of a causal relationship would boost the urgency for physical activity and inactivity research because a premise of medicine is that mechanisms of disease must be known to optimise scientifically-based therapies. Currently, it is difficult to get governmental and non-governmental agencies in some countries to fund “exercise” research applications. We can only speculate why, but one possibility is the stereotype of “exercise” and its connotation with elite athletes and sports performance rather than with fundamental medical science. Consequently, the perception of exercise science may be that it relates to athletes and sport, and not to public health, and that physical activity is not a fundamental environmental factor that establishes physiological genomics and can modify genomic expression to improve metabolic health. What if, in fact, research on elite athletes and chronic disease prevention by exercise are studying the same biochemical, physiological and genomic phenomena?

Here we begin to address this question. We will first apply the concept of Darwinian medicine which allows us to speculate that survival of the fittest and current elite athleticism have common gene-environmental interactions. Our idea is not new. Peak physical performance has previously been related to survival and selection, as described by Bennett and Ruben in 1979:

The selective advantages of increased activity capacity are not subtle but rather are central to survival and reproduction. An animal with greater stamina has an advantage that is readily comprehensible in selective terms. It can sustain greater levels of pursuit or flight in gathering food or avoiding becoming food. It will be superior in territorial defense or invasion. It will be more successful in courtship and mating.⁸

An experimental selection model supports our evolutionary-selection speculation. Over 11 generations, rats that ran for the longest time on motor-driven treadmills were selected and bred.⁹ Those who ran for the longest time had higher maximal oxygen consumption and lower risk factors for metabolic diseases than the subgroup of rats that ran the shortest time. Together, the evolutionary-related observations support the notion that peak aerobic and strength performance were probably selected during evolution.

Similarities in phenotypes (defined as the observable physical or biochemical characteristics of an organism, as determined by both genetic make-up and environmental influences) exist between sur-
vival in ancient times and athleticism. Restated another way, current characteristics of elite aerobic and strength athletes are similar to presumed functions that would enhance survival during previous human existence where automation, mechanisation and on-demand food sources did not exist. For example, the metabolic phenotype of high aerobic capacity that enhanced survival during gene selection over the past 100 000 years is similar to the phenotype of improved aerobic capacity that is developed after endurance training by both athletes and formerly sedentary individuals.\(^\text{10}\) The (mesomorphic) phenotype that improved the probability of survival by escaping predators/hunting for food during gene selection is also associated with survival in ageing and lower disease risk. Indeed, aerobic capacity, skeletal muscle strength, physical function and survival rate all decline with ageing. Remarkably, the rate of these declines can be slowed by aerobic and strength training. We therefore contend that, although many causal relationships remain to be elucidated for the delay of biological ageing by habitual physical activity, associative relationships currently exist. Our initial question can now be expanded to include whether the triple association of survival, athletic performance and prevention of most chronic diseases by physical activity are causal or associatively related.

According to Darwin, survival required adaptation to new environments. To survive, humans likely had to adapt to their need to change types of physical activity. Adaptation involves changes in gene transcription and protein levels, which requires altering the fractional distribution via protein turnover. For example, endurance-type physical activity requires more mitochondrial and enzymatic proteins while strength-type physical activity requires more contractile proteins.\(^\text{11}\) The ability to modify aerobic capacity and muscle mass was therefore a genetic characteristic selected to oscillate during alternating periods of activities requiring endurance (such as hunting for food) versus periods requiring strength (such as constructing shelters and defence).

Periods of detraining/inactivity can also be considered as parallels between athletes and the general population. We know that when training ceases there is a loss of performance due to the absence of the training stimulus. Most readers have experienced the feeling of changed performance on returning to perform physical activity after a lengthy absence. Biochemical and physiological changes during the reduced physical activity underlie the decline in performance on returning to that type of physical activity. The consequences of training cessation are already known in sports medicine. Athletes who become sick, injured or overtrained, “detrain” and lose their performance capacity. By the same token, in the current sedentary world, the removal of most daily physical activity in the general population by automation and technology does not maintain gene expression in its ancestral state.

