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## Lack of exercise is a major cause of chronic diseases

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### Abstract

Chronic diseases are major killers in the modern era. Physical inactivity is a primary cause of most chronic diseases. The initial third of the article considers: activity and prevention definitions; historical evidence showing physical inactivity is detrimental to health and normal organ functional capacities; cause vs. treatment; physical activity and inactivity mechanisms differ; gene-environment interaction [including aerobic training adaptations, personalized medicine, and co-twin physical activity]; and specificity of adaptations to type of training. Next, physical activity/exercise is examined as primary prevention against 35 chronic conditions [Accelerated biological aging/premature death, low cardiorespiratory fitness (VO<sub>2</sub>max), sarcopenia, metabolic syndrome, obesity, insulin resistance, prediabetes, type 2 diabetes, non-alcoholic fatty liver disease, coronary heart disease, peripheral artery disease, hypertension, stroke, congestive heart failure, endothelial dysfunction, arterial dyslipidemia, hemostasis, deep vein thrombosis, cognitive dysfunction, depression and anxiety, osteoporosis, osteoarthritis, balance, bone fracture/falls, rheumatoid arthritis, colon cancer, breast cancer, endometrial cancer, gestational diabetes, preeclampsia, polycystic ovary syndrome, erectile dysfunction, pain, diverticulitis, constipation, and gallbladder diseases]. The article ends with consideration of deterioration of risk factors in longer-term sedentary groups; clinical consequences of inactive childhood/adolescence; and public policy. In summary, the body rapidly maladapt to insufficient physical activity, and if continued, results in substantial decreases in both total and quality years of life. Taken together, conclusive evidence exists that physical inactivity is one important cause of most chronic diseases. In addition, physical activity primarily prevents, or delays, chronic diseases, implying that chronic disease need not be an inevitable outcome during life.

## 1. Organization of article

### 1.1 Entire article

An underappreciated primary cause of most chronic conditions is the lack of sufficient daily physical activity (“physical inactivity”). Overwhelming evidence proves the notion that

reductions in daily physical activity are primary causes of chronic diseases/conditions and that physical activity/exercise is rehabilitative treatment (therapy) from the inactivity-caused dysfunctions. The general strategy of presentation divides the article into three major sections: 1) Conceptual information forming the foundation to understand the remaining article; 2) Primary literature supporting physical inactivity as a primary cause to a myriad of chronic conditions/diseases, and 3) additional considerations. The aim of the entire article is to bring better understanding and insight into the observation that a lack of physical activity at ancestral levels initiates 35 pathological and clinical conditions.

### 1.2 First third of article

Conceptual information is presented in five parts in the first third of the article. 1) Definitions of forms of physical activity, functional capacity, types of fitness, chronic diseases, types of prevention so that the reader understands how the article employs these words; 2) A brief chronology of the three-millennia history that recognizes that physical inactivity reduces functional capacity and health; 3) Cause vs. treatment are discussed to emphasize that physical inactivity is a primary cause of chronic conditions/diseases; 4) Growing evidence that mechanisms by which inactivity causes disease differ from mechanisms by which physical activity is a therapy/treatment to act as a primary preventer of disease; and 5) Gene-environment interactions have varying degrees of gene involvement in the magnitude of change to physical activity.

### 1.3 Center portion of article

Physical inactivity is a primary cause initiating 35 separate pathological and clinical conditions. Many of the 35 conditions are subdivided under major categories, such as loss of functional capacities with chronological aging; metabolic syndrome, obesity, insulin resistance, prediabetes/type 2 diabetes, non-alcoholic liver disease, cardiovascular diseases, cognitive functions and diseases, bone and connective tissue disorders, cancer, reproductive diseases, and diseases of digestive tract, pulmonary, and kidney.

### 1.4 Final portion of article

The article ends with considerations of clinical significance, increasing risk factors during long-term sedentarism, the developmental and clinical consequences of inactive childhood/adolescence, and policy.

## 2. Definitions

### 2.1 CDC definitions of forms of physical activity

Verbatim definitions for exercise and health are from the US Centers for Disease Control and Prevention (CDC) are used where possible due to the authority they carry (90). US governmental definitions were selected for the article to provide the framework for this article's discussions of how 1) exercise/physical activity prevents chronic diseases and 2) lack of physical activity is a primary event that causes chronic diseases.

**Exercise**—“A subcategory of physical activity that is planned, structured, repetitive, and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective”, as defined by CDC (90).

**Exercise training**—“Physical activity performed during leisure time with the primary purpose of improving or maintaining physical fitness, physical performance, or health”, as defined by CDC (90).

**Physical activity**—“Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level. Physical activity generally refers to the subset of physical activity that enhances health”, as defined by CDC (90).

**Health**—“A human condition with physical, social and psychological dimensions, each characterized on a continuum with positive and negative poles”, as defined by CDC (90).

**Health-enhancing physical activity**—“Activity that, when added to baseline activity, produces health benefits. Brisk walking, jumping rope, dancing, playing tennis or soccer, lifting weights, climbing on playground equipment at recess, and doing yoga are all examples of health-enhancing physical activity”, as defined by CDC (90).

As previously stated, this article will concentrate on the use of physical activity to prevent physical inactivity, and, thus, prevent many chronic diseases.

## 2.2 Definition of physical inactivity

CDC definitions for exercise do not include a definition of “physical inactivity”. We define physical inactivity as “physical activity levels less than those required for optimal health and prevention of premature death”. Further consideration of the definition is given in section entitled, “Prevention of death by primary prevention of physical inactivity”.

## 2.3 Definition of functional capacity

We define “functional capacity” as the ability of a cell, organ, system, or body to maintain homeostasis within their narrow limits of survival in response to a specified stress. If an external stress disrupts homeostasis beyond an organism's functional capacity, life may not be sustained. Diminished ability to adapt to stressors increases the likelihood of death. Functional capacity is pliable; declining rapidly with extreme physical inactivity or more slowly with aging, while preventing inactivity can increase functional capacity (considered in specific detail in the aging section). Importantly, a direct relationship between functional capacity and survival is a cornerstone of general medicine theory. A major predictor of functional capacity is maximal aerobic capacity ( $VO_2\text{max}$ ), which while directly testing cardiovascular fitness and integrity also represents a combination of other physiologic components. For instance,  $VO_2\text{max}$  also depends on pulmonary and muscle function, health status of other organ systems, nutritional status, medications, orthopedic limitations, and others (352). An aerobic functional capacity in patients under 4-metabolic equivalents (METs), a typical demand during normal daily activities, increases postoperative (time from admission to discharge from surgery) cardiac and long-term risks (155). In another study,

patients were grouped by MET capacity in relationship to complication prevalence after they underwent angiographically verified coronary artery disease and subsequent open abdominal nonvascular surgery. (265). Those from the group < 4 METs had cardiologic complications in 64% of cases, the 4–7 METs group had 29%, and the 7–10 METs group had 8%. These remarkable findings can be extrapolated to other stresses where the probability of complications, and even survival, is dependent upon the functional capacity needed to maintain homeostasis.

#### 2.4 Physical fitness vs. physical activity

Some people incorrectly use physical fitness and physical activity interchangeably. The CDC defines physical fitness as “The ability to carry out daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and respond to emergencies. Physical fitness includes a number of components consisting of cardiorespiratory endurance (aerobic power), skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, balance, speed of movement, reaction time, and body composition”. The CDC defines physical activity as “Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level” (90)..

Inherited genes and their interaction with physical activity levels determine physical fitness. However, chronic physical activity levels themselves modulate fitness. Further, the levels of physical activity, themselves, modulate whether fitness improves. For example, Sisson et al. (478) concluded that the most important finding of their study was that greater volumes of exercise were associated with a lower probability of being a nonresponder. The percentage of non-responders at a given level of training progressively decreased as the exercise volume increased.

#### 2.5 Cardiorespiratory fitness (CRF)

We define CRF as the capacity of the cardiovascular (heart and blood vessels) and respiratory (lungs) systems to supply oxygen-rich blood to the working skeletal muscles and the capacity of the muscles to use oxygen to produce energy for movement. The gold standard to determine CRF is the aforementioned  $VO_2\text{max}$ , or maximum aerobic fitness. However in large clinical human studies, an acceptable surrogate for  $VO_2\text{max}$  is the length of time running or cycling in standardized test, assuming appropriate physiological/biochemical/psychological proof of exhaustion is obtained (65, 263).

The majority of data about fitness and physical activity is focused on aerobic fitness. Data indicates that rapid, severe physical inactivity can rapidly decrease CRF. For instance, in the Dallas Bed Rest study, healthy, young males'  $VO_2\text{max}$  decreased 27% after 20 days of continuous bed rest (454) and another study in Denmark 2 weeks of reducing daily step number from 10,501 to 1344  $VO_2\text{max}$  decreased 7% (389).

#### 2.6 Strength fitness

We define strength fitness as the capacity of the skeletal muscle to move an external load. Strength is highly dependent upon skeletal muscle mass, which contains a major genetic

component (Discussed later in Twin studies-Modulation of twin health by physical activity), and is sensitive to decreased mechanical loading resulting in skeletal muscle atrophy regardless of endowed muscle mass (49, 508).

## 2.7 Balance and flexibility fitness

We define balance fitness as the ability to control the body's position throughout movement, and flexibility fitness as the ability to achieve an extended range of motion. Both have components of genetic inheritability and are also trainable (Discussed later in Twin studies-Modulation of twin health by physical activity).

## 2.8 Definition of chronic diseases and their prevalence

We define chronic disease as a disease slow in its progress (decades) and long in its continuance, as opposed to acute disease, which is characterized by a swift onset and short course.

Medicine, public health, pharmaceutical industry, and educational systems have reduced infectious diseases and early life mortality resulting in record average life spans for much of the human population. In place of infectious diseases most people in the US now die of chronic diseases.

The CDC Website states, “Chronic diseases—such as heart disease, cancer, and diabetes—are the leading causes of death and disability in the United States. Chronic diseases account for 70% of all deaths in the U.S., which is 1.7 million each year (85). These diseases also cause major limitations in daily living for almost 1 out of 10 Americans or about 25 million people (85). The CDC further wrote, “Chronic diseases – such as heart disease, stroke, cancer, diabetes, and arthritis – are among the most common, costly, and *preventable* of all health problems in the U.S.” (86). In addition to the CDC, former US Secretary of Health and Human Services, the Honorable Michael O. Leavitt in the 2008 Physical Activity Guidelines for Americans, wrote,

Along with President Bush, I believe that physical activity should be an essential component of any comprehensive disease prevention and health promotion strategy for Americans. We know that sedentary behavior contributes to a host of chronic diseases, and regular physical activity is an important component of an overall healthy lifestyle. There is strong evidence that physically active people have better health-related physical fitness and are at lower risk of developing many disabling medical conditions than inactive people (532).

## 2.9 Definitions of types of prevention

For the purposes of this article, *physical activity* is presented as *primary prevention of physical inactivity*. The CDC defines physical inactivity as an actual cause of chronic conditions (213, 345). Physical activity, itself, rarely causes chronic conditions, e.g., participation in specific sports improves general health, but can increase the risk of osteoarthritis in specific populations (71); discussed later in section “Osteoarthritis”. The next definitions are taken from a commissioned paper by the U.S. Institute of Medicine (267).

**Prevent**—Prevent implies taking advanced measures against something possible or probable. Prevention in medicine has been divided into three progressive stages – primary, secondary, and tertiary (267).

**Primary prevention**—“Primary prevention refers to health promotion, which fosters wellness in general and thus reduces the likelihood of disease, disability, and premature death in a nonspecific manner, as well as specific protection against the inception of disease” (267).

**Secondary prevention**—“Secondary prevention refers to the detection and management of pre-symptomatic disease, and the prevention of its progression to symptomatic disease. Screening is the dominant practice...The margins between primary and secondary prevention can at times blur (268).”...For example, “If hypertension is defined as a disease, its treatment is secondary prevention; if defined as a risk factor for coronary disease that does not yet exist, it is primary prevention” (267).

**Tertiary prevention**—“Tertiary prevention refers to the treatment of symptomatic disease in an effort to slow its further progression to disability, or premature death...there is a legitimate focus on prevention even after disease develops, such as the prevention of early cancer from metastasizing, or the prevention of coronary disease from inducing a myocardial infarction or heart failure. This domain also encompasses rehabilitation, the purpose of which is to preserve or restore functional ability, and thus prevent its degeneration” (267).

### 2.11 Application of exercise to prevention categories

Examples for our view that exercise is a primary, secondary, and tertiary preventer of disease are as follows: 1) Primary prevention (direct treatment of cause to prevent disease occurrence) is voluntary avoidance of physical inactivity or treatment of physical inactivity with physical activity; 2) Secondary treatment [eliminating one cause (physical inactivity) of existing hypertension by eliminating physical inactivity] is treatment of existing hypertension with physical activity; and 3) Tertiary prevention with physical activity is cardiac rehabilitation where exercise benefits do not reverse the anatomical pathology from myocardial infarction. We propose that the greatest health benefit of physical activity is primary prevention of 35 chronic diseases/conditions to become clinically overt. This article is largely restricted to consideration of primary prevention of inactivity as an actual cause of chronic conditions.

### 3. Overview for next three sections

While, concerns that physical inactivity is detrimental to health have been documented for over three millennia, much remains unknown, e.g., a) how to change the sedentary behavior of the 92% of U.S. adolescents and > 95% of adults who do not met the U.S. Department of Health and Human Services guidelines for physical activity (527), b) how to have health care professionals provide effective individualized exercise prescriptions, and c) what are the molecular links between inactivity and chronic disease that will provide a policy tool in

the same way as the molecular link between the carcinogen in tobacco and lung cancer did (129).

#### 4. Summary of daily step reductions from antiquity

Historical evidence shows that physical inactivity is prevalent in today's society relative to historical levels (385). **Estimated daily step numbers have declined ~50% to ~70% since the introduction of powered machinery.** (Table 1).

#### 5. History of inactivity's compromising effects on function and health

Three millennia of evidence exist to indicate historical recognition that physical inactivity is detrimental to health by reducing the functional capacity of most organ systems in humans, mammals, and rodents.

##### 5.1 Ancient India (~1500–600 BC)

A historical review by Tipton (519) described the tridosha doctrine in India, which contended that the three humors regulated all functions of the body. When humors were in equilibrium, good health was present. However, sedentary living and lack of exercise could displace one or more of the humors, impairing health and potentially leading to illness and death. Susruta (600 BC) was convinced a sedentary lifestyle elevate the kapha humor to a level that could disrupt humoral equilibrium resulting in a disease state and potential death. He included exercise in his recommendations to prevent the occurrence of diseases.

##### 5.2 Hippocrates (~450 BC)

Quotations attributed to Hippocrates promote the primary prevention of disease by physical activity.

“If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health” (240).

“If there is any deficiency in food and exercise the body will fall sick” (477).

“Walking is man's best medicine” (240).

“All parts of the body, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are unused and left idle, they become liable to disease, defective in growth and age quickly” (278).

##### 5.3 Bed rest (1945–1955)

**Three days of physical inactivity produces glucose intolerance** (47). Paul Dudley White, one of Dwight Eisenhower's cardiologists after the President's heart attack on September 24, 1955, prescribed physical activity to President Eisenhower long before the end of the standard treatment of **6-months bed rest for a heart attack**. The medical community followed White's practice of substituting physical activity for bed rest in management of acute coronary syndromes, with bed durations **progressively decreasing to 2 weeks in 1980** in



2005 (340). A 2011 meta-analysis concludes that exercise training has greatest beneficial effects on left ventricular remodeling in clinically stable post-MI patients when training starts one week following the MI (227).

#### 5.4 Initial epidemiology (1949–1953)

Jeremiah Morris is recognized as the person who first used physical activity in epidemiology (his history is available (43). In 1953, Morris and co-workers compared bus drivers, who are sedentary in their occupation, with the physically active bus conductors, who were constantly moving up and down double-decker buses to collect fares in London. Physically active conductors had a 30% lower incidence rate of coronary heart disease (CHD) than the physically inactive bus drivers (353). Furthermore, even the physically active conductors who did develop CHD with age were better off, presenting with less severe disease and lower fatality rates than the inactive bus drivers (353). However, while  $VO_2\max$  was not determined in Morris' report, others have since shown that workers in physically active occupations have higher aerobic capacity than their inactive peers (220). Morris' 1953 report (353) is a milestone as the initial publication documenting daily physical inactivity is associated with increased morbidity and mortality (43).

In his 10<sup>th</sup> decade of Morris' life, he wrote, “We in the West are the first generation in human history in which the mass of the population has to deliberately exercise to be healthy. How can society's collective adaptations match?” (43, 354).

#### 5.5 Primary prevention: Human space flight (1957–1961)

The Space Race for national security began in earnest in 1954 leading to the successful launch and orbit of Sputnik from the USSR on October 4, 1957. Four years later on April 12, 1961 Yuri Gagarin became the first human in outer space and the first to orbit the Earth. The Space Race hastened physiological exploration that the microgravity experienced in space reduced human functional capacities. As an outcome, NASA researched countermeasures to the microgravity-induced functional loss during spaceflight that relied on experimental bed rest on Earth, an extreme form of inactivity. However, interest in the primary mechanisms of inactivity was a lower priority.

Today over 6500 publications arise from a PubMed search for the terms spaceflight and physiology. Inspection of this body of literature led Vernikos and Schneider (540) to contend that spaceflight results in losses of functional capacities in multiple organ systems, similar to an accelerated model mimicking aging. For example, they conclude that bone atrophy occurs 10-times faster in spaceflight than with aging. Similarly, reductions in immune function, sensitivity of arterial baroreflex, maximal stroke volume, maximal cardiac output, and  $VO_2\max$  also occur more rapidly in spaceflight than in aging (540, 561). (Cross-reference: Importance of exercise in microgravity)

#### 5.6 Bed rest book (1965)

The preface of Browse's book “The Physiology and Pathology of Bed Rest”, published in 1965 states that the principle purpose of the book,



...is to lay bare our ignorance of the whole subject, to stimulate research...The dangers of bed rest are so many, and in some cases so final, that we should always be striving to discard it from our therapeutic armamentarium...and to emphasize the absurdity of using a non-specific treatment for specific diseases without reason or proven value (68).

The book carefully documents the widespread systemic deterioration of the body when continuous bed rest occurs. Some of the pathologies documented are: postural hypotension, tachycardia, kidney stones (renal calculi), loss of skeletal muscle mass, weakness in antigravity muscles, pressure ulcers, osteoporosis, constipation, deep vein thrombosis, pulmonary embolism, pneumonia, and difficulty with micturition.

### 5.7 Dallas Bed Rest Study (1960's)

Saltin, et al. (454) studied five healthy college-age males during 20 days of continuous bed rest. During acute exercise following bed rest reductions of 28%, 11%, 26%, and 29% in  $\text{VO}_2\text{max}$ , ventricular volume (ml), maximal cardiac output, and maximal stroke volume occurred, without a change in maximal A- $\text{VO}_2$  difference. Further detrimental changes with bed rest were increased heart rate at a submaximal workload of 600 kpm/min from 129 to 154 beats/min and total peripheral resistance (TPR) increasing from 449 to 520 TPR units. From the 10<sup>th</sup>–20<sup>th</sup> day of bed rest day resting heart rate increased from 47 to 51 beats/min.. (Cross-reference: Cardiac Function; Cardiac output during exercise: contribution of the cardiac, circulatory and respiratory systems)

### 5.8 Sitting studies (2000's)

A perspective was proposed as to whether **too** much sitting is distinct from too little exercise (218, 317, 392, 393). Owen et al.'s 2010 review states,

Further evidence from prospective studies, intervention trials, and population-based behavioral studies is required...many scientific questions remain to be answered before it can be concluded with a high degree of certainty that these adverse health consequences are uniquely caused by too much sitting, or if what has been observed so far can be accounted for by too little light, moderate, and/or vigorous activity (392).

A 2010 review co-authored from multiple research sites concluded from an examination of 43 papers, "Limited evidence was found to support a positive relationship between occupational sitting and health risks. The heterogeneity of study designs, measures, and findings makes it difficult to draw definitive conclusions at this time" (537). The concept of intermittency of lack of weight bearing by sitting is supported by older basic science research. In rats cycling 4 times/day through periods of weight bearing and non-weight bearing (hindlimb suspension), soleus muscle atrophy was prevented by 4 × 15-min periods of ground support during 12 hrs of the day (118).

### 5.9 Animal wheel lock studies (2000's)

In order to optimize primary prevention by physical activity, mechanisms by which physical inactivity initiates risk factors for chronic diseases must be elucidated for the optimal

science-based physical activity prescription. One animal model used young male rats that underwent 3 weeks of voluntary running and then had their wheels locked (WL) for 5 hrs (WL5), 29 hrs (WL29), or 53 hrs (WL53). Within 53 hrs two major changes in functional capacities were observed, decreased submaximal insulin sensitivity and enhanced storage of TG in visceral adipose tissue. (For the purposes of this article, visceral and intra-abdominal adipose tissues are considered similar and the term visceral is used). Specifically, submaximal insulin-stimulated 2-deoxyglucose uptake, insulin binding, insulin receptor  $\beta$ -subunit (IR $\beta$ ) protein level, submaximal insulin-stimulated IR $\beta$  tyrosine phosphorylation, glucose transporter-4 protein level, and Akt/protein kinase B Ser473 phosphorylation (an index of proximal insulin signaling) in the epitrochlearis muscle, returned to sedentary levels at WL53 (293). Further, the epididymal adipose tissue mass at WL53 weighed 25% more than at WL5 in the same rats as studied for insulin sensitivity above.

#### 5.10 Translation studies - Reduced stepping studies in humans (2000's)

While continuous bed rest is a model examining the absence of physical activity, a novel human reduced-activity model was designed to test the effects of reduced, rather than lack of, physical activity on metabolic health. Step numbers were reduced by taking elevators instead of stairs and riding in cars instead of walking or bicycling within a free-living environment by young, healthy male adults who were not undertaking >2 hrs/wk exercise at the start of the study. After reducing daily step number from 6203 to 1394 for 3 weeks, areas under the curve (AUC) for plasma insulin during an oral glucose tolerance test (OGTT) progressively increased 53%, 61%, and 79% after 1, 2, and 3 weeks, respectively (389).

In a second study, subjects reduced daily steps from 10,501 to 1,344 (where there are ~2000 steps in a mile). After 2 weeks, VO<sub>2</sub>max decreased 7%, peripheral insulin sensitivity decreased by 17% with concurrent decreases in insulin-stimulated ratio of pAkt-Thr<sup>308</sup>/total Akt in skeletal muscle. Body composition was also significantly altered by 2 weeks of reduced stepping with visceral adipose tissue mass increased 7%, total fat-free mass decreased by 1.2 kg, 0.5 kg of it in the legs, while total-body fat mass and BMI were unchanged (286, 389). Thus, an inverse relationship existed between gain of visceral adipose tissue and loss of lean mass, indicative of body composition repartitioning. Similar observations have been made in a rat WL model. In a different WL experiment visceral adipose tissue mass, but not lean mass increased independent of food intake after 173 hours of WL followed 6 weeks of voluntary running (310). Thus, both human and rat models of reduced daily steps increased visceral adipose tissue while diminishing lean mass, independent of caloric increases.

#### 5.11 Clinical significance

Short-term reductions in daily step number (producing less daily physical activity) cause decreased CRF, loss of insulin sensitivity, reduced lean mass and increased visceral adipose tissue. These functional decrements help explain the link between reduced physical activity and the risks that have been associated with the progression of chronic disorders and premature mortality (389). Using physical activity prescriptions to prevent physical inactivity would help maintain functional capacities.

## 5.12 Summary: Inactivity causes loss of functional capacities

Taken together, the historical work provides overwhelming evidence that physical inactivity cause decreases in capacities of functional systems, leading to premature deterioration of health in humans. The Copenhagen study of reduced stepping, while low in subject number, is particularly relevant to everyday living because the reduced physical activity level is similar to the step numbers performed in a free-living environment by billions of humans worldwide in both developed and developing countries.

## 6. Cause vs. treatment

A sedentary lifestyle over several years is associated with increased risk for type 2 diabetes, cardiovascular disease, and premature mortality. What is much less appreciated is the high cost of physical inactivity even in the short term. Booth *et al.* have been drawing attention for years to the societal and individual burden of inactivity-related chronic diseases. They remind us that while exercise is a treatment to prevent many chronic diseases, it is the lack of regular exercise or physical inactivity that is one of the actual causes of many of these diseases” (481).

Convincing proof that physical inactivity causes primary deterioration of function is provided from extensive historical and scientific evidence. Thus, physical activity can prevent physical inactivity-induced chronic diseases (left panel of Fig 1). In contrast (right panel of Fig 1), physical activity can treat against lung cancer-induced dyspnea, a common side effect 1 to 6 years after lung cancer resection (179) (Right panel Fig. 1). Thus, in the left panel physical activity addresses the cause of the disease, while in the right panel physical activity only acts as a treatment against a disease in which it cannot prevent. We will focus on the disease processes of the left panel in this article.

## 7. Mechanisms of physical inactivity and activity differ

Mechanisms of physical inactivity are considered anti-parallel, rather than in series (continuum) to physical activity (210, 570). Physical activity and inactivity reside in different mechanistic planes, and are not merely mirror images of each other as is commonly considered (discussed below). Optimal therapies and preventive strategies require knowledge of causal mechanisms. Thus, it is important to understand that some of the mechanisms by which inactivity causes chronic diseases differ from mechanisms by which exercise acts as primary prevention of same diseases.

One example is that inactivity and exercise differ with regards to time courses of structural changes in conduit arteries and changes in endothelial function. This difference is summarized nicely in a review where Thijssen *et al.* state: “However, the nature and impact of inactivity and exercise on vascular structure and function suggest that inactivity and exercise are not simply the opposite ends of a linear spectrum of physiological adaptation” (506). In our figure 2, distinct mechanisms by which inactivity and/or exercise alter conduit size and endothelial function are outlined. For instance inactivity results in immediate negative remodeling of the vessel, while activity requires 4–6 weeks to positively remodel the vessel.

A second example that inactivity and exercise are not mirror images of one another is found from global analysis of skeletal muscle gene expression, before bed rest, immediately after bed rest, and after 4 weeks of post-bed rest training. Compared to pre-bed rest levels, 9 days of bed rest altered 4500 mRNAs. If physical activity were merely the reverse of inactivity then all 4500 would be hypothesized to return to pre-bed rest levels following 4 weeks of training. However, a normalization of expression failed to occur in 20% of the 4500 genes that changed with bed rest. This observation led Vaag and co-workers (8) to speculate that rather severe and long lasting adverse alterations in mRNA levels may develop in important biological pathways relevant to their general health after 9 days of bed rest.

A third example is by Stein and Bolster (491) who compared muscle atrophy (311) to skeletal muscle regrowth from atrophy (184), and reiterated by Greenhaff and Hargreaves (210). Again, if physical activity were the opposite of physical inactivity, then the expected result would be many of the same genes changes would be similar for atrophy and regrowth. However, comparison of these two gene lists showed virtually no common gene names on both lists. These examples illustrate a fundamental principle of biochemistry, which Stein and Bolster concisely state, “This is a common finding in biochemistry. Anabolic and catabolic pathways are usually separate” (491), or put another way, opposite processes work through entirely different mechanisms rather than altering the level of one pathway. Further biochemical examples include; irreversible steps in glycolysis and glycogen synthesis, protein synthesis and degradation, lipolysis and lipogenesis, and mitochondrial biogenesis and mitophagy, all of which support the idea that exercise and inactivity are not merely opposites of each other. Thus, a single molecular paradigm to explain adaptations to exercise and inactivity does not exist.

## 8. Gene-Exercise/physical inactivity interactions

Physical fitness and physical activity/inactivity interact with genes. While many fitness examples of gene-environment could be chosen,  $\text{VO}_2\text{max}$  will be used because it is well studied and integrates the function of multiple organs at multiple levels (i.e. tissue, cell, protein, and gene). (Cross-reference: Genetics: environment and their interaction)

### 8.1 Genetic Component Alone

Phenotype responsiveness variability to aerobic training

Using untrained pairs of monozygotic twins, dizygotic twins, and brothers approximately 40–50% of  $\text{VO}_2\text{max}$  was estimated to be due to genetics (57). Similarly, pairs of identical twins had significantly more similar increases in  $\text{VO}_2\text{max}$  than unrelated twin pairs after aerobic training in three papers in the mid-1980s (217, 421, 474). The papers led to the milestone paper reporting that some individuals experiencing little or no gain in  $\text{VO}_2\text{max}$ , whereas others gained  $>1.0$  L/min in 481 sedentary subjects (55). A 2.5-times greater variance existed between families than within families in the  $\text{VO}_2\text{max}$  response variance.

### 8.2 Higher $\text{VO}_2\text{max}$ associates with better health

The 1996 US Surgeon General's Report (531) concluded that high CRF decreases the risk of cardiovascular disease (CVD) mortality. High  $\text{VO}_2\text{max}$  is associated with “positive health”;

low VO<sub>2</sub>max is associated with “negative health.” Remarkably, low CRF was a stronger predictor of death than clinical variables or established risk factors, such as hypertension, smoking, and diabetes, as well as other exercise-test variables, including ST-segment depression, the peak heart rate, or the development of arrhythmias during exercise in both healthy subjects and those with CVD (363). Specifically, subjects aged 60 and older with low CRF had notably higher mortality risk from all causes than those with high CRF (499). Maintaining the highest possible VO<sub>2</sub>max is a primary preventer of morbidity and mortality from low VO<sub>2</sub>max (discussed later). Further information on the role of genes, physical activity, VO<sub>2</sub>max (CRF), and health is presented next.

### 8.3 Using VO<sub>2</sub>max to identify “health” genes

**Theoretic selection of specific genes to optimize functional capacities—**In 1979, Bennett and Ruben elegantly described a basis for natural selection of genes by physical activity to maximize inherited potential VO<sub>2</sub>max,

“We believe that this increased stamina and sustainable activity were important selective factors from the outset... 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” (34).

The quotation hints that some genes were selected during evolution to support high levels of physical activity and the ability to adapt to physical activity. However, recent observations that a small portion of the population is low responders for VO<sub>2</sub>max suggest a greater biological complexity than known in 1979.

**Genes associated with plasticity of VO<sub>2</sub>max—**In 1998, Bouchard and co-investigators published, “Maximal heritability estimates were at least 50%, a value inflated to an undetermined degree by inclusion of nongenetic shared factors” (56). Timmons employed a novel approach to improve the examination of complex physiological variables in human models. To identify genes responsible for variance of VO<sub>2</sub>max plasticity, Timmons et al. (517) used a novel approach by first conducting mRNA expression microarray profiling, which were then used to produce molecular predictors to locate or rank a discrete number of genes that correlate with the change in VO<sub>2</sub>max following endurance training. Follow up studies allowed for subsequent targeted genotyping and, hence, discovery of key genetic variants responsible for the variance of VO<sub>2</sub>max plasticity. A signature of 29 mRNAs and of 11 single nucleotide polymorphisms (SNPs) were identified that predicted ~50% and ~23%, respectively, of the estimated variance for VO<sub>2</sub>max plasticity following aerobic training in humans (517). Timmons et al. (517) noted two remarkable characteristics in their identified 29 predictor mRNAs: 1) pretraining levels were greater in high than low responders for VO<sub>2</sub>max; and 2) >90% of the 29 mRNAs did not change with aerobic training. They suggested that individuals with a low responder predictor gene profile would require alternative exercise intervention paradigms or more intensive pharmacological and dietary protocols to help compensate for their genomic profile.

Timmons and co-authors further examined the same subjects after 6 weeks of endurance training at 70% of maximal  $\text{VO}_2\text{max}$  (517). They observed that low-responders did not switch on their proangiogenic network genes effectively (269). (Cross-references: Molecular mechanisms and muscle plasticity with acute and chronic exercise; Muscle plasticity: energy demand and supply processes; Regulation of gene expression in skeletal muscle by contractile activity).

Timmons et al.'s (517) development and validation of mRNA predictors to hunt for genetic markers have many advantages over existing approaches of SNP. Each SNP seems to contribute only weakly for chronic complex human diseases. For example, after genome-wide association analysis in type 2 diabetes (T2D) patients, 18 robust SNPs explain <7% of the total disease variance (484). As to generalization of a low responder to all of tens of health benefits from exercise training from  $\text{VO}_2\text{max}$  alone, Timmons cautions, “No systematic analysis allows us to be certain that a ‘nonresponder’ for one trait does not cluster with a poor response for another” (516). Thus, additional research is needed to determine whether low responders for gain in  $\text{VO}_2\text{max}$  with endurance training respond to other “positive health” benefits of physical activity, such as improved cognitive function, bone density, skeletal muscle strength, visceral adipose tissue quantity and quality, and the tens of other “positive health” benefits detailed later in this article (52). Blair, Church, and co-workers (478) reported that non-responders to for increase in  $\text{VO}_2\text{max}$  comprised a total of 44.9%, 23.8%, and 19.3% of the 4-, the 8-, and the 12-kcal/kg/wk treatment groups, respectively. They concluded that greater volumes of exercise were associated with a lower probability of being a nonresponder. In summary then, additional research is needed to determine if low responders to aerobic exercise are low or high responders to high-intensity interval training, to resistance training, balance, or flexibility training.

**Proof due to experimental selection of physical aerobic-fitness genes in animals**—Britton and Koch's experimental selection, based upon a single volitional/behavioral forced running test to exhaustion, provided experimental evidence that natural selection for high aerobic capacity during evolution is a feasible concept (569). Selection of rats on the basis of the longest or shortest running distances during a single exercise test resulted in selection of a 58% higher aerobic capacity in the high-distance line than the short-distance line over 11 generations. Rats with high  $\text{VO}_2\text{max}$  had healthier cardiovascular systems (12% lower mean 24-hr blood pressures and 48% better acetylcholine-induced vasorelaxation), and healthier metabolic risk factors (16% less fasting plasma glucose, 39% less visceral adipose tissue, 63% lower plasma triglyceride levels, and greater mitochondrial protein concentrations). These data provides evidence of a genetic role in inter-animal variation in  $\text{VO}_2\text{max}$  that is correlated with better health outcomes.

#### 8.4 Phenotype responsiveness variability to resistance training (RT)

In addition to  $\text{VO}_2\text{max}$  variance among subjects in response to aerobic training, RT also has a tremendous amount of variability in adaptive responsiveness. In 585 subjects undergoing 12 weeks of RT, changes from 2 to +59%, 0 to +250%, and -32 to +149% occurred in cross sectional area, one repetition max, and maximal isometric contraction, respectively (250). The variability in muscle mass may, in part, be related (but not limited) to inter-individual



differences in genome code (as with IGF2 in the aforementioned porcine model) (377), the individual's ability to activate intramuscular mTORC1 signaling within skeletal muscle in response to exercise (333), and/or different responses of microRNA (miRNA) to RT(120). Successful RT-induced hypertrophy in human skeletal muscle was associated with specific differences in miRNA expression to RT in high- and low- responders, respectively, which Davidsen et al. (120) suggest means that miRNAs may play a role in regulating the translation of key gene networks responsible for human skeletal muscle growth. One possible pathway is the PI3K/Akt/mTOR pathway, which is up-regulated during skeletal muscle hypertrophy in humans, and related to the ability for satellite cells to proliferate and/or differentiate (411).

### 8.5 Pharmacogenetics interactions with exercise

The efficacy of drugs is affected by physical fitness/activity status (104, 328) in addition to genetic disposition. For instance, in patients with abnormal left ventricular (LV) relaxation and preserved LV ejection fraction, exercise and weight loss plus drug reduced the LV relaxation dysfunction that was not reduced by the drug alone (104). Martin et al. (328) speculate that drugs with good efficacy in sedentary overfed (overweight) animal models may be less effective in active normal weight animals.

### 8.6 The future of personalized human medicine

The findings of the previous sections have led Timmons et al. (517) to predict that they could apply gene data for changes in VO<sub>2</sub>max in personalized medicine to tailor exercise prescription. Medicine will continue to become more personalized with the looming question of how to optimize how it is applied to ensure the greatest patient benefit. Carl Sagan wrote, "It is the tension between creativity and skepticism that has produced the stunning and unexpected findings of science" (452). It is the spirit of Sagan's quotation that we now raise issues about which we are skeptical. We are skeptical that exercise experts will be used to inform health care professionals on how to make personalized exercise prescriptions based on science. The fear is that a patient will be informed that they have low-responder genes for VO<sub>2</sub>max, which may lead to failure of the patient to exercise or lack of compliance to alternative exercise prescriptions. We hope that solutions, such as encouraging low responders to aerobic exercise or to engage in resistance exercise, can lead to striking improvements in personalized health.

### 8.7 Clinical significance

In a statement in *Science*, NIH Director Francis Collins wrote,

However, the best opportunity to reduce risk in genetically susceptible people for the foreseeable future will not be to re-engineer their genes, but to modify their environment. We need to understand how genetic factors and environmental exposures interact in individuals to alter normal biological function and to affect the risk of disease development (464).

The clinical significance of low- and high-responders for a given dosage and type of exercise, implies that individualized medicine, if exclusively restricted to viewing genetic background in vacuum, will result in less than optimal prescriptive therapy. Rather,



individualized medicine for primary prevention of disease and premature death must also be based on individualized variation of inherited genes for: a) disease susceptibility, b) responsiveness to exercise training and type of exercise, and c) drug-exercise interactions, if appropriate. Thus, fully capturing personalized gene-environment interactions.