Very little is known about the molecular regulatory mechanisms in the first several hours and days when physical activity is reduced. A recent review in *Nature* joins our previous publications in underscoring, “The mechanisms that mediate the therapeutic effects of exercise and the physiologic changes elicited by a sedentary lifestyle remain enigmatic.”\(^\text{12}\) A misconception is that molecular changes that initiate adaptations to detraining are the exact opposite molecular adaptations to exercise training. For example, endurance training and detraining increase and decrease mitochondrial density, respectively, so superficially they might appear mediated by reversible molecular changes. However, mitochondrial biogenesis requires 1500 nuclear-encoded proteins.\(^\text{13}\) In contrast, the loss of mitochondria requires a decline in mitochondrial membrane potential and mitochondrial autophagy by lysosomes,\(^\text{14}\) implying different molecular mechanisms. A second example is that, while resistance training and detraining induce hypertrophy and atrophy of skeletal muscle respectively, muscle protein degradation rates increase in the non-steady period for changes in muscle mass for both hypertrophying\(^\text{15}–\text{19}\) and atrophying skeletal muscle.\(^\text{20}\) In addition, Stein and Bolster\(^\text{21}\) have pointed out that a comparison of mRNAs from microarrays of atrophying skeletal muscle versus post-atrophy regrowth show minimal overlap. It is therefore our contention that it is unwarranted to state dogmatically that everything is known about the molecular mechanisms that initiate either detraining or loss of health by sedentary lifestyle, and we hypothesise that many molecular mechanisms differ between exercise training and detraining, as well as between natural physical activity and sedentarism.

An additional notion of ours is that causal determinations can only be made in the non-steady period of the first hours or days of reduced physical activity, not in a new steady state period after weeks of reduced physical activity. We speculate that initial changes in biochemistry on cessation of exercise training in elite athletes or at the beginning of a sedentary activity level in the general population without structured exercise may initiate a common cascade of events that both lower maximal exercise performance in the former and start protein maladaptations that lead to increased risk factors for chronic diseases in the latter. One example to support our contention is the drop in glucose tolerance noted in athletes with acute detraining. After as little as 2 days of no exercise in endurance-trained humans, insulin sensitivity declines to sedentary levels.\(^\text{22}–\text{23}\) This is analogous to a phenotype change experienced in the physical inactivity transition noted in young adult men who exhibit activity levels much below the historical norm for daily physical activity with only 6000–10 000 steps per day. When their physical activity levels decreased from 6000 to 1400 steps per day for 1 week, they exhibited raised plasma insulin levels during an oral glucose tolerance test.\(^\text{24}\) Furthermore, a second group of subjects performing 10 000 steps per day had elevated high plasma insulin levels during both oral glucose and oral fat tolerance tests, gained 7% intra-abdominal fat, and lost 1.2 kg of lean body mass after 2 weeks of 1300 steps per day.\(^\text{24}\) We contend that the loss of physical activity from their expected homoeostatic set points selected during evolution decreases metabolic fluxes and lean body mass in these physically inactive individuals, resulting in chronic disease risk phenotypes. This drop in insulin sensitivity from endurance trained to sedentary levels suggests that health status phenotypes are on a continuum,\(^\text{25}\) supporting our original idea. Along these lines, it has recently been estimated that metabolic syndrome is present in 30% of retired National Football League (NFL) players, with a prevalence of 60% in retired linemen.\(^\text{26}\) Thus, a potential cause of most chronic diseases that merits further investigation is the deviation from a natural set point of high physical activity.

We continue to remain sceptical that a single drug will be developed as a treatment to counter the predicted hundreds of detrimental biochemical and genomic changes that occur when physical activity is reduced,\(^\text{27}\) and others are now joining our earlier contention.\(^\text{28}\) Our doubt is based on the ideas that (1) training adaptations to exercise are specific to the type of exercise; (2) adaptations to exercise are widespread, occurring in multiple cell types, tissues, organs and cell-cell communication; and (3) no single drug action will collectively mimic the protective effects of physical activity on the development of...
coronary artery disease, type 2 diabetes, hypertension, stroke, breast cancer, colon cancer, sarcopenia, osteoporosis and decline in cognitive performance.

While to some the inverse association between mortality and elite performance may not be surprising, others dismiss the science of adaptive mechanisms to habitual physical activity and sedentary lifestyle as not meritorious of research support. Nay-sayers need to understand that our failure to know molecular mechanisms of disease from sedentary living to today’s major chronic, non-communicable diseases has produced a void in knowledge that prevents optimal therapies to improve health. In the age of “translational medicine”, important clues for better health can probably be revealed by investigating the potential causal relationships among survival, athletic performance and prevention of most chronic diseases by physical activity.

Taken together, it is our contention that many of the same inherited genes whose proteins functioned to maximise aerobic capacity and skeletal muscle strength for survival during selection set the physiological norm for fluxes in metabolic pathways, anabolic events for hypertrophied skeletal muscle mass, high endothelial function, healthy storage of intramuscular fat, etc. Remarkably, the loss of our ancestral norm for physical activity reverses the aforementioned processes, contributing to chronic disease risk. We contend that the knowledge of the natural gene expression that allows one individual to excel in elite athletics can be applied to non-athletes to prevent chronic disorders, delay decline in most organ systems (biological ageing) and improve health. Hopefully, the realisation that the genetic mechanisms in those who inherited genes whose proteins functioned to maximise aerobic performance and prevention of most chronic diseases by physical activity.

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REFERENCES