Kujala et al. (289) wrote, “When tailoring clinical physical activity interventions, we must remember that not all individuals are suited to the same guidelines for exercise intensity, because the ability to exercise seems to vary not only by training background but also by genetic predisposition.”

## 9. Twin studies - Modulation of twin phenotype by physical activity

Claude Bouchard has extensively used the experimental approach of MZ twins to minimize genetic variability for estimating the percentage contribution of environmental (physical activity) interventions since the mid-1980s. In addition to studies where twins were subjected to exquisitely controlled exercise protocols, a number of studies used overfeeding protocols to look at the effect of excess calories (not included in the following tables). The twin approaches have been critical to our ability to separate genetic from environmental effects related to health and chronic disease in humans. Future, twin-activity studies will contribute to prescription of exercise types and of dose-response thresholds for primary prevention of chronic diseases.

### 9.1 Comprehensive presentation of twin-activity (gene-environment) studies

In this section, we take the approach of searching the literature for all articles (that we could find) that have examined a variety of health outcomes in monozygotic twins (MZ) to attempt to control for genetic variation.

### 9.2 MZ twin-activity comparisons show high mortality component

To summarize the most important health outcome, mortality, Table 2 is presented to show the mortality outcome in MZ twins discordant for physical activity in a large cohort of Swedish twins (77). The higher physically active MZ had a 36%–66% lower mortality than their inactive MZ pair.

### 9.3 MZ twin activity comparisons show variable chronic disease component

These studies have taken the approach of either *a priori* separating pairs of MZ that are discordant for physical activity (Table 3), looking at exercise responses in MZ twins relative to dizygotic twins (Table 4), correlating health parameters with physical activity or fitness levels in MZ twins (Table 5), and looking at the genetic component of physical fitness and activity parameters (Table 6). By evaluating this approach, we can obtain an idea about which factors are controlled mainly by genetics and which are most modifiable for physical activity levels. However, it should be noted that many of these studies have methodological limitations including a wide range of physical activity levels and outcomes that differ from classical exercise physiology adaptations.

As expected many of the tested health parameters had both genetic and environmental components. In many studies, questionnaires were used to evaluate physical activity levels, a

less than optimal method to collect such data. Thus, while the design of the studies analyzed was not optimized for elucidating the effects of physical activity independent of genotype, some cautious conclusions may be made from Tables 2–6, presented next.

#### 9.4 Important physical activity component to activity adaptation

The data indicate that inactivity increases both visceral and total fat masses independent of genetic disposition. Additionally, Alzheimer's and dementia both have a large physical inactivity component. However, changes in muscle morphology (length, shortening velocity, of ventricular diameter) do not exhibit compelling genetic components. Genotype is apparently not a major determinant of the changes in insulin levels and sensitivity brought about by negative energy balance with exercise (390) (see insulin resistance later in article).

#### 9.5 Important gene component to activity adaptation

In these studies, while physical activity levels themselves exhibit a large genetic component; it varies tremendously between countries and cultures. In addition to activity levels, a major genetic component is found for both measures of strength fitness (muscle strength and power) and in endurance fitness as well as responses (lactate levels, blood pressure) to exercise. More surprisingly is the minor effect of physical activity on overall “well-being”, which is in contrast to a number of cross-sectional studies suggesting that physical activity is strongly negatively correlated with depression and anxiety. Another surprisingly result is that twins discordant for physical activity do not differ in generalized bone mass or spinal cord bone mass (542), despite the well-known effects of bed rest and inactivity on increasing bone loss. These contradictory results may simply be due to the lack of specific measures of bone mass in the active limbs, or to the variation in types of load-bearing physical activity, and thus bone health, in the physically active group.

#### 9.6 Clinical significance

Taken together, data in Tables 2–6 provide conclusive evidence that physical inactivity alone is sufficient to increase chronic diseases and death. “Together, the 80 monozygotic publications unequivocally show that co-twins with lower physical activity levels exhibit increased risks for chronic diseases regardless of genotype. Such data, therefore, empowers physicians and other health care providers to prescribe physical activity as primary preventative medicine”

### 10. Variety of training types to primarily prevent disease

Specificity of training (i.e., adaptation to training is specific to the class of exercise (aerobic vs. resistance) is dogma. For example in 1976, one of us wrote that the nature of the exercise stimulus determines the type of adaptation (243). One type of adaptation involves hypertrophy of the muscle cells with an increase in strength; it is exemplified in its most extreme form by the muscles of weight lifters and body builders. The second type of adaptation involves an increase in the capacity of muscle for aerobic metabolism with an increase in endurance and is found in its most highly developed form in the muscles of competitive middle- and long-distance runners, long-distance cross-country skiers, bicyclists, and swimmers. Further, hypertrophied muscles of weight lifters did not have the

increased mitochondria of aerobic training and that prolonged daily run training increases mitochondria, but does not hypertrophy the muscles. Application of the information to elderly individuals is that they must perform both types of exercise to prevent physical (endurance and strength) frailty.

Recent information expands and emphasizes the specificity dogma. High-intensity interval training (HIT) (near peak performance for short bursts alternating with longer periods of low-intensity aerobic activity) has been said to “prove more benefit than traditional continuous exercise programs in several metabolic, muscular, and cardiovascular parameters” (278). For example, HIT-walking resulted in greater increases in  $VO_{2peak}$  and thigh muscle strength and a greater reduction in SBP than moderate-intensity continuous walking in older men and women (375). In contrast, one HIT report indicates that HIT by untrained men produced greater ( $VO_{2max}$ ), the same (improvements in oral glucose tolerance), and less (resting bradycardia, total-body fat percentage, and reducing ratio between total and HDL plasma cholesterol.) adaptations than in a second group performing continuous training (384).

## 11. Disease of physical inactivity (35 diseases/conditions)

The term “disease of physical inactivity” was presented by Pedersen (403) to describe a clustering of diseases. Our article enlarges Pedersen's cluster to include over 35 diseases/conditions and death, which constitute most of the remaining article (Fig. 3). (Cross-reference: Muscle as an endocrine organ) Joyner and Pedersen (260) contend that it is a failure of regulation at multiple levels that causes many common diseases. They further argue that a lack of fluency to use key physiological concepts (like homeostasis, regulated systems and redundancy) as major intellectual tools to understand at multiple levels how whole animals adapt to exercise and maladapt to physical inactivity.

## 12. Inactivity accelerates loss of functional capacities with years of life

### 12.1 Definitions

**Primary aging**—Inevitable deterioration of cellular structure and function, independent of disease (241)

**Maximal lifespan**—Maximum amount of time one member of a species has been observed to survive between birth and death

**Secondary aging**—Aging processes which result from disease, bodily abuse, and/or disuse and which are often preventable

**Life expectancy**—Average lifespan of a population

**Functional capacity**—Absolute maximal value of a function

Relative functional capacity Relative age of functional capacity of an organ system, an organ, or cell to its lifetime highest value at a given calendar age

## 12.2 Etiology

**Primary prevention**—The next quotation is impactful because of its source, a report from top exercise scientists that was accepted by the top official of the U.S. Department of Health and Human Services.

The data very strongly support an inverse association between physical activity and all-cause mortality. Active individuals — both men and women — have approximately a 30% lower risk of dying during follow-up, compared with inactive individuals. This inverse association has been observed among persons residing in the United States, as well as in other countries, older persons (aged 65 years and older), and persons of different race/ethnic groups. In one study of persons with impaired mobility (unable to walk 2 km and climb 1 flight with no difficulty), physical activity also appeared to be associated with lower all-cause mortality rates. (412)

### **Less physical activity shortens years of life relative to average lifespan**—

Healthy behavioral choices in Californian Adventists extend life expectancy by several years, even as much as a decade, (190). Various reports estimate that higher physical activity levels may extend life expectancy relative to average lifespan by 2.1 (405), 2.5 (395), 5.1 (men)(181), and 5.7 (women)(181) yrs for the physically active population.

Another example of lifetime physical activity shortening years lived is the increased risk of chronic diseases such as type 2 diabetes (See type 2 diabetes later in article). Diagnosis of type 2 diabetes at the age of 20 yrs is associated with 17.2 and 17.9 yrs of life lost in males and females, respectively (366).

**Less physical activity increases percentage of population that is disabled**—At the same age for death, the high physical activity group spent less time disabled than the overall population of men (2.5 vs. 3.0 years), while the low physical activity group actually spends more time disabled than all men (2.6 vs. 1.4 years)(181). Thus, less lifetime physical activity shortens years of life. (Cross-reference: Implications of aging and athletics)

## 12.3 **Dose-response relationship between sitting time and prediction of premature death**

**Longitudinal studies**—Katzmarzyk et al. (268) reported a dose-response association existed between sitting time and mortality from all causes and CVD, but not for cancer, independent of leisure time physical activity in 17,000 Canadians, such that hazard ratio was 1.54 for the greatest sitting time. Dunstan et al. (151) found that each 1-hour increase in TV viewing time was associated with 11% and 18% increased risks of all-cause and CVD mortality, respectively, in 20,000 Australian men and women. Further, all-cause and CVD mortalities increased 46% and 80%, respectively for TV viewing time >4hr/day as compared to <2 hrs/day, which were independent of smoking, blood pressure, cholesterol, diet, waist circumference, and leisure-time exercise.

**Mechanisms**—While light physical activity is associated with rather low-intensity muscle contractions, it still has favorable improvements on plasma glucose in glucose tolerance tests (228), and differs substantially from the absence of muscle activity while sitting The

detrimental effects of sitting have been hypothesized by Stamatakis et al. (489) to occur in the following sequence of events: excessive sitting lowers skeletal muscle blood flow, lowering shear stress on vascular endothelial cells, and decreasing endothelial nitric oxide synthase (NOS) expression. They also noted that the low-grade inflammatory marker, CRP was approximately 2 times greater in subjects with >4 hr/day in screen time, compared to those <2 hr/day. However, two weeks of reduced daily stepping (286) and 5 days of bed rest (216) do not increase inflammatory markers so CRP is unlikely to be the first initiating mechanism. Rapid biochemical changes in a rodent models of sitting, hindlimb unloading, have demonstrated decreases in rat skeletal muscle protein synthesis rates within the first 6 hrs (54, 357, 507, 529, 550) and loss of insulin-stimulated glucose uptake into the mouse soleus muscle after 1 day (466).

#### 12.4 Biomarkers of premature death

Low values of functional capacities for maximal aerobic capacity ( $VO_2max$ ) and for maximal skeletal muscle mass/strength, each alone, are biomarkers for death as they are associated with shorter life expectancies.

**Sedentary lifestyle speeds secondary aging of  $VO_2max$  by 30 yrs (illustrated by shifting of age- $VO_2max$  relationship leftward in shown example)**—As previously discussed,  $VO_2max$  is a measure of CRF. CRF is a health-related component of physical fitness defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity. While physically active and inactive individuals lose a  $VO_2max$  at a similar rate (slope of the curve) due to primary aging, the inactive individuals have a leftward shift of the curve. For instance, 80-yr-old, physically active women had  $VO_2max$ 's that were equivalent to 50-yr-old physically inactive women. (Fig. 4) (503).

**Low  $VO_2max$  increases prevalence of death**—Convincing evidence exists that lower CRF is associated with increased mortality in both men and women, independently of other risk factors (79, 96, 277, 312, 313).

An inverse relationship between CRF and death was present with a cross-sectional comparison between lesser fit men and women with greater fit men and women showed. When CRF in the second lowest CRF quintile is compared to the lowest quintile, the risk of all-cause death in the lowest CRF quintile is increased by 39% and 67% in a prospective study of 40,451 men and 12,831 women, respectively (312) (Fig. 5). Likewise comparing the highest CRF quintile to the second lowest increased all-cause death risk by 26% and 28% in men and women, respectively. Thus, comparing the top quintile to the lowest quintile increased all-cause death risk by 75% and 113% in men and women, respectively.

Changes in CRF level result in a similar change in mortality risk. Men ( $n = 9777$ ; aged 20–82 at baseline) had two CRF assessments with an average period of 4.9 years between first and second examinations (44, 312). The men were then followed an average of 5.1 years for mortality after the second CRF test. Men who were unfit at both visits had the highest death risk while men who were fit at both visits had the lowest death risk. Remarkably, men who changed fitness status between the two CRF assessments had intermediate risk of death

between the fit-that-stayed-fit group and unfit-who-stayed-unfit group. Fit-who-became-unfit between assessments had an increased risk of death. Unfit-men who-became-fit between CRF assessments decreased their risk of death. Erikssen et al. (165) found similar trend and concluded that even small improvements in physical fitness are associated with a significantly lowered risk of death.

**Sedentary lifestyle speeds secondary aging of skeletal muscle power by 24 yrs (illustrated by shifting of age-power relationship leftward in shown example)**

—Low muscle strength has been inversely associated with all-cause-mortality in thirteen studies using subjects > 65 yrs of age (see (451) for refs). While, aging causes a similar rate of loss in power between 40 and 90 yrs of age, untrained, healthy men generate 35% less average power than male competitors at a World Masters Weight-Lifting Championships (402) (Fig. 6). Recreational resistance training results in strength gains ranging from 10%–257% after 9–52 weeks of 2–3 days/week resistance training in subjects mainly aged between 60–80 years of age (252), however a cross-sectional study spanning 20–80 yrs of age in recreational weight-lifters is not available to our knowledge. (Cross-references: Influence of exercise on protein and amino acid metabolism; Physical activity and skeletal muscle size)

## 12.5 Mechanisms

**Cardiovascular system**—According to Blair and co-authors (313), several possible biological mechanisms exist for the risk reduction of all-cause mortality in individuals with higher CRF. Higher CRF is associated healthier values for risk factors including insulin sensitivity, blood lipid and lipoprotein profile, body composition, systemic inflammation, blood pressure and the autonomic nervous system functioning.

**Evolutionary origin**—Maximal functional capacity defines the upper limit of a cell, tissue, system, or whole body to maintain homeostasis to stress. Hayflick (226) and others argue that greater functional capacity in vital organs ensures survival, reproductive success, and thus is favored by natural selection. Hayflick lists some stresses that higher capacities in organ systems would be more likely to favor natural selection as

...more efficient healing process, faster sensory responses, or greater strength or speed to avoid predation or natural disasters, finding food, and surviving disease, accidents, and environmental extremes. The favored animals will have developed redundant capacity, or greater physiological reserve, thus increasing chances for survival to reproductive success. (226)

In an extreme stress, such as needing maximal caloric expenditure (reflected in  $VO_2\max$ ) or skeletal muscle strength, animals whose vital systems have the largest redundant functional-capacity would be better able to survive the stress. Thus, the ability to adapt to and develop greater physiological capacity in response to repeated stressors (i.e. physical activity) was likely a consequence of natural selection.

## 12.6 Clinical significance

Low CRF ( $\text{VO}_2\text{max}$ ) and handgrip strength predict the risk of impending death. To minimize the all-cause death risk, lifelong efforts, starting in youth, are needed to develop high CRF and skeletal muscle strength within the limitations of one's inherited genes. Slowing of secondary aging of CRF and strength functional capacities can delay the age for inevitable threshold of frailty due to primary aging. A more detailed coverage of inactivity and aging is given in our review (50).

## 13. Prevention of death by primary prevention of physical inactivity

### 13.1 Etiology

Blair et al. (45) first showed in 1989 that an asymptote exists between metabolic equivalents (METs) and age-adjusted mortality rates. Mortality was independent of MET values  $> \sim 9$  METs in women and  $> \sim 10$  METs in men, but increased when lower than these values.

Kokkinos and Myers found an identical trend in 15,000 older veterans (Fig. 7) (278). An age-related threshold for mortality risk reduction at 4 to 6 METs and an asymptote occurred at  $\sim 9$  METs for women and  $\sim 10$  METs for men (MET values are multiples of resting metabolic rate).

Figure 7, shows 20% increase in mortality exists for an individual when maximal exercise MET values grouped between 4.1–6.0 METs fall into 2.1–4.0 MET group, with no further increase between groupings of MET values  $< 2.0$  METs and 2.1–4.0 METs (278). This suggests that a threshold at around 4.0 METs below which, no further increase in mortality exists. Further, an asymptote around 9.0–10.0 METs indicates that no differences in mortality risk were reported in comparisons among the higher MET ranges of 10.1–12.0, 12.1–14.0, and  $> 14.0$ .

Cautionary statements are necessary though. Maximal MET values decrease  $\sim 10\%$ /decade with aging, in part due to decreased physical activity levels. Thus, physical activity levels need to be maintained or increased to remain in or near to the asymptotic region ( $> 9$  METs) as long as possible with aging..

### 13.2 Clinical significance

Primary prevention of death (shortening of life expectancy) is possible by increasing CRF.

## 14. Metabolic syndrome (MS)

All risk factors for MS are exasperated by sedentary lifestyle (Fig. 8). In other words, physical inactivity is a primary cause of MS risk factors by virtue of its being upstream to the common MS risk factors. Alternatively, risk factors for MS are secondary to sedentary lifestyle. Consequently, increased physical activity is primary prevention of MS. (Cross-reference: Metabolic syndrome: Impact of lifestyle)



### 14.1 Disease definition

MS is currently defined as a cluster of three of five risk factors for CVD and type 2 diabetes, which tend to cluster together in the same individual (Fig. 8) (6). Four of the five factors have drug treatments in attempts to normalize them, and include elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure, and elevated fasting glucose. The fifth factor, elevated waist circumference (as a marker of elevated visceral obesity) does not have as an effective drug treatment. Three abnormal findings out of the five risk factors indicate that an individual has MS. In addition, MS is associated with increased risk of certain forms of cancer, polycystic ovarian disease, nonalcoholic fatty liver disease, and neurodegeneration (39).

### 14.2 Etiology

The total number of U.S. adults who have MS ranges from 77–86 million (34.3%–38.5% of total age-group) (187). A Joint Scientific Statement indicates that patients with MS have twice the risk of developing CVD and type 2 diabetes, respectively, over the next 5 to 10 years, as compared to individuals without MS (6). Physical inactivity has been shown to be an important risk factor of MS (38, 186, 296, 560). The proportion of sedentary time, determined by accelerometry was strongly related to metabolic risk, independent of physical activity (22).

### 14.3 Mechanisms

A 2009 Joint Scientific Statement from the American Heart Association states, “Most persons with the metabolic syndrome have abdominal obesity and insulin resistance. Both of the latter conditions appear to contribute to the development of metabolic risk factors, although the mechanisms underlying these contributions are not fully understood (6).” However, it is understood that physical inactivity is a primary causal mechanism of every MS risk factor – dyslipidemia, hypertension, hyperglycemia, visceral obesity, prothrombosis, and pro-inflammatory events (Fig 8).

Several risk factors for MS are associated with physical inactivity, including low-grade inflammation and impaired metabolism (403, 404). Conversely, prevention of physical inactivity through physical activity improves inflammatory markers by reducing resting CRP, interleukin-6 (IL-6), and tumour necrosis factor- $\alpha$  concentration (403). On potential mechanism is highlighted by Pedersen (404) who has put forth the hypothesis that the muscle secretome (termed myokines) is involved in mediating some of the health effects of regular exercise, in particular chronic diseases associated with low-grade inflammation and impaired metabolism, as well as the brain. For example, contracting skeletal muscle during exercise produces interleukin-6, which has anti-inflammatory properties (490). Cross-reference: Muscle as an endocrine organ)

### 14.4 Clinical significance of primary prevention of MS

Physical activity is primary prevention for every major MS risk factor. In addition, Bankoski et al. (22) have results that led them to suggest that individuals >60 yrs of age may benefit from reducing total sedentary time and avoiding prolonged periods of sedentary time by increasing the number of light physical activity bouts during sedentary time.

## 15. Presentation strategy for diseases composing MS

Each risk factor for MS and chronic diseases resulting from MS will be individually considered next.

## 16. Obesity

### 16.1 Disease definition

The CDC defines overweight for adults as BMIs of 25.0–29.9; obese class I as 30.0–34.9 BMI; obese class II of 35.0–39.9 BMI; and obese class III >40.0 BMI. A future auxiliary definition will likely include waist circumference as a proxy for intra-abdominal adipose tissue since all fat is not equally unhealthy.

**Etiology** 45% of the U.S. adult population was estimated to be overweight or obese in 1960–1962. Overweight and obesity began a continual rise in U.S. adults, aged 20–74 yrs, in the 1980's. The percentage of overweight and obese were 45%, 47%, 56%, 65% and 66% in survey years 1960–62, 1976–80, 1988–94, 1999–2000, and 2003–04, respectively, with men ~10% higher than women (87, 387); (Fig. 9). A recent publication establishes that 68% of U.S. adults in 2007–2008 are overweight and obese (182).

### 16.2 Misconception that obesity is independent of physical inactivity

The next sections document historical declines in physical activity, putatively reflecting increases physical inactivity.

### 16.3 Caloric expenditure from physical activity has decreased historically

**Caloric expenditure of modern day hunter-gatherers and U.S. Amish vs. sedentary**—The modern hunter-gatherers' daily estimated energy expenditures for physical activity are at least 600 kcal more than the average U.S. sedentary adult of today, as documented in column labeled “EE PA” (Table 7) (385). The authors of the data in Table 7 commented, “The systematic displacement from a very physically active lifestyle in our natural outdoor environment to a sedentary, indoor lifestyle is at the root of many of the ubiquitous chronic diseases that are endemic in our culture” (60). Astrand and Rodahl have made a similar comment,

Close to 100 percent of the biologic existence of our species has been dominated by outdoor activity. Hunting and foraging for food and other necessities in the wilds have been a condition of human life for millions of years...there is obviously no way to revert to our natural way of life...but with insight into our biological heritage we may yet be able to modify our current life, Knowledge of the function of the body at rest, as well as during exercise under various conditions is important as a basis for an optimization of our existence” (17).

Table 7 shows that agrarian Amish men and women undertake 900 and 700 calories worth of daily physical activity, (439). They eat a typical American dieting terms of macronutrients consisting of meat, potatoes, gravy, cakes, pies, and eggs (439). Nonetheless, only 25% and 27% of these Amish men and women, respectively, are overweight; and 0% and 9%, respectively, are obese (439). Several simple observations give rise to conclusions

that the lower physical activity levels of modern inactive humans contributes to the obesity epidemic more so than an increase in caloric intake. Agrarian Amish physical activity expenditures exceed modern sedentary by at least 600 kcal/day (Table 7). If modern caloric intake remained unchanged then on average each individual would have a positive energy resulting in 73 pounds of fat/year. Clearly this is untrue and therefore caloric intake must have dropped. However, if the modern population had a decrease in caloric intake of more than 600 kcal/day then obesity rates between Amish and the general population would be similar, which is also untrue. Thus, while caloric intake has dropped between 0 and 600 kcal/day in the general population it is the lack of 600 kcal/day of physical activity has led to a large discrepancy in the obesity rates between the modern general population and Amish societies.

**Modern human caloric expenditure is less than free-ranging mammals—**

Compared to other free-ranging mammals, Hayes et al. (225) calculate that sedentary humans have a significantly lower level of relative physical activity-induced energy expenditure. However, highly active humans have relative physical activity-induced energy expenditure that nears that of other free-ranging mammals (Fig. 10).

**Decreases by physical activity type in past few decades: U.S.—**A misconception is that leisure time physical activity reflects directional trends of all types of daily physical activity. Brownson et al. (67) reported the following trends in U.S. (up to 50 years when possible) according to physical activity type: relatively stable or slightly increasing levels of leisure-time physical activity. However, declines occurred in work-related activity, transportation activity, and home-related activity as well as an increase in sedentary activity. Therefore, overall trends for all physical activity types were for declining caloric expenditure by physical activity in recent decade(s).

**Decreases by physical activity type in past few decades: China—**James (256) shows that transfer from working in the field in China to city work would drop caloric expenditure by ~315 kcal/day (men) and ~375 kcal/day (women). James comments,

...these calculations are set out to illustrate how foolish it is to focus on only one of the two parts of the energy balance equation. The calculations also illustrate the magnitude of the required drop in intake, given the transformation in our working conditions” (256).

Further, instead of walking to fields, motorized transportation is taken, reducing caloric expenditure by an additional ~200 kcal/day. James concludes,

“Thus, intakes may need to fall by 400–800 kcal/day for each Chinese adult as their working and living conditions change, and the physical revolution transforms working conditions and transport, with city living and home entertainment with television and cinema viewing taking over from the major sustained demands of an agricultural life” (256).

The misconception of “overnutrition” is due to a widening positive caloric balance due to food intake not falling calorie with calorie to the decline in caloric expenditure (PubMed cites >100,000 papers with the term “overnutrition”).

**Caloric cost of engineering physical activity out of lifestyle**—Energy expenditure was significantly greater when daily domestic tasks were performed without the aid of machines or equipment. An estimated 110 kcal/d was estimated to be expended by the combined impact of domestic mechanization (304) (Table 8). The annualization of 110 kcal/day is the caloric equivalent of 11.5 pounds of fat/yr. Levine and co-authors concluded, “the magnitude of the energetic impact of the mechanized tasks we studied was sufficiently great to contribute to the positive energy balance associated with weight gain” (304).

We followed Levine's model and calculated an annualized loss of 64,349 calories (caloric equivalent of 18.4 pounds of fat in one year) would not be expended when walking/standing is selected out of lifestyle in our hypothetical model (Table 9).

**Alternative interpretation that physical activity has not declined**—Westerterp concluded,

“Physical activity energy expenditure, as measured with doubly labeled water (DLW), has not declined since the start of the obesity epidemic in the 1980s (554) ... it is unlikely that decreased expenditure has fuelled the obesity epidemic.”

Our view of the above quotation follows. Indeed, DLW estimates of energy expenditure determined between 1988 (555) and 2006 (554) did not significantly differ. However, from ~1980 to 1988 the increased prevalence of obesity was already occurring and the slope of the increase remained unchanged through 2006 (Fig. 9). The unchanged slope suggests that whatever was responsible for the increasing prevalence of obesity was maintained, not increased or decreased through 2006. Thus, physical activity levels may have been altered downward prior to 1988 and maintained from 1988–2006 at their low levels, which could be one possible explanation for the inconsistency between the DLW results and lack of change in physical activity levels

#### 16.4 Primary prevention of total-body fat gain by physical activity

It is preferable to avoid, in the first place, the excess weight gain that leads to overweight and then obesity...A major emphasis on obesity prevention is needed in the population at large to prevent the development of obesity in those adults who are still in the normal weight range and in successive generations of children and adolescents during development. Treatment will continue to be of critical importance, but treatment alone cannot curb the epidemic...prevention has not been the primary focus (292).

Miminal research exists on preventing weight gain.

Primary prevention is demonstrated by one human study. A threshold of ~60 minutes a day of moderate-intensity activity throughout a 13-yr study was needed to gain <2.3 kg in 34,079 healthy US women consuming a usual diet. In a 3-yr sub-study, the only group having significantly less weight gain than other groups was women whom fit all 3 of the next criteria: BMI < 25, moderate-intensity exercise >60 min/day, and < 64 yrs of age (314).

Primary prevention of further weight gain in already overweight to obese individuals was accomplished with 8 months of low volume-moderate intensity activity (caloric equivalent of walking 12 miles/wk at 40–55% of  $\text{VO}_2\text{max}$ ), while high-volume (caloric equivalent of jogging 20 miles/wk at 65–80% of  $\text{VO}_2\text{max}$ ) decreased total fat mass by 4.8 kg (480)

Primary prevention of weight regain was calculated retrospectively, after 12 months in previously obese female, to be 80 min/day of moderate activity, 35 min/day of vigorous activity, or 0.011 kcal physical expenditure/kg body weight/day (461). Maintenance of a 10% reduced body weight in humans with BMIs >30 is associated with a significant decrease in total energy expenditure of ~300–500 kcal/day greater than that predicted by changes in body mass and composition, which is due predominantly to increased work efficiency of skeletal muscle at low work intensities (203).

Joyner and Pedersen (260) present another example. Low prevalence of obesity has been related to poor economic conditions. Collapse of the Soviet empire in at the end of the 1980s led to decreased food availability, increased physical activity and ~50% decrease in adult obesity prevalence in Cuba (441). Upon economic recovery, obesity rose 50% from 1993 to 1996.

### 16.5 Preferential decrease in visceral adipose tissue (VAT) by exercise

Primary prevention of VAT obesity by physical activity has been demonstrated in numerous human studies. Physical training of T2D patients produced a greater loss in VAT (48%) than subcutaneous adipose tissue (SAT) (18%), did not significantly affect body weight (360). Ross *et al.* (447) reported that exercise without weight change in obese men reduced VAT more than SAT. Likewise, a greater percentage loss in VAT percentage than in body weight occurred after 12 months in a moderate-intensity exercise intervention study of sedentary, overweight, postmenopausal women. VAT loss was exercise dose-dependent (253).

A 6-month study examined the dose-response relationship for exercise volume-VAT mass in men and women whose BMI's ranged from 25–35 (479). Low volume-moderate intensity (caloric equivalent of walking 12 miles/wk at 40–55% of  $\text{VO}_2\text{max}$ ) was sufficient to prevent any further gains in VAT mass, while high-volume, high-intensity activity decreased VAT by 6.9% (Fig. 11).

Remarkably, the non-treatment group (no exercise) had an 8.6% increase in VAT. Extrapolated to 10 years, this would have been a 172% increase in VAT. Kraus *et al.* (482) later wrote about the non-exercise group, “current levels of physical activity may be so low that significant metabolic deterioration occurs in numerous health-related parameters in as little as 6 months of continued inactivity.” The study provides the evidence that a primary cause of VAT obesity is lack of exercise and that primary prevention for the expansion of VAT is physical activity (Fig. 1).

### 16.6 Primary prevention of inactivity prevents obesity with predisposed obesity gene

Sedentary lifestyle reveals an obesity phenotype that is primarily prevented by enhanced physical activity.

**Humans**—The 16% of sedentary adults who are homozygous for the risk allele of AA in rs9939609 in the *fat mass and obesity-associated (FTO)* gene weighed ~3 kg more and had 1.67-fold increased odds of obesity when compared with those not inheriting a risk allele (191). Physically inactive homozygous risk A-allele in rs9939609 carriers had a 2 kg/m<sup>2</sup> greater BMI compared with homozygous T-allele carriers in a cross-sectional study of 17,000 Danes (14). A second study replicated the primary preventative effect of physical activity. Adolescents meeting the daily physical activity recommendations overcame the effect of the *FTO* rs9939609 AA polymorphism on obesity-related BMI, body fat, and waist circumference traits seen in sedentary subjects (450). High physical activity levels in additional studies were associated with attenuated BMI and waist-circumference obesity traits for two additional *FTO* polymorphisms [rs1861868 (422) and rs1121980 (543)]. Women with the *FTO* allele rs8050136 only have obesity risk if they are less active (5). In summary then, physical inactivity is required to elicit the phenotype of obesity with polymorphisms predisposing to obesity for the human *FTO* gene.

**Animals**—Obesity is primarily prevented in at least two genetically modified, obese rodent models by allowing natural, instinctive voluntary running. Voluntary running prevented obesity and its comorbidities [T2D and non-alcoholic fatty liver disease] with no significant reductions of food intake in cholecystokinin-1 receptor (OLETF) rats having a mutant cholecystokinin gene (37, 355, 429, 470). Mice lacking expression of the melanocortin-4 receptor (MC4-R) exhibit maturity-onset obesity with hyperphagia, hyperinsulinemia, and hyperglycemia, that is prevented by providing access to wheels for voluntary running (224). Lack of voluntary wheel running reveals the obesity phenotypes.

## 16.7 Mechanisms

Physical inactivity, as one of the two components in the caloric balance equation, is an actual cause of positive caloric balance, i.e., obesity. The most effective control of obesity is primary prevention of physical inactivity by moderate levels of physical activity, rather than secondary or tertiary prevention of obesity associated co-morbidities.

## 16.8 Clinical significance

Physical inactivity is a primary cause to VAT and whole-body obesities. Primary prevention of obesity is possible today for almost all able-bodied individuals able to exercise. According to the CDC primary prevention of overweight/obesity would reduce risks for coronary heart disease, T2D, hypertension, dyslipidemia, stroke, non-alcoholic fatty liver disease, gallbladder diseases, sleep apnea and respiratory problems, osteoarthritis, gynecological problems (abnormal menses, infertility), endometrial, postmenopausal, breast, prostate, and other cancers, and premature death (89).

## 17. Inactivity fosters obese co-morbidities

### 17.1 Obesity co-morbidities

Risks for the following conditions increase with physical inactivity: Coronary heart disease, T2D, cancers (endometrial, breast, and colon), hypertension, dyslipidemia (for example, high total cholesterol or high levels of triglycerides), stroke, liver and gallbladder disease,



sleep apnea and respiratory problems, osteoarthritis, and gynecological problems (abnormal menses, infertility).

**Death**—A recent systemic review by Fogelholm (185) of 36 papers made the next conclusions for the lowering of disease risk with physical activity in obese individuals (conclusions may not apply to BMI >35). **Poor fitness or low PA in physically unfit individuals is a greater all-cause and cardiovascular mortality risk than obesity in physically fit individual (185).**” A study published since the above review essentially concurs with the review by its conclusion made from veterans population that overweight and obese men with moderate CRF fitness had mortality rates similar to those of the highly fit normal-weight reference group (334).

## 17.2 Clinical significance

Physical inactivity is a cause of some obesity co-morbidities. Thus, even if primary prevention for the loss in body fat fails, primary prevention of some, but not all, of obesity's co-morbidities is possible with physical activity.

## 18. Insulin sensitivity/resistance

### 18.1 Etiology

A summary of the medical literature describing U.S. population-based data on the incidence of 54 endocrine and metabolic disorders in the United States found that the prevalence of impaired fasting glucose and impaired glucose tolerance was 26% and 17%, respectively (202). Both of these conditions increase risk for the development of type 2 diabetes.

### 18.2 Insulin sensitivity

How successful blood glucose is lowered by blood insulin

### 18.3 Insulin resistance

Diminished ability of skeletal muscle and liver cells to respond to the action of a given dose of insulin by transporting glucose from the bloodstream into these tissues, or by reducing glucose production, respectively (B to D in Fig. 12)

A hyperbolic relationship between insulin sensitivity and insulin secretion has been defined as by Bergman (36). Fig. 12 illustrates the progression from normal glucose tolerance (Point A) to overt clinical T2D (Point D), as described in Harrison's textbook,

glucose tolerance remains to near-normal (NGT), despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output (Points A to B). As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. Impaired glucose tolerance, characterized by elevations in postprandial glucose, then develops (Points B to C). A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia (Point D). Ultimately, beta cell failure may ensue (418).



We have further modified Harrison's redrawing of Bergman's original figure to indicate that Point A is representative of a daily physically active human and point B is an occasionally active human. Based on a number of studies we propose that increases and decreases in daily physical activity over a time frame of hours to a few days places subjects between Points A and B. Thus, daily physical activity prevents the progression to Point B, making it impossible to continue from Point B, to Point C and Point D, overt diabetes. Therefore, only if continual physical inactivity is present can the progression to Point C, impaired glucose tolerance, and eventually into Point D, overt diabetes, occur. As Zimmet astutely and succinctly wrote, "A large proportion of cases of type 2 diabetes is preventable" (579).

#### 18.4 Impaired glucose tolerance (IGT) may increase cardiovascular disease (CVD) risk

After adjusting for age and sex, an increased risk of CVD mortality was observed in those with postchallenge hyperglycemia (PCH) and fasting glucose  $\geq 7.0$  mmol/l, with 2-h glucose  $\geq 7.8$  and  $<11.1$  mmol/l and fasting glucose  $<7.0$  mmol/l, or with PCH and fasting glucose  $<7.0$  mmol/l (459).

#### 18.5 T2D was preventable 35–70 years ago

Diabetes prevalence has risen from 1.4% in 1950 to 7.8% in the U.S. (367) and from 1% in 1975 to 9.7% in 2007–2008 in China (576). Zimmet commented, "In conjunction with genetic susceptibility, particularly in certain ethnic groups, type 2 diabetes is brought on by environmental and behavioral factors such as a sedentary lifestyle, overly rich nutrition and obesity" (579). We will propose the notion that proper volumes of physical activity would essentially primarily prevent most of T2D, as illustrated by maintaining at point A in Fig. 12.

#### 18.6 Inactivity/exercise rapidly change insulin sensitivity

**Reduced activity**—LaMonte, Blair, and Church (300) hypothesized that the most proximal behavioral cause of insulin resistance is physical inactivity. Highly endurance trained men's high insulin sensitivity returns to sedentary levels after cessation of training for 38 hrs (391) or 60 hrs (72) as measured by euglycemic-hyperinsulinemic clamp. Measured 12, 60, and 168 hrs after the last exercise bout, peripheral tissue glucose disposal dropped from 15.6 to 10.1 to 8.5 ml/kg/min, respectively, compared to 7.8 ml/kg/min in sedentary subjects (72). Similarly, 14, 38, 86, and 144 hr after the last exercise bout by endurance trained athletes glucose disposal declined from 9.40 to 7.78 to 6.82 to 7.11 mg/kg/min compared to 6.80 in sedentary subjects (391). Therefore, only days after ceasing exercise training, endurance athletes the same insulin sensitivity as long-term sedentary subjects. Like humans, rats who cease 3 weeks of voluntary wheel running drop their submaximal insulin-stimulated glucose uptake to sedentary values on the 2<sup>nd</sup> day of no running in skeletal muscle normally recruited during wheel running (293). Less extreme reductions in physical activity, such as humans decreasing daily step numbers from 6203 to 1394 for 1 week lead to a 53% increase in the area under the curve for plasma insulin following an oral glucose tolerance test, a response that occurs due to reduced peripheral insulin sensitivity (389). Conversely, more extreme physical inactivity such as strict bed rest for 24-hr/day

lasting 5 days (216), 7 days (46, 342, 495), and 9 days (7) is also associated with substantial increases in insulin resistance. Two days of bed rest did not affect insulin resistance (152).

**Increasing activity improves insulin sensitivity in muscle**—A single bout of muscle contraction increases insulin sensitivity in perfused hindquarters of healthy animals (242, 255, 434) and in the whole body of healthy humans (230, 343). Seven days of aerobic training increases whole body insulin sensitivity in 22- and 58-yr-old men and women (244), 66-yr-old men and women (BMI = 33) (486); 60- to 80-yr old men and women (112), and T2D patients (274, 444). Resistance training also enhances insulin sensitivity and improves glucose tolerance in a wide range of human subjects (526). A systemic review of 20 studies found that supervised resistance training improved glycemic control and insulin sensitivity in adults with T2D (206).

## 18.7 Biochemical mechanisms

**Exercise-induced glucose uptake into skeletal muscle**—A 2009 review wrote, “Within the past 25 years, characterizing the beneficial interaction between acute exercise and subsequent insulin action has been an area of much focus; although progress has been made recently, the underlying mechanisms are still poorly understood” (193).

**Animals**—Independent of insulin action, exercise acts to prevent hyperglycemia by improving glucose uptake in animal skeletal muscle primarily by independently activating the translocation of glucose transporter, GLUT4, from intracellular locations to the plasma membrane of rats (145, 205), and also by increasing transcription in mice (528) and translation in rats (294) of GLUT4 leading to greater GLUT4 protein content.

**Humans**—In human subjects, a positive correlation exists between GLUT4 protein content in the vastus lateralis muscle with insulin sensitivity in both sexes (247). The relationship remained in men after adjustment for overall adiposity, regional adiposity, and CRF (247). Endurance-trained healthy individuals have higher GLUT4 mRNA and protein content than do sedentary (245, 467). Physical training also increases muscle GLUT4 protein and mRNA in patients with T2D (128). GLUT4 transcription is controlled in part by calcium signaling and the energy sensor 5'-AMP-activated protein kinase (AMPK) during exercise (435, 567, 568).

**Skeletal muscle insulin sensitivity with contraction and inactivity**—Conversely, much less effort has gone into investigating the mechanisms through which lack of physical activity decreases insulin sensitivity. Although low-grade inflammation can worsen insulin resistance in a variety of models circulating inflammatory markers were unchanged, while insulin resistance increased during 5 days of bed rest, implying that systemic inflammation is not a mechanism for initial insulin resistance (216). Reduced mitochondrial content or dysfunction has also been postulated to cause insulin resistance by leading to an increased accumulation of lipid intermediates in skeletal muscle (457). The lipid intermediates putatively activate serine kinases that reduce insulin signaling ultimately leading to reduced insulin stimulated GLUT4 translocation to the plasma membrane. However, the links between insulin resistance and an accumulation of lipid intermediates are associative at this

time, and an increasing number of reports have found that the relationship does not always hold true (460). Another possibility is oxidative stress. Anderson et al. (13) report that both acute and chronic high-dietary fat intake lead to a dramatic increase in the H<sub>2</sub>O<sub>2</sub>-emitting potential of rat or human mitochondria in the absence of any change in respiratory function, consequently generating a shift to a more oxidized cellular redox environment that, if persistent, precedes the development of insulin resistance in skeletal muscle.

Insulin sensitivity in rat epitrochlearis muscle declines at a time (2 days after stopping 3 weeks of voluntary wheel running) when the mitochondrial marker, citrate synthase activity, remains unchanged and elevated from the wheel running (293). No differences in skeletal muscle mitochondria and insulin sensitivity existed between non-obese sedentary controls and hyperphagic, voluntary running in OLETF rats. Rector et al. (430) suggest a constant caloric overload and expanding adiposity may be the primary driver to insulin resistance in the OLETF sedentary animal model. Thyfault (511) suggested “It may be that a hypercaloric/lipidomic environment plus low energy flux (physical inactivity) is required to induce skeletal muscle insulin resistance in obesity” (511). Inactive skeletal muscles in physically inactive rats have insufficient electron transport flux to completely oxidize mitochondrial intermediates of  $\beta$ -oxidation, producing lipid toxicity (281, 512). However, acute exercise prior to insulin stimulation can restore insulin stimulated glucose transport in muscle from obese Zucker rats (513), without improving signaling through the insulin-signaling pathway. Thus it appears that contraction induces a robust mitochondrial energy flux increasing in a coordinated fashion with both  $\beta$ -oxidation and the TCA cycle, that can override existing perturbations of the insulin-signaling pathway to enhanced insulin-stimulated glucose uptake in insulin resistant muscle in obese Zucker rats (512). The links between the contraction-induced energy flux and insulin action are at this time unknown, however according to a comprehensive review of the topic, the molecule Akt substrate 160 may play an integral role as it is activated by both insulin and muscle contraction and plays a major role in activation of GLUT4 translocation to the plasma membrane (82).

### 18.8 mRNA mechanisms

Global mRNA analysis of human vastus lateralis muscle identified 4500 transcripts changing after development of insulin resistance following 9 days of continuous bed rest in 20 healthy young men (8). They found that 54% of 162 transcripts in the oxidative phosphorylation pathway decreased. Vaag and coauthors (8) emphasized that they could not exclude the possibility that down-regulation of oxidation phosphorylation as well as other genes may have occurred as a result of – not as a causal factor for – skeletal muscle insulin resistance during bed rest. Two potential physiological mechanisms may be decreased capillarization (not determined), as suggested by decreases in both VEGF $\alpha$  mRNA and PGC1 $\alpha$  mRNA, or increased fat accumulation due to decreased CPT1B mRNA and thus decreased fatty acid oxidation (8). Furthermore, increased reactive-oxygen species generation and endoplasmic reticulum stress were also identified as potential mechanisms of inactivity induced insulin resistance (8).

## 18.9 Clinical significance

Physical inactivity is a primary cause of loss of insulin sensitivity in skeletal muscle, and thus whole-body. Primary prevention of almost all of insulin resistance by high levels of daily physical activity is possible for almost all humans up their seventh decade of life (305). Continued long-term reductions in physical activity are a primary cause of insulin resistance.

The clinical consequences of insulin resistance, alone, have been delineated by Reaven (425): Some degree of glucose intolerance/impaired fasting glucose/impaired glucose tolerance, dyslipidemia ( $\uparrow$  triglycerides,  $\downarrow$  HDL-C,  $\downarrow$  LDL particle size,  $\uparrow$  postprandial accumulation of triglyceride-rich lipoproteins), endothelial dysfunction ( $\uparrow$  nonnuclear cell adhesion,  $\uparrow$  plasma cellular adhesion molecules,  $\uparrow$  plasma asymmetric dimethylarginine,  $\downarrow$  endothelial-dependent vasodilation), Procoagulant factors ( $\uparrow$  plasminogen activator inhibitor-1,  $\uparrow$  fibrinogen), hemodynamic factors ( $\uparrow$  sympathetic nervous system activity,  $\uparrow$  renal sodium retention), markers of inflammation ( $\uparrow$  C-reactive protein,  $\uparrow$  white blood cell count) abnormal uric acid metabolism ( $\uparrow$  plasma uric acid concentration,  $\downarrow$  uric renal acid concentration),  $\uparrow$  testosterone (ovary), and sleep-disordered breathing. By a direct cause of insulin resistance, physical inactivity indirectly, directly, or both in some cases (endothelial dysfunction) causes all of the aforementioned.

## 19. Prediabetes

**Condition's definition** A person with prediabetes has a fasting blood glucose level between 100 and 125 mg/dl and/or 2-hour blood glucose between 140 and 199 mg/dl during an oral glucose tolerance test.

### 19.1 Etiology

It is estimated that 57 million people have prediabetes in the U.S (88). Prediabetes is a condition in which blood glucose levels are higher than normal, but not high enough to be classified as T2D. Prediabetics have an increased risk of developing T2D, and T2D's-associated comorbidities of heart disease, and stroke.

### 19.2 Clinical significance

We speculate that physical inactivity is an actual cause of much of prediabetes cases in those  $<60$  yrs of age. The speculation is based upon the Finnish DPS and DPP RCTs in prediabetics. However, to our knowledge, no large RCTs have been performed to test whether a physically active lifestyle over time primarily prevents prediabetes in healthy individuals as compared to healthy inactive individuals.

## 20. Type 2 diabetes (T2D)

### 20.1 Physical activity can reverse prediabetes

While early prediabetes, late prediabetes, and diabetes are in a continuum, they differ in success of primary prevention by physical activity. For instance, daily physical can reverse insulin resistance in healthy individuals (points B to A in the modified Bergman Fig. 12),

and prediabetes (to point A). However, microvascular (retinopathy, neuropathy, nephropathy) damage in T2D seems to be non-repairable by physical activity (418).” Thus, the risk of chronic complications that are unable to be reversed by daily physical activity increases as a function of the duration of hyperglycemia, many of which maybe present in individuals when finally diagnosed with T2D (418).

## 20.2 Etiology

Nearly 24 million people in the U.S. are diagnosed with T2D in 2007 (11). Today the number is likely even higher. By 2020 > 50% of Americans could have diabetes or prediabetes, at a cost of \$3.35 trillion based according to new projections by UnitedHealth Group's Center for Health Reform and Modernization (533). **The estimated lifetime risk of developing diabetes for babies born in 2000 is 32.8% for males and 38.5% for females, with Hispanics having the highest estimated lifetime risk (males, 45.4% and females, 52.5%) among ethnic groups (366), Remarkably, some adolescents have been reported to have T2D in the past 5 years, a disease once called adult-onset diabetes because of its time of onset.**

## 20.3 Primary prevention of T2D - overview

The CDC Website states that progression to diabetes among those with prediabetes is not inevitable (88). The National Physical Activity Guidelines Advisory Committee Report (NPAGCR<sup>1</sup>) (412) states that usage of physical activity questionnaires in large prospective cohort and cross-sectional observational studies all show that increased physical activity levels show associations with reduced risk for developing T2D. A systemic review of follow-up, case-control or cross-sectional studies by Fogelholm (185) concludes for individuals with BMI of 25–35 having high BMI even with high physical activity were at a greater risk for the incidence of T2D and the prevalence of cardiovascular and diabetes risk factors, compared with normal BMI with low physical activity. Nonetheless, in men with a BMI of 25 or more, a history of hypertension, a positive parental history of diabetes, or any combination of these factors, the incidence of T2D declined by 41% from the lowest to the highest levels of energy expenditure (234) (Table 10).

## 20.5 Primary prevention of T2D - Exercise clinical trial

**Prescribed** exercise was associated with a 46% reduction in risk of developing T2D in 110,000 men and women with impaired glucose tolerance in Da Qing China over a 6-yr intervention period (398).

## 20.6 Primary prevention of T2D- Lifestyle clinical trial

Prediabetic individuals who incorporate lifestyle modification including increases in their physical activity prevent or delay the onset of T2D by returning their elevated blood glucose levels to normal. During the Finnish Diabetes Prevention Study (Finnish DPS), T2D risk was reduced in prediabetics by 58% (530). In the U.S. Diabetes Prevention Program (DPP), T2D incidence was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and diet-exercise groups, respectively, with reductions, compared to placebo, of 31% and

<sup>1</sup>Major source for disease frequency data in chapter is US government report on physical activity by National Physical Activity Guidelines Advisory Committee, which will be referred to as NPAGCR.

58% in metformin, and diet-exercise groups, respectively (276). The result led Knowler et al. (276) to conclude that the lifestyle intervention was significantly more effective than metformin. However, the 58% reduction in the diet-exercise group and 31% reduction with metformin in the Finnish DPS and DPP were both intent-to-treat values. Intent-to-treat values in both studies are the sum of behavioral and biological mechanisms for 100% of the subjects, providing data for physicians on effectiveness of prescription. However, intent-to-treat does not separate behavioral from biological mechanisms. Thus, the biological effectiveness of diet and exercise, independent of behavior, is underestimated due to lower compliance rates in the lifestyle versus metformin groups.

### 20.7 Physical activity can prevent T2D without weight loss

Primary prevention of T2D without weight loss has major public health importance due to media and medical emphasis on weight loss.

**Randomized clinical trials (RCT)**—Subjects were 80% less likely to develop T2D when they did not reach the percentage goal of weight loss, but achieved the goal with respect to exercise volume (more than four hours per week) as compared to the reference group, in the Finnish DPS (530).

**Prediabetes independent of changes in body weight**—To determine the effect of leisure-time physical activity on the occurrence of T2D in prediabetics of the Finnish DPS, subjects filled out a 1-yr questionnaire for leisure-time activity and then were followed for an additional 4.1 yrs after the original 3.2-yr DPS. Subjects within the upper third of total leisure-time physical activity had ~70% lower risk of T2D than those in the lowest third, in overweight, prediabetic men and women in the Finnish DPS (297, 299), despite similar baseline physical activity, age, baseline BMI and dietary variables and their changes during the study. In the U.S. DPP, a follow-up analysis was made for those subjects who made one goal, but not a second goal. Subjects who met the activity goal (>150 min/wk in the U.S. DPP, but did not meet the weight loss goal (>7%), had a 44% reduction in diabetes incidence, independent of the small weight loss (–2.9 kg) that occurred in the DPP (219).

### 20.8 Mechanisms

A recent review describes available evidence suggesting that exercise primarily acts to lower hyperglycemia by improving glucose sensitivity and mechanisms that interfere directly with endothelial metabolism (4). Another review indicates that it is likely that one of the mechanisms by which physical fitness and activity reduce health risk associated with high BMI is by decreasing fat-to-lean mass ratio and also by decreasing visceral-to-subcutaneous fat ratio. The review indicates that decreasing VAT is particularly important for BMIs between 25 and 30 (185). Physical activity also improves glucose-induced insulin secretion in pancreatic beta cells, likely through enhanced gastric inhibitory protein (GIP) secretion (483).

### 20.9 T2D predisposing genes-environmental interactions

A complex disease such as T2D has, at present, 18 multiple candidate loci that account for only a small percentage (< 7%) of the total identifiable genetic load. Snyder et al. wrote,



“Thus, the interpretable genetic contributions that can be identified are quite minor... Presumably, either many low-frequency alleles at different loci contribute to the genetic load or perhaps the many phenotypes are because of other phenomena such as synergistic effects between variants at more than one locus or between different loci and factors in the environment, recurrent spontaneous mutations, or epigenetic defects.” (484).

Contemporary hypotheses are that many individual rare gene variants play a much larger role in the genetic predisposition to T2D (436), but currently there is little data to support this speculation.

### 20.10 Clinical significance

Physical inactivity is an actual cause of insulin resistance and of prediabetes, and therefore, according to disease progression of T2D, itself. T2D is primarily prevented by primary prevention of insulin resistance (prevents movement from point A to B in the modified Bergman figure (Fig. 12), and of decreased beta-cell insulin secretion and of prediabetes (prevents movement from point B to C in Bergman's Fig. 12).

T2D is estimated to cost men 11.6 life-years and 18.6 quality-adjusted life-years and women 14.3 life-years and 22.0 quality-adjusted life-years when at the age 40 years (366). Complications given at the American Diabetes Website (11) are: heart disease and stroke (death rate is 2–4 times greater than non-diabetics); hypertension (75% of diabetes); blindness (12,000–24,000 new cases/yr); kidney failure (~47,000 new cases/yr); neuropathy (60–70% of diabetics); and lower limb amputation (~71,000 cases/yr).

## 21. Non-alcoholic fatty liver disease (NAFLD)

### 21.1 Definition

NAFLD is a liver disease in females and males who drink less than 10 and 20 grams of alcohol/day, respectively. NAFLD is a progressive disease first apparent by benign fatty liver (steatosis), which can evolve to non-alcoholic steatohepatitis (NASH) that adds inflammation to steatosis. Later progression leads to steatosis with inflammation and mild to advanced fibrosis, to steatosis with fibrosis alone, to cirrhosis and finally to end-stage liver disease. Histologic findings of pediatric NAFLD may or may not differ from adult NAFLD (69). Serious outcomes of NAFLD include cirrhosis, hepatocellular carcinoma, coronary heart disease, and diabetes (449).

### 21.2 Etiology

NAFLD is recognized as the leading cause of chronic liver disease in adults and children (518). Prevalence estimates are ~20% of adult Americans have benign fatty liver without inflammation or damage and 2–5% have NASH (164). Prevalence of NAFLD in a subpopulation of morbidly obese population ranges from 75–92%. The prevalence of NAFLD in American children is estimated at 13% (472) and has emerged as the leading cause of chronic liver disease in children and adolescents in the United States (322).



**NAFLD independent of changes in body weight**—St. Gorge et al. (488) concluded that “maintaining or increasing physical activity provides health benefits for patients with fatty liver, independent of changes in weight.” Caldwell and Lazo (74) contend that increased physical conditioning appears to be closely linked to improved hepatic metabolism independent of changes in body weight.

### 21.3

Church found lower CRF directly associated with higher NAFLD prevalence in healthy, nonsmoking, nonalcoholic 33–73-yr-old men (101). A second study reported a low level of habitual physical activity was associated with higher intrahepatic fat content in healthy, nonalcoholic males and females ages 19–62 (407).

### 21.4 Interventions/animals

**OETF rats have a spontaneous mutation that inactivates cholecystokinin receptor 1 protein to signal satiety. Without the satiety signal, hyperphagia leads to concurrent obesity and NAFLD between the ages of 5 and 8 wks old, which progress to T2D (429). Sixteen weeks of voluntary running of 4-wk-old OETF rats totally prevented the development of NAFLD. Morphologically, livers of runners had both fewer and smaller lipid droplets compared non-runners.**

### 21.5 Cross-sectional

Habitual leisure-time physical activity, especially anaerobic, may play a protective role in NAFLD by a reduced rate of abdominal obesity in 24–70-yr old human subjects (578). Further, only the association with resistance physical activity remained significant with further adjustment for BMI. **Lower VO<sub>2</sub>peak was associated with increasing NAFLD activity and with disease severity by NASH diagnosis (283).**

### 21.6 Intervention

Maintaining or increasing physical activity provides health benefits for patients with fatty liver, independent of changes in weight (488). An intensive lifestyle intervention program can successfully produce a 7%–10% weight reduction and significant improvements in liver chemistry and histological activity in patients with NASH (420). Targeting weight loss by energy restriction alone or in combination with exercise training has been shown to reduce NAFLD pathology. In patients with and without NAFLD, nine months of diet and exercise intervention led to three important outcomes: 1) reduction in liver fat was approximately twice reduction of VAT; 2) subjects who resolved NAFLD tended to have higher CRF at prior to the intervention; and 3) VO<sub>2</sub>max at baseline was a predictor of change in liver fat, independently of total- and VAT mass (264). The study indicated that CRF fitness and liver fat are related to each other.

### 21.7 Clinical trials

Long-term RCTs examining the effects of exercise, independent of weight loss, on NAFLD are lacking.

## 21.8 Mechanisms

Two approaches were tested. The first approach compared OLETF rats with and without 16 weeks of voluntary running. OLETF rats that underwent the voluntary running had 3-fold higher rates of hepatic fatty acid oxidation (complete palmitate oxidization to CO<sub>2</sub>); lower TG synthesis [70% and 35% lower protein concentrations of fatty acid synthase and acetyl-coenzyme A carboxylase (ACC), respectively], and higher oxidative capacity (35% and 30% higher ACC phosphorylation and cytochrome c concentrations, respectively), as compared to sedentary OLETF rats (429). The second approach was to suddenly cease 16 wks of daily voluntary running by OLETF rats. The times for hepatic metabolic adaptations to occur with stoppage of running were: 2 days (malonyl-CoA protein increased while phospho-acetyl-CoA carboxylase (ACC) decreased) and 7 days (fatty acid synthase increased and cytochrome oxidase activity and fatty acid oxidation decreased). Thus, reduced physical activity for less than 7 days initiates biochemical sequences that leads to NAFLD in OLETF rats (428).

## 21.9 Clinical significance

A recent title on PubMed was “Some experts suggest that fatty liver disease will be the next big metabolic disorder associated with obesity and inactivity” (15). Physical inactivity is an actual cause of NAFLD. Most cases of NAFLD can be primarily prevented by sufficient physical activity. Reversal of NAFLD with sufficient physical activity can also occur before hepatofibrosis occurs.

## 22. Cardiovascular diseases (CVD): All types

### 22.1 Definition

CVD includes all diseases that affect heart and blood vessels. The American Heart Association (321) lists major CVDs as: of subclinical atherosclerosis, coronary heart disease, acute coronary syndrome (myocardial ischemia), angina pectoris, stroke (cerebrovascular disease), high blood pressure, congenital cardiovascular defects, cardiomyopathy and heart failure, and other less prevalent CVDs. Physical inactivity increases the prevalence of all major CVDs.

### 22.2 Known and unidentified risk factors

Of the identified CVD risk factors, modest percentage changes occur with habitual physical activity. Mora and Lee (349) indicate that changes in individual risk factors with physical activity are on the order of 5% for blood lipids, 3 to 5 mm Hg for blood pressure, and 1% for hemoglobin A1c, in contrast to the large (30% to 50%) reductions seen in CVD risk with physical activity.

Mora and Lee (349) presented an analysis that showed that almost one-half of risk factors by which physical activity lowers CVDs are not identified. Subjects were 27,000 women compared by >1500 kcal/wk vs. <200 kcal/wk. Differences in “known” risk factors explained 59.0% of CVD and 36% of coronary heart disease (CHD) of the inverse association between higher physical activity levels and fewer CVD events (349). Respective contributions of “known” risk factors for CVD and CHD were inflammatory/hemostatic

(33% and 21%), blood pressure/hypertension (27% and 15%), traditional lipids (19% and 13%), BMI (10% and 7%), HbA1c/diabetes (9% and 5%), and homocysteine (0.7% and 0.3%) (349). Mora and Lee (349) caution that some or all of the aforementioned risk factors have interactions, or are acting in concert, since they add up to more than 59% for CVD and 36% for CHD. The deduction then is 41% and 64% of mechanisms by which physical activity primary prevents CVD and CHD, respectively remained to be identified in 2007.

**CVD independent of changes in body weight**—Physical activity predicts lower CVD risk independent of obesity (552). BMI's >25 contributed only 10% and 7% of physical activity's protection from CVD and CHD, respectively (349). Public health ramifications are that BMI is a minor contributor as to how physical activity prevents CVD and CHD. Increased physical activity levels in women with elevated BMI considerably reduce the risk of coronary heart disease (553). However, the risk is not completely eliminated, reinforcing the importance of being lean and physically active (553).

### 22.3 Unknown pathophysiological mechanisms

Joyner and Green (261) proposed a global hypothesis that might include some, or all, the unknown ~40% and ~60% of unidentified risk factors by which physical activity reduces CVD and CHD, respectively. Their suggestions for additional risk factor candidates that are improved by habitual physical activity include:

- Enhanced vagal tone via improved peripheral baroreflex function and central nervous system cardiovascular regulation. In populations, this will be protective and be seen as improved or maintained heart rate variability.
- Enhanced or maintained endothelial function that will both favor vasodilatation and contribute to enhanced peripheral baroreflex function by limiting age- or risk factor-associated increases in vascular stiffness.
- Positive interactions between enhanced endothelial function and sympathetic outflow that limit the effects of high levels of baseline sympathetic outflow on blood pressure (261).

### 22.4 Coronary vascular disease (CVD) gene-environmental interaction

CVD is a complex disease. Physical inactivity adaptations in gene expression are very complex, varying by tissue type and time. Thus CVD x physical inactivity interaction promises to be highly individualized, depending on the degree of accuracy of the desired prediction.

## 23. Presentation of individual cardiovascular diseases

The strategy for the presentation of individual cardiovascular diseases follows. The order of cardiovascular diseases presented will be coronary heart disease, peripheral artery disease, hypertension, stroke, and congestive heart failure. (Cross-references: Chronic cardiac disease)

## 24. Coronary heart disease (CHD)

### 24.1 Definition

CHD is a disease of the heart and the coronary arteries that is characterized by atherosclerotic arterial deposits that block blood flow to the heart, causing myocardial infarction.

### 24.2 Etiology

CHD caused ~1 of every 6 deaths (~425,000) in the U.S. in 2006. In 2010, an estimated 785,000 Americans will have a myocardial infarction, and approximately 470,000 will have a recurrent attack. The American Heart Association recognized physical inactivity as a risk factor for CHD and CVD in 1992 (183) and the Surgeon General concluded in 1996 that “regular physical activity or cardiorespiratory fitness (CRF) decreases the risk of CVD ... and CHD” (531).

### 24.3 Primary prevention of CHD

Each 1-MET decrease in maximal aerobic exercise capacity increases the adjusted hazard ratio for death by 12% (279). Using those individuals with 4 MET maximal aerobic exercise capacity as a reference value of 1.0, the mortality risk was 38% lower for those who achieved 5.1 to 6.0 METs, mortality risk declining progressively to 61% for those who achieved >9 METs, regardless of age. Unfit individuals who improved their fitness status with serial testing had a 35% lower mortality risk compared with those who remained unfit (279). The NPAGCR reports the literature shows a strong inverse relation between the amount of habitual physical activity performed and CHD morbidity and mortality (412). Sedentary behavior is a major independent risk factor for CHD as middle aged or older individuals of both genders who have moderate or higher amounts of physical activity lower their CHD risk 20% and 30%, respectively, compared to sedentary (412).

### 24.4 Mechanisms

Positive effects of chronic exercise on primary prevention of CHD could be explained by several mechanisms including: increased nitric oxide and antioxidants, decreased pro-inflammatory cytokine levels in blood by decreasing production from multiple tissues, and increased regenerative capacity of endothelium expressed by an increased number of circulating endothelial precursor cells, according to a recent comprehensive review of the topic (433). However, these mechanisms do not totally explain the primary prevention of CHD.

### 24.5 Clinical significance

Physical inactivity is a cause of at least 1 of 3 deaths from CHD. Sufficient physical activity primarily prevents CHD.

## 25. Peripheral arterial disease (PAD)

### 25.1 Definition

Narrowed arteries reduce blood flow to limbs, sometimes causing leg pain, generally referred to as claudication when walking. (Cross-reference: Exercise and peripheral arterial insufficiency: Control of blood flow to cardiac and skeletal muscle during exercise)

### 25.2 Etiology

PAD affects 8–12 million people in the U.S. (12%–20% > 65 yrs old have PAD). The NPAGCR concludes that a lack of RCT exercise studies exists to evaluate the effect of exercise training on preventing PAD (412). However, the Report does find support that physical inactivity contributes to accelerated disease progression in those who have PAD. A recent review concludes that the magnitude of effect from a supervised exercise program exceeds that achieved with any of the pharmacologic agents available to treat PAD (388).

### 25.3 Mechanisms

Mechanisms by which physical activity is primary prevention of PAD are potentially similar to those given for coronary artery disease.

### 25.4 Clinical significance

Physical inactivity may be a factor increasing the risk of PAD. PAD is a strong predictor of myocardial infarction, stroke, and death due to vascular causes. As atherosclerosis is by far the most common etiology of PAD, and as physical activity primarily prevents coronary artery disease, speculation could be made that physical activity could also primarily prevent PAD. However, insufficient large RCT studies have been performed. Some tertiary preventive evidence exists in PAD patients that walking performed 3 times or more weekly have less functional decline during the next year (336) and that greater than light physical activity reduces mortality (194). (Cross-reference: Peripheral Circulation)

## 26. Hypertension

### 26.1 Definition

With prehypertension, systolic blood pressure (SBP) is 120–139 mmHg and diastolic blood pressure (DBP) is 80–89 mmHg. Hypertension is defined as SBP  $\geq$  140 mmHg or DBP  $\geq$  90 mmHg, or taking antihypertensive medicine.

### 26.2 Etiology

In the United States, >62% of adults have blood pressures above optimal levels. The NPAGCR concluded that both aerobic and progressive resistance exercise cause reduced SBP and DBP in adult humans, although aerobic exercise evidence is stronger (412). The influence of exercise intensity on post-exercise hypotension occurred in dose-response fashion such that for each 10% increase in relative  $\dot{V}O_{2peak}$ , SBP decreased 1.5 mmHg and DBP 0.6 mmHg, thus showing a dose-response relationship for physical activity intensity and lowering of blood pressure post exercise (post-exercise hypotension) (156).

## 26.3 Mechanisms

Eicher et al. (157) suggest potential mechanistic clues for post-exercise hypotension involve the renin-angiotensin system and sympathetic nervous systems and include modulation by cardiometabolic, inflammatory, and hemostatic factors.

## 26.4 Clinical significance

With decreased daily physical activity, increases in SBP and DBP were 2.4 mmHg and 1.6 mmHg, respectively, in normotensive; 3.1 mmHg and 1.7 mmHg in prehypertensive; and 6.9 mmHg and 4.9 mmHg in hypertensive subjects, respectively (412). A 3.0 mmHg higher systolic and a 2.3 mmHg higher DBP translates into an estimated 12% increased risk for CHD and 24% increased risk for stroke (416). Physical activity is one of a number of primary preventive measures against hypertension.

## 27. Stroke

### 27.1 Definition

Stroke is a sudden diminution or loss of consciousness, sensation, and voluntary motion caused by rupture or obstruction (as by a clot) of a blood vessel of the brain.

### 27.2 Etiology

Each year ~800,000 individuals experience a new (~610,000) or recurrent (~185,000) stroke with ~185,000 deaths in the U.S. The most physically active men and women have a 25% to 30% lower risk for stroke incidence and mortality. Data on ischemic and hemorrhagic stroke subtypes is quite limited according to the NPAGCR (412). Thirteen of 992 articles satisfied all eligibility criteria to be included in a meta-analysis. Compared with low physical activity, moderate physical activity caused an 11% reduction in risk of stroke outcome and high physical activity a 19% reduction. No significant risk reduction associated with moderate physical activity in women (137). A meta-analysis of 33 prospective cohort studies and 10 case-control studies found that physical activity reduces the relative risk of 0.75 for fatal or non-fatal cerebral infarction, while the corresponding relative risks for cerebral hemorrhage and stroke of unspecified type are 0.67 and 0.71, respectively. The reduction of risk was only statistically significant for men (432).

### 27.3 Mechanisms

Reimers et al. (432) suggest potential mechanisms of risk reduction by physical activity on stroke. They include: antihypertensive effect, beneficial effect on lipid metabolism, and improved endothelial function (increased endothelial NOS activity and extracellular superoxide dismutase expression). Other mechanisms that may play a role include a lowered blood viscosity, a tendency toward platelet aggregation, increased fibrinolysis, reduced plasma fibrinogen, increased activity of plasma tissue plasminogen activator activity, and higher of HDL-cholesterol.

## 27.4 Clinical significance

Physical inactivity causes deteriorations in multiple mechanisms that cause stroke, as mentioned above. Physical activity could be primary prevention of 10–30% of stroke, depending on the volume of activity.

## 28. Congestive heart failure (CHF)

### 28.1 Definition

The heart fails to pump adequate amounts of blood through arteries to tissues, which causes blood to back up and accumulate in other parts of the body, such as lungs and feet. CHF is often accompanied by distension of the ventricles, peripheral and pulmonary (causing shortness of breath) edema.

### 28.2 Etiology

After 65 yrs of age, ~10 per 1000 individuals have CHF. Hypertension precedes 75% of CHF cases. RCTs for prevention of congestive heart failure are not available. Observational data supports the notion that habitual endurance training is primary prevention against development of CHF.

### 28.3 Mechanisms

Levine and co-authors (16) have concluded that prolonged, sustained endurance training preserves ventricular compliance with aging and may be an important approach to reduce the probability of heart failure with aging. Preservation of ventricular compliance with endurance training probably includes preservation of viscoelastic myocardial properties (absence of increased ventricular stiffening) and eccentric ventricular hypertrophy (a balanced enlargement of ventricular mass and dimensions) (16). These adaptations lead to profoundly improved cardiac performance without apparent change in contractility, which thus is largely explained by enhanced diastolic filling due to low stiffness (16). Together these are coupled with endurance training prevention of arterial stiffening with aging result in preserving ventricular-vascular coupling of compliance, lowering afterload on the left ventricle (16).

### 28.4 Clinical significance

Physical inactivity contributes development of CHF. Physical activity can primarily prevent some CHF.

## 29. Known mechanisms for CVD risk factors

### 29.1 Endothelial dysfunction

**Definition**—Endothelial dysfunction is characterized by vascular endothelium exhibiting reduced vasodilation along with greater proinflammatory and prothrombic markers (161).

**Conditions associated with endothelial dysfunction**—Félétou and Vanhoutte's review states that endothelial dysfunction has been associated not only with hypertension or atherosclerosis, but also with the following long list of conditions:



Since then the term “endothelial dysfunction” has been referred to in the scientific literature more than 20,000 times (PubMed search, November 2005) and has been associated not only with hypertension or atherosclerosis, but also with physiological and pathophysiological processes, including aging, heart and renal failure, coronary syndrome, microalbuminuria, dialysis, thrombosis, intravascular coagulation, preeclampsia, Type I and Type II diabetes, impaired glucose tolerance, insulin resistance, hyperglycemia, obesity, postprandial lipemia, hypercholesterolemia, hyperhomocysteinemia, elevated asymmetric dimethylarginine plasma levels, inflammation, vasculitis, infections, sepsis, rheumatoid arthritis, periodontitis, trauma, transplantation, low birth weight, postmenopause in women, mental stress, sleep apnea syndrome, smoking, nitrate tolerance, glucocorticoids, and so on” (180).

The list of associations would now have to include physical inactivity since the 2005 list is out-of-date.

**Etiology**—Sedentary men at ages of 50–76 years of age have impaired endothelium-dependent dilation in response to both acetylcholine and increased shear stress in humans (465). In contrast, 50–76 yr-old, long-term, exercise-trained men do not show age impairment as they have similar endothelium-dependent dilation to acetylcholine-mediated vasodilation as healthy, 22–35-yr old men have (132, 167). Regular aerobic exercise can restore the loss of endothelium-dependent vasodilation in previously sedentary 50–76 yr-old men, implying that physical inactivity is responsible for nearly 100% of endothelial dysfunction in this group of men (132) Seven days of dry immersion, a human model of extreme physical inactivity diminished endothelium-dependent vasodilation by 59% (371).

**Clinical outcomes**—Davignon and Ganz (121) contend that endothelial dysfunction is an early marker for atherosclerosis and can be detected before structural changes to the vessel wall are evident. If, as claimed by Davignon and Ganz (121), endothelial dysfunction is an early marker for atherosclerosis and can be detected before structural changes to the vessel wall are evident, then a prevention of endothelial dysfunction by a lifetime of physical activity would therefore also prevent most of atherosclerosis reaching a clinical level at the age of 50–76 yrs in men (132, 167) or even initiation of aerobic physical activity within lifestyle (132).

**Biochemical adaptations to inactivity**—Singularly caged, healthy, young male mice had ~30% less endothelium-dependent vasodilation to acetylcholine and ~50% less eNOS protein than did five mice in large cages, where the multiple housed mice ran, climbed, and fought during their active cycle (501). With other data, they suggest that an impaired nitric oxide/cGMP-pathway signaling is most likely not involved in endothelial dysfunction induced by a sedentary lifestyle in mice. In a second report, mice in cages without wheels for voluntary running had 148% higher vascular lipid peroxidation, 176–188% higher superoxide release, 154% greater NADPH oxidase, and 161% higher rac1 protein than mice voluntarily running in wheels for 6 weeks (307). Expression levels for subunits nox1, p47phox and p67phox were increased, which suggests increased oxidative stress. A tissue that is not involved in limb movement of running or cycling is the penis. Treadmill training

of diabetic rats restored impaired endothelial-dependent and neurogenic nitric oxide relaxation in corpus cavernosum (102). The exercise training increased depressed plasma superoxide dismutase (SOD) levels of sedentary diabetic rats. The paper hypothesized that nitric oxide bioavailability to corporal smooth muscle was increased by plasma's SOD's antioxidant action.

**Mechanisms of inactivity**—Lack of shear stress from transient bouts of exercise initiates a cascade of unhealthy events that can be inferred if the sedentary group in exercise studies is considered (308). Extreme 7-day physical inactivity in humans causes microvascular impairment with 32% and 59% decreases in basal flow and endothelium-dependent vasodilation, respectively that was associated with a selective increase in circulating endothelial microparticles (371), that have pro-coagulant and pro-inflammatory properties (99).

**Clinical significance**—Physical inactivity is a cause of endothelial dysfunction by lack of increased blood flow by exercise in sedentary condition. Exercise signals a beneficial endothelial cell phenotype, at least in part through changes in shear stress and wall stretch in the arteries.

## 29.2 Atherogenic Dyslipidemia

**Definition**—Atherogenic dyslipidemia is defined as the presence of abnormally low serum concentrations of high-density lipoprotein cholesterol (HDL-C) and elevated concentrations of high triglycerides and small, dense low-density lipoprotein cholesterol (LDL-C).

**Etiology**—The NPAGCR concludes that habitual physical activity increases serum HDL-C and decreases serum TG. Threshold volumes are from 7 to 15 miles per week of regular aerobic exercise (equating to an approximate 600 to 800 MET-minutes), with no sex differences (412). The NPAGCR also concludes that evidence is inconsistent as to whether and if LDL-C responds favorably to exercise training. A meta-analysis of 29 RCTs of progressive resistance training found statistically significant improvements of  $-2.7\%$  for total cholesterol,  $-11.6\%$  for ratio of total cholesterol /HDL-C,  $-5.6\%$  for non-HDL-C,  $-4.6\%$  for LDL-C, and  $-6.4\%$  for TG ( $-8.1$  mg/dl,  $-14.5$  to  $-1.8$ ) (270). The change for HDL-C was not significant. The clinical importance of reductions in LDL-C by resistance training is that for every 1% reduction in LDL-C levels, a 1% reduction occurs in relative risk for major CHD events.

**Clinical significance**—Physical inactivity contributes to worsening of atherogenic dyslipidemia. Exercise improves blood lipid values. Lakka and Laaksonen (299) caution not to underestimate the clinical significance of small changes in plasma LDL-C, HDL-C, and TG concentrations with aerobic exercise training because they occur concurrently with benefits on other cardiovascular and metabolic risk factors. Traditional lipids contribute to 19% and 13% of physical activity's contributions of “known” risk factors to reduce CVD and CHD, respectively, according to Mora et al. (349). Another report found that traditional lipid risk factors account for only 20% of total risk of CVD risk events in 27,000 women (349).

### 29.3 Hemostasis

**Definition**—Hemostasis is the arrest of bleeding either by physiological properties of vasoconstriction and coagulation or by surgical means.

**Etiology**—In a 1990 review, physical inactivity had been associated with the following: low plasma volume, high hematocrit, high plasma fibrinogen, elevated blood viscosity, increased platelet aggregation, and diminished fibrinolysis (158). Low physical fitness and self-reported sedentary lifestyle have been associated with a pro-thrombotic blood profile in middle-aged women with CHD (364). Plasma levels of the hemostatic factors such as fibrinogen, FVIIa, FVIIc, vWFag showed an inverse relation to self-reported physical activity. Regular physical exercise has beneficial long-term effects on hemostasis in studies including male subjects (See (364) for refs.).

**Clinical significance**—Numerous reviews suggest that physical activity has long-term healthy benefits on hemostasis (2, 28, 158, 320).

### 30. Deep vein thrombosis (DVT)

DVT is the formation of a blood clot (“thrombus”) in a deep vein. its prevalence is ~12,000/yr with 6% dying within 1 month. DVT is caused by physical inactivity. The lack of shear stress along with low blood flow likely may account for deep vein thrombosis (“economy-class syndrome”) at the back of vein valves where white cells adhere to fibrin strands (48). The clinical significance of DVT results when a clot breaks off as an embolus and flows to the lung where it blocks a portion of pulmonary blood flow, causing lack of gas exchange in pulmonary capillaries. Primary prevention is muscle pumping from muscle contraction that “squeezes” venous blood to return blood past venous valves back to the right atrium.

### 31. Cognitive Function

#### 31.1 Disease definitions

Cognitive function is a broad term defined as the “an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering” (358). Cognitive decline is considered an aging disease with two of the most severe forms being Alzheimer's and dementia. Thus, cognitive function can arbitrarily be divided into studies of developing cognition and of primary prevention of the decline in cognition. (Cross-reference: Dementia and Alzheimer's disease; Effects of exercise on brain function and cognitive development)

#### 31.2 Epidemiology of developing better cognition

Research in exercise and prevention of cognitive decline is relatively new and moving rapidly. Recent reviews exist (239, 341).

**Lifetime**—Aerobic exercise and physical activity improve cognitive health across the lifespan (239). Dutch men, but not women, who were physically active at a young age (15–25 yrs old), had less of a decline in informational processing capabilities versus individuals

physically inactivity early in life (138). Women who reported being physically active at any point in life had a lower likelihood of cognitive impairment in late life (341). Women who began physical activity later in life after inactive teenage years also had lower rates of cognitive impairment in late life. Of the four ages examined, teenage physical activity appeared to be most strongly related to better cognitive function and lower prevalence of cognitive impairment in old age (341).

**Children**—A 2003 meta-analysis in children (aged 4–18 yrs) demonstrated a significant positive relationship between physical activity levels and perceptual skills, intelligence quotient, achievement, verbal tests, mathematic tests, developmental level/academic readiness, with only an effect on memory not found (172). Chaddock et al. (91) found improvements in relational, but not item memory in children. Children who have low physical activity levels have poorer academic achievement scores and inferior cognitive performance as compared to physically fit children (70, 84, 91, 92, 100, 144, 172, 174, 237, 238, 273, 417, 565). A 2008 review concluded that exercise facilitates children's executive function, (i.e., organize thoughts and activities, prioritize tasks, manage time efficiently, and make decisions) similar to improvements reported for other age groups (520).

**Adolescents**—A cohort study of Swedish men born in 1950 through 1976 who were enlisted for military service at age 18 (N = 1,221,727) (1) reported that cardiovascular fitness, as measured by ergometer cycling, was positively associated with global intelligence scores with aerobic capacity most strongly associated with logic and verbal intelligence. The longitudinal arm of the Swedish study showed that between the ages of 15 and 18 yrs of age those with the top 10% of improvement in cardiovascular fitness scores had highest enhancement of global intelligence, logical, verbal, visuospatial, and technical scores while those subjects with declines in cardiovascular fitness had less than mean intelligence scores. Further, an association between better cardiovascular fitness at age 18 yrs, a higher socioeconomic status, and educational attainment later in life existed.

**Older adults**—18 RCTs (published prior to 2001) focused on aerobic physical activity interventions in older adults. Aerobic exercise had an overall effect size of 0.48 was found with the largest effect on executive functioning, followed by attention, visuospatial, and speed dependent processes (108). In a prospective study of 18,000 women aged 71–80 yrs old, higher levels of long-term regular physical activity were strongly associated with higher levels of cognitive function and a 20% lower risk of cognitive impairment (556). Physical inactivity (less than 3 bouts of exercise/week) increased the risk of dementia from 13.0 per 1000 person-years to 19.7 per 1000 person-years (306). Each 10 blocks that were walked/day in women >65 years old resulted in 13% less impairment in cognitive function (574). Moderate and high levels of physical activity were associated with significantly lower risks for Alzheimer disease and for dementia of any type (309). An inverse relationship between physical activity levels and dementia was found in men and women aged 65 years and older (413). Higher  $\text{VO}_2\text{peak}$  was associated positively with preservation of cognitive function over a 6-year period in 349 subjects over the age of 55 (24).

Increased aerobic fitness can be neuroprotective and can enhance cognitive function (108, 110, 282). Kramer et al. reported in 1999 that those who received aerobic training (walking)

showed substantial improvements in performance on tasks requiring executive control compared with stretching- and toning-trained subjects aged 60–75 yrs (282). Resistance exercise also had a positive impact on cognitive function in 65–75-yr-old males (83).

**Physical activity, not fitness, improves cognitive function**—A meta-analysis was performed on 571 fitness effect sizes from 1306 subjects from 37 studies prior to 2005. Etner et al. (172) concluded that the empirical literature did not support a relationship between aerobic fitness and cognitive performance. Rather across the same 37 studies designed to test the effects of fitness on cognition, the summary statistic indicated that a positive association existed between physical activity and cognitive performance (172), confirming the findings of three previous meta-analytic reviews of this literature (108, 173, 473).

**Dementia: Primary prevention**—The NPAGCR (see (412) for refs)] found that physical activity delayed the onset of cognitive decline or dementia in most studies with sample sizes >1,000 individuals, but with inconsistent findings for underpowered studies containing low subject numbers. Nine of 16 prospective studies had odds ratios (OR = 0.63) showing protection by physical activity from dementia or Alzheimer's Disease [Figure G8.8 in NPAGCR (412)]. To date, no RCT has been performed to show that regular physical activity prevents dementia (445).

### 31.3 Mechanisms

As a new frontier in inactivity disease, we chose to provide a more extensive presentation on the inactivity/exercise mechanisms for cognitive function.

#### **Physiological/Structural**

**Human:** Highly cardiorespiratory-fit or aerobically-trained individuals had reduced activation of the anterior cingulate cortex concomitantly with lower indecision that arises when multiple conflicting responses are elicited in response to a stimulus during a task that required variable amounts of executive control, relative to untrained individuals (110). Fit and trained subjects also had greater task-related activity in regions of the prefrontal and parietal cortices that are involved in spatial selection and inhibitory functioning (110).

Reductions in hippocampus volume are associated with a decline in memory performance, specifically acquisition and recall measures (410) hippocampal volume is positively correlated with physical fitness in adults (163) and children 10-yr olds (91), and can be increased by aerobic training of both schizophrenic and healthy subjects' (397). Likewise, a 6-month aerobic exercise intervention increased grey matter volume in the frontal and superior temporal lobes(109). Further, results suggest that aerobic fitness does not have a general impact on the volume of all structures in the brain in children (92). Electrical function is increased in “high” hit older (50–62 year old) adults (154) in potentially due to increased synaptic plasticity and long-term-potential (544).

**Animal:** Exercise increases neurogenesis in the dentate gyrus, a hippocampal region that is important for spatial recognition. Van Praag et al. (535) showed increased voluntary

exercise is sufficient for enhanced survival of newborn cells in 3-month-old adult mouse dentate gyrus. Another study found that improved spatial pattern separation in 3-month-old mice was tightly correlated with increased neurogenesis and vasculature in the dentate gyrus after 10 weeks of voluntary wheel running (117). Rat voluntary runners have longer-lasting LTP following tetanic stimulation (due to lower threshold of LTP induction) in dentate gyrus, which is dependent upon the activation of N-methyl-D-aspartate (NMDA) receptors (538). Another anatomical change associated with improved cognitive is improvements in brain blood flow. Voluntary wheel running can increase blood vessel density, blood flow, and capillary perfusion of the motor cortex in rats (42, 502). Potential mechanisms include the increased density of microvessels (141), angiotensin 1 (141), VEGF protein (141), or endothelial proliferation (141, 160). Angiogenesis in the brain is associated with enhanced improvement in a functional outcome like water maze time (536), but not the ability to activate the motor limbs (275).

### Biochemical adaptations

**Human:** The human brain is responsible for ~70–80% of circulating BDNF at rest (423). BDNF mRNA and protein expression were increased in human skeletal muscle after exercise, but muscle-derived BDNF appeared not to be released into the circulation (332).

**Animal:** Physical activity can induce local and systemic expression of many growth factors that protect the brain from physical inactivity-related declines in function. Brain-derived neurotrophic factor (BDNF) plays an important role in the growth, development, maintenance, and function of several neuronal systems (372). BDNF mRNA was upregulated in a dose-response manner following 2, 4, and 7 days of voluntary distance run by rats (372). Three days of voluntary wheel running had as much effect as 28 days in increasing mRNAs for growth factors (BDNF, neural growth factor, fibroblast growth factor-2), synapse related proteins (synapsin, syntaxin, synaptotagmin), neurotransmitter systems (reduced  $\gamma$ -aminobutyric acid (GABA) neurogenic signaling, which is associated with increased recovery), and intracellular kinases ( $\text{Ca}^{2+}$ /Calmodulin-Dependent Protein Kinase II, MAPK/ERK kinase 1/2, mitogen-activated protein kinase 1/2) (346). Whether 1 day would have the same effects is unknown. Conversely, cessation of voluntary wheel running in spontaneously hypertensive rats can decrease the BDNF and BDNF/NT-3 growth factor receptor (TrkB) system mRNA in hippocampus for a duration lasting at least 10 days (559).

Another critical growth factor for neuroprotection and brain health is IGF-1. A number of studies show that IGF-1 increases in the brain following exercise. Infusion of IGF-1 mimicked the effects of exercise, while infusion of an anti-IGF-1 antibody blocked the effects (80). Blocking hippocampal IGF-1 receptors, but abolished the effect of exercise on augmenting recall in rats during 5 days of wheel running (140). Anti-IGF-1 antibody can also abrogate the protective effects of exercise in many types of brain lesions (81). Like BDNF, the levels of IGF-1 increase in the circulation in response to physical activity (521) and both exercise and systemic infusion of IGF-1 increases new and survivability of BrdU+ cells in the hippocampus (323, 521), likely signaling through IGF-receptors located on the luminal side of the brain (323). In culture, IGF stimulates VEGF via a HIF mechanism



(323). Blockage of peripheral VEGF prevents the increase in BrdU-positive cells and mitosis in immature neurons of exercising animals only (175).

### Genetic

**Human:** Polymorphisms in the APOE4 genotype have been examined in relationship to physical activity, with mixed results (399). For instance in cross-sectional studies examining physical activity by questionnaire, two studies suggest that carriers of APOE4 benefit from physical activity (127, 462), while one does not (413). However, higher aerobic fitness levels in older women having the APOE4 genotype had better cognitive function in another cross-sectional study (171), suggesting that physical activity levels that are capable of increasing aerobic fitness are needed to improve cognitive function in those with APOE4 genotypes.

**Animal:** Animal studies support this. Mice with the APOE4 genotype that voluntarily ran in wheels for 6 months rescued cognitive function and BDNF levels within the hippocampus by returned them to that found in APOE3 (control) mice (379).

## 31.4 Clinical Significance

Epidemiological, interventions, and mechanistic insights from human and rodent studies all suggest that physical inactivity can accelerate declines in cognitive function; a decline that be attenuated or potentially reversed by physical activity. However, questions remain regarding the best-practice for mode, duration, intensity, the long lasting effects, potential gender specific effects, and the interaction with genetic components.

## 32. Depression and anxiety

**32.1 Definitions** Dr. Paul - Anxiety is much higher today then it was in 2012, when this study was published. I attached an article on this topic in this last email. It is very interesting.

**Depression**—A mood disorder marked especially by sadness, inactivity, difficulty with thinking and concentration, a significant increase or decrease in appetite and time spent sleeping, feelings of dejection and hopelessness, and sometimes with suicidal thoughts or an attempt to commit suicide. (Cross-reference: Depression)

**Anxiety**—An abnormal and overwhelming sense of apprehension and fear often marked by physiological signs (as sweating, tension, and increased pulse), by doubt concerning the reality and nature of the threat, and by self-doubt about one's capacity to cope with it.

**32.2 Etiology** Dr. Paul - Anxiety and depression are much higher today

Depression is relatively common affecting 8% of women and 4% of men, having a lifetime prevalence of 16%, and an annual cost of \$83 billion dollars in the United States (208).

Anxiety is prevalent in 10% of the general public, has many similar symptoms and treatments to depression, but can also include a wide range of phobias. Both depression and anxiety are associated with increased risks of many other diseases. Genetic, biological, chemical, hormonal, environmental, psychological, and social factors all likely intersect to contribute to depression in women (see (369) or details). Some of these same factors play a



role in men. For anxiety, disorders last at least 6 months and commonly occur along with other mental or physical illnesses, including alcohol or substance abuse.

Since 1995, more than 100 population-based observational studies have been completed. Looking at these studies, the 2008 NPAGCR (412) concluded that active people were nearly 45% less likely to have depressive symptoms than inactive people. Looking at the 28 prospective cohorts allows for examination of physical activity levels before depression symptoms occur. Nearly 4 years of physical inactivity increased risk for depression by about 49% without adjustment for depression risk factors and by 22% after adjusting for known risk factors such as age, sex, race, education, income, smoking, alcohol use, and chronic health conditions. In 66 of 67 cohort studies, physical inactivity increased the risk of depression. While many of the studies relied on self-questionnaires, 8 cohort studies contained clinical diagnosis of depression symptoms, which reported an increase of 40% in the inactive group. Physical working capacity was found in depressed male patients but not female patients (350). Morgan et al, who noted that both grip strength inversely related to hospital length stay and lower in depressed patients (351). In Britain, children under the age of 15 had an 8% reduction in depression symptoms for every hour of exercise completed/week (448). Likewise, lower fitness was found in depressed male patients but not female patients (350).

Treatment of depression with exercise has also been shown to be effective. In 1979, Greist et al (211) found that running and time-limited/unlimited psychotherapy reduced depression symptoms similarly. Depressed patients that participated in exercise had less of a need for medication and less relapse (18), and adhere to exercise (66%) greater than medication (40%). An exercise dose consistent with public health recommendations in 1998–2001 (about 12 miles/week of walking for 12 weeks) reduced depressive symptoms 47% from baseline while a lower dose exercise (5 miles/week) group did not respond any better than the exercise placebo control group (150). Other studies have found a relatively quick effect of exercise involving 10 days of walking for 30 min/day resulted in a decrease in the Hamilton Rating Scale for Depression and self-assessed intensity of symptoms (139).

The NPAGCR (412, 532) concluded that after examining 4 population-based cross-sectional studies of over 121,000 Americans that regular physical activity decreases the odds of an anxiety disorder. Specifically, the national Co-Morbidity study found physical inactivity increased anxiety disorder by 1.75 times in raw odds and 1.38 times once adjusted for sociodemographic and illness (204). Australians reporting no activity were 2.1 times more likely to develop anxiety disorders than those conducting more than 3 hours of vigorous activity a week (30); similar results were found in inactive young Germans (493). In summary of all random controls trials the Committee Report concluded a strong effect of a moderate (>25minutes/day) amount of physical activity (both resistance and aerobic) in reducing anxiety symptoms.

### 32.3 Mechanisms

**Physiological**—A decline in cognitive function may be a cause of depression. For instance, in over 5,000 elderly women (mostly white), increasing symptoms of depression were associated with reduced cognitive function in each of 3 tests, showing a negative

correlation (575). Those with 6 cognitive-impairment symptoms had a relative risk of 2.3 times to be depressed than those with 0–2 impairments. While it is unknown whether the mechanisms of increased depression and decreased cognitive function are similar in different populations (for example young vs. old), reduced brain tissue, blood flow, or otherwise are found in both suggesting a similar cause if not similar mechanism.

### **Biochemical adaptations**

**Human:** Potential roles of elevated glucocorticoids due to a failure to suppress the hypothalamic-pituitary-adrenal (HPA) axis have also been studied in healthy humans. Physically active individuals have less stress response to the same absolute exercise in terms of cortisol release (324). Furthermore, the most fit group had a diminished release of cortisol in response to intravenous ovine corticotropin-releasing hormone (324).

**Animal:** In rats, physical inactivity increases the ACTH levels rather than cortisol in response to a stressor (143, 178). However, questions remain about the level of physical activity necessary for beneficial HPA adaptations with some studies suggesting intense physical activity can have a detrimental effect (97).

Changes in monoamines and other circulating markers may also be involved in inactivity-induced increases in depression and anxiety, similar to changes in cognitive function. Catecholamines, specifically norepinephrine (NE) signaling and production, is increased with physical activity in the pons medulla, which is where the only NE-producing nerves are found that serve the frontal cortex, hippocampus, thalamus, and cerebellum; a major source of NE-serving nerves to the hypothalamus, amygdala, and spinal cord [reviewed in (142)]. A decrease in NE levels in response to repeated stress is prevented by chronic VWR in rats (142), with a threshold of as little as 30 min/day of VWR (149). In addition to increased NE levels at the site of production, microdialysis showed increased levels and turnover of NE where the neurons terminate in the spinal cord is found after just 1 hour of treadmill running in rats (396).

Levels of 5-hydroxytryptamine (serotonin), an important neurotransmitter for mood, and its receptor are potentially increased by acute treadmill running due to the increased lipolysis and FFA binding to albumin. By reducing albumin, tryptophan levels are higher in circulation and have an increased entry into the brain, leading to increased synthesis of serotonin (95).

### **Genetic**

**Human:** In a large twin-population based in the Netherlands, data about leisure-time exercise and anxiety and depression symptoms were measured. Interestingly, in genetically identical twin-pairs, the lack of leisure-time exercise did not increase anxiety or depression symptoms (126). However, this study took a very narrow approach at looking at exercise level, whereby physical activity, such as walking or cycling work, or vocational related physical activity were not considered (571). Lastly, adolescent girls with an allele for high BDNF received no protective effects against depression and anxiety symptoms by avoiding

physical inactivity, while those with the allele causing lower BDNF level were protected (330).

**Animal:** Exercise stress response has been looked at using rats selected for either high endurance (high capacity runners; HCR) or low endurance (low capacity runners; LCR) based on a run to volitional/behavioral exhaustion. Counter to the hypothesis, the HCR had more anxiety-like behavior on a maze test and higher levels of cortisol in response to a restraint test (547). The surprising result may be in part due to the fact that the HCR selection is based on avoiding the electrical shock and, thus, avoiding stress in addition to their volitional/behavioral endurance capacity.

### 32.4 Clinical significance

Physical inactivity causes up to 1/3<sup>rd</sup> of depression. Physical activity can primarily prevent 20–30% of depression.

## 33. Bone (Osteoporosis)

### 33.1 Definition

Decrease in bone mass with decreased density and enlargement of bone spaces producing porosity and brittleness.

### 33.2 Etiology

Among males >50 yrs old, prevalence of osteoporosis and osteopenia was 6% and 47%, respectively; and in females >50 yrs of age, prevalence was 7% and 40%, respectively (202).

**Etiology – Lack of gravity and physical inactivity**—Four cosmonauts who spent up to 7 months on the Russian space station Mir lost ~1–1.6% of bone mineral density mainly from the spine, femoral neck, trochanter and pelvis (540). The spaceflight data shows that loading bone (gravity) is a powerful stimulus to maintenance of bone mass. In spinal cord injury to one monozygotic twin, as compared to their non-injured monozygotic twin, bone mineral content and bone mineral density were reduced 42% and 35% in the legs, respectively, and 50% and 29% in the pelvis, respectively (29). Non-weight-bearing athletes (bicycling) had lower bone mineral mass of whole-body and spine than weight-bearing athletes in males (426, 427). The spinal cord injury and cycling data demonstrate that absence of gravitational loading is a powerful stimulus for loss of bone mass.

**An actual cause: lack of exercise**—Bone is lost from the lumbar spine and femoral neck at the rate of ~1% per year in sedentary pre- and postmenopausal women (Fig. 13). Inactivity, i.e., reduced gravitational loading and muscle contraction forces on the skeleton, might contribute to aging-associated bone loss as suggested by the studies described below. (Exercise: the key to bone health through the life span)

### 33.3. Primary prevention

Exercise-training programs prevent or reverse almost 1% of bone loss per year in the lumbar spine and femoral neck in both pre- and postmenopausal women, who were presumably

sedentary, in a meta-analysis (572). Mixed loading exercise programs combining jogging with other low-impact loading activity and programs mixing impact activity with high-magnitude resistance exercise were effective in reducing postmenopausal bone loss at the hip and spine (329). In a first study, a 3-yr program of combined low-volume, high-resistance strength training, and high-impact aerobics maintained bone mineral density at the spine, hip, and calcaneus, but not at the forearm (which lost 3%), in early post-menopausal women (162). Importantly, the non-trained group bone mineral density decreased 2–8% over the same 3-yr period. These findings emphasize the clinical importance of avoiding inactivity in the early post-menopausal period and the specificity of the lack of impact on critical bones with high fracture rates in later life (162). In a second study, site-specific increases in bone density by resistance training happened in 50–70 year-old postmenopausal women and men who exercised ~3–4 days each week for 1 yr (212). As in the first study, inactive “control” subjects lost bone mass.

Finally, it is important to emphasize the site-specificity of exercise on bone. Only bones subject to loading will become stronger as adaptations are site-specific. Further, not all “weight-bearing” exercise is equivalent when it comes to increasing bone mass/strength, e.g., comparisons of walking (which does relatively little) < jogging < jumping.

### 33.4 Physiological mechanisms

Physical inactivity results in reduced mechanical, both gravitational and muscle contraction, forces which in turn induces catabolism (resorption) by promoting osteoclastogenesis with concurrent suppression of both bone formation and osteoblastogenesis. Dynamic exercise alters the balance between bone formation and resorption to favor anabolism through osteoblast recruitment and activity.

Mechanical loading of bone occurs in response to compressive forces from gravity during walking or running, or to in response to muscular forces at the bone attachments during contractions. Physical activity, alone, only increases strain on bone by ~0.1%. However, strains of 1–10% are needed to activate bone cells. The implication, then, is that a mechanism must therefore exist to amplify strains from physical activity (compressive impact forces from striking surfaces and tensile forces from contracting skeletal muscle at attachment sites to bone) to exceed the threshold needed to activate bone cells. Ozcivici et al. (394) conclude that mechanical targeting of the bone marrow stem-cell pool might, therefore, represent a novel, drug-free means of slowing the age-related decline of the musculoskeletal system.

### 33.5 Cellular mechanisms

Current thought for how a bone strain of ~0.1% can be amplified to a 1–10% has been suggested based upon 25 years of publications by Riddle and Donahue (437). Deformation of skeletal tissues induces pressurization of interstitial fluid, producing a positive pressure gradient from the matrix to the haversian canals, allowing bone cells perceive changes in their mechanical environment (an amplification mechanism) (437). It is not completely settled whether the conversion of the physical force of fluid flow to a biochemical signal is

by means of integrin/cytoskeletal transduction of forces or chemotransport ion channels, or both.

### 33.6 Clinical consequences

Physical inactivity is a primary cause of bone loss in weight-bearing bones. Physical activity results in both gravitational and muscle-contraction loading of the skeleton and, therefore, is primary prevention of osteoporosis.

## 34. Osteoarthritis (OA)

### 34.1 Definition

Degeneration of cartilage and its underlying bone within a joint (Cross-reference: Osteoarthritis and exercise: cause and effects)

### 34.2 Etiology

The type and duration of physical activity is a key factor determining whether exercise is beneficial to joint health or not. Buckwalter wrote,

Participation in sports that cause minimal joint impact and torsional loading by people with normal joints and neuromuscular function may cause osteophyte (bony projections that form along joints) formation, but it has minimal, if any, effect on the risk of osteoarthritis. In contrast, participation in sports that subject joints to high levels of impact and torsional loading increases the risk of injury-induced joint degeneration. People with abnormal joint anatomy or alignment, previous joint injury or surgery, osteoarthritis, joint instability, articular surface incongruity or dysplasia, disturbances of joint or muscle innervation, or inadequate muscle strength have increased risk of joint damage during participation in athletics” (71).

The NPAGCR(412) lists sports/activities associated with an increased prevalence of incident osteoarthritis as being ballet/modern dance, orienteering, running, track and field, football (American and Australian rules), team sports (basketball, soccer, and ice hockey), boxing, weight lifting, wrestling, tennis, and handball. Confirming the specificity of sport/activity is a longitudinal study that followed 45 long-distance runners and 53 control subjects from age 58 in 1984 until 2002 with a series of knee radiographs to examine the progression of OA (93). In 2002 20% of runners and 32% of controls had prevalent OA, with 2.2% and 9.4% being severe. The small size of this study prevented this difference from reaching statistical significance. The NPAGCR(412) concluded that no evidence presently exists to indicate that regular moderate to vigorous physical activity of 30–60 minutes for general health benefits increases the risk of developing osteoarthritis in those without pre-existing major joint injury.

### 34.3 Clinical significance

Primary prevention would be to avoid those sports predisposing to later life development of osteoarthritis.

### 35. Balance

**Balance** is defined as the ability to maintain the center of gravity for the body within the base of support that produces minimal postural sway. Its etiology can be related to lack of usage of nervous system controlling skeletal muscle movement against gravity. For example, living in space for as little as 9 days accelerates problems of equilibrium on standing, walking and coordination on return to Earth (caused by inappropriate neurovestibular responses) (540). With eyes closed on this platform astronauts complain of having no sensation of falling. Similar balance dysfunctions occur with aging. It is likely that improper balance upon return to Earth from spaceflight and with aging have a common denominator of insufficient exercise against gravity. Lack of appropriate balance occurs in later life. The NPAGCR (412) concluded that the strong evidence exists in old Americans that the risk of falls is reduced from physical activity programs that emphasize both balance training and muscle-strengthening activity with some aerobic activity, especially walking. The NPAGCR (412) further indicates that no evidence indicates that planned physical activity reduces falls in adults and older adults who are not at risk for falls. The clinical significance for primary prevention requires exercises that retain normal balance to reduce falls in individuals at risk for falls (124).

#### Bone fracture/falls

Bone fracture is defined as a break, rupture, or crack in bone or cartilage. Physical inactivity, specifically lack of loading bones against gravity, will cause loss in bone density, which increases the risk of bone fracture. Physical inactivity is directly associated with fracture risk, particularly for fractures of the proximal femur (i.e., increased physical inactivity increases fracture risk), according to NPAGCR (412). Based on epidemiologic studies that evaluated present dose-response associations, the minimal levels of physical activity that were significantly associated with reduced fracture risk were at least 9 to 14.9 MET-hours per week of physical activity. The METs translate to >4 hours per week of walking (types of exercise that mechanically load the proximal femur as opposed to cycling (426) or other activities that do not load the femur). Primary prevention with exercises that load bones can reduce falls in those with balance irregularities, fall-related fractures, and several risk factors for falls in individuals with low bone density (124).

### 37. Rheumatoid Arthritis (RA)

**RA** is a chronic autoimmune disease characterized by inflammation of the joints, frequently accompanied by marked deformities, and ordinarily associated with manifestations of a general, or systemic, affliction. While no preventive measures are currently known, physical activity is critical to not allowing RA to progress. Studies show no harmful effects of physical activity, and some even show a positive effect in the reduction of symptoms (73). High-intensity physical activity is better than low at preventing the worsening of symptoms. The mechanism by which physical activity has a beneficial effect on RA might be its countering the global increase in inflammation that normally occurs during the progression of RA.

## 38. Cancer

### 38.1 Definition

A malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis.

### 38.2 Comments on cancer types

**Majority of cancer prevalence has environmental component**—Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms, implying that the environment has the principal role in causing sporadic cancer (319). A review on targets and pathways for cancer prevention exists (442).

**Risks of only some cancers rise with physical inactivity**—Physical inactivity increases the prevalence of some site-specific (colon, breast, and endometrial cancers), but, to date, not all cancer types. The specificity of cancer types enhanced by physical inactivity supports a notion that mechanisms of inactivity-induced cancers are specific to each site-specific cancer. Stated in an opposite manner, some cancer types are not caused by physical inactivity. (Cross-reference: Cancer)

Those cancers whose risk is enhanced by inactivity will be considered next.

## 39. Colon cancer

### 39.1 Cross-sectional and longitudinal studies

A literature review through March 1997 found 23 case-control (cross-sectional) studies and 17 cohort (longitudinal) studies. In both types of studies, those in the highest physical activity category had ~40%–50% reduction in risk of colon cancer compared with the least active category (111). A decade later, the NPAGCR(412) concluded physical activity produced a medium reduction of 30% in colon cancer from 8 case-control and 12 cohort studies, respectively.

### 39.2 Randomized control trials

The NPAGCR (412) states that RCTs have demonstrated effects of physical activity interventions on cancer risk factors, which further support a role of physical activity in reducing risk for cancer.

### 39.3 Mechanisms

**Human:** Suggestions by others how physical inactivity might increase prevalence of colon cancer are: 1) lengthening the transit time of feces, thus prolonging exposure to fecal carcinogens (114); 2) causing higher levels of blood insulin, thus producing insulin resistance, which is a risk factor for cancer (198, 207); 3) causing higher levels of blood free IGF-I (198), exposing the rapidly turning over colon epithelium to higher levels of anabolic hormone that is associated with greater colon cancer incidence (198); 4) preventing synthesis and release of exercise-derived, anti-inflammatory myokines, thus removing their



systemic effect (62); and/or 5) producing positive energy expenditure, increasing body fat (9).

**Animal:** *ApcMin*<sup>+/+</sup> mice have a nonsense mutation at codon 850 in the *Apc* (*Adenomatous polyposis coli*) gene that predisposes them to both small and large intestinal adenomas, thus these mice have been used as a model of colon cancer (359). Colbert et al. reported two exercise studies using *ApcMin*<sup>+/+</sup> male mice. In their first study, 3 weeks of voluntary running followed by 5 weeks of treadmill running did not alter polyp development or serum IGF-I (106). In their second study of *ApcMin*<sup>+/+</sup> mice, 10 weeks of voluntary running decreased polyp number and increased serum IGF-I in male *ApcMin*<sup>+/+</sup>, with IGF-I not being related to polyp number (107). Carson and co-authors observed that treadmill exercise reduced polyp number and size in male, but not female *ApcMin*<sup>+/+</sup> mice, while voluntary wheel running did not elicit a change in polyp number or size (337). Carson and co-authors reported that treadmill training caused intestinal polyps of *ApcMin*<sup>+/+</sup> mice to have 35%, 73%, and 43% decreases in macrophages, terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL)-positive cells (index of apoptosis), and Bax protein 43% (proapoptotic protein), respectively (21).  $\beta$ -Catenin phosphorylation was elevated 3.3-fold in polyps from these exercised mice. Ju et al. (262) found that colon tumorigenesis was ~40% greater in sedentary than voluntary running mice *Apc*<sup>Min/+</sup> mice. The sedentary mice had higher IGF-1/IGFBP-3 ratios and aberrant  $\beta$ -catenin signaling, as compared to the voluntarily running mice (262).

### 39.4 Clinical significance

The lowest activity group has ~40% increased prevalence of colon cancer compared to the highest activity group. Physical activity is a primary preventer of colon cancer.

## 40. Breast cancer

### 40.1 Cross-sectional and longitudinal studies

The NPAGCR (412) concludes from 63 published studies that physical activity was associated with a medium reduction of 20% across all studies. However, the NPAGCR reports the range of reductions in breast cancer for all population-based case-control studies to be 20%–70% and for cohort studies to be 20%–80%.

The effect of physical activity on breast cancer reduction differs between pre- and postmenopausal conditions. A 2007 systemic review of 19 cohort and 29 case-control studies found a strong evidence for risk reductions ranging from 20% to 80% by physical activity for postmenopausal breast cancer (347). However, much weaker evidence is available for physical activities reduction on risk of premenopausal breast cancer, so no effect existed. Combining pre- and postmenopausal breast cancer resulted in a 15–20% decreased risk by physical activity. **A trend analysis indicated a ~6% decrease in breast cancer risk for each additional hour of physical activity per week assuming that the level of activity would be sustained.**

## 40.2 Mechanisms

Neilsen (373) suggests that physical inactivity might increase breast cancer prevalence by any or the following: higher than normal BMI, androgens, estrogens, lifetime exposure to estrogen, leptin, insulin, insulin resistance, TNF- $\alpha$ , IL-6, CRP, and inflammation. Lower levels of steroid hormone binding protein by physical inactivity have been suggested to increase breast cancer risk. The mechanisms by which long-term physical activity lowers postmenopausal breast cancer risk, however, remain unclear (373).

Thompson et al.'s comprehensive review provides extensive literature to support three hypotheses by which physical inactivity could enhance breast cancer's prevalence (509). Hypothesis 1 proposes that inactivity-induced changes in circulating growth factors and hormones activate the mTOR-signaling network to increase proliferation and decrease apoptosis in breast cells while stimulating new blood vessel formation. Hypothesis 2 states that inactivity increases breast cells responsiveness to physiological stresses, potentially through FoxO, Sirtuin, and/or adipokine/myokine signaling. Hypothesis 3 says that inactivity increases glucose and glutamine availability in mammary carcinomas, thereby attenuating breast cell apoptosis and, thus, increasing the accumulation of breast tumor masses.

## 40.3 Clinical significance

The lowest activity group has ~25% increased prevalence of breast cancer compared to the highest activity group. Physical activity is a primary preventer of breast cancer.

## 41. Endometrial cancer

The NPAGCR (412) found growing evidence to support reduced risk of endometrial cancers in physically active versus sedentary persons. A meta-analysis of prospective studies published through to December 2009 found that physical activity was clearly associated with a 30% lower risk of endometrial cancer (348).

## 42. Activity prevention of female reproductive disorders

### 42.1 Pregnancy

Multiple methodological pitfalls exist in the studies published (196), so conclusions made about benefits of physical activity on female reproductive health remain for further testing. Nonetheless, the consensus is that exercise can serve as primary prevention during pregnancy (196, 339). Maternal outcomes to be briefly discussed are gestational diabetes mellitus (GDM), preeclampsia, and weight gain [Summaries below are taken from an extensive review (196)].

### 42.2 Gestational diabetes mellitus (GDM)

**Definition**—Any degree of glucose intolerance with onset, or first recognition, during pregnancy. Women in the high-risk category not found to have GDM at initial screening should be retested between 24 and 28 wks of gestation.

**Etiology**—Overall prevalence of gestational diabetes is 4%-8%, depending on U.S. locale (202). The American Diabetes Association has stated, “Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing... as soon as feasible” (10). Note the statement does not include physical inactivity as a risk factor.

**Exercise outcomes**—Gavard and Artal's have a lengthy review (196). They conclude that the balance of evidence is that exercise is protective against GDM. The protective effect seems to be particularly strong for vigorous or intense exercise, particularly for women reporting physical activity both before and during pregnancy. Studied in their review mentioned no deleterious exercise effects. Obviously, exceptions may occur and obstetricians should be consulted.

**Clinical significance**—GDM occurs during pregnancy and having GDM increases the risk of T2D later in life in both mothers and their offspring carried during GMD. Physical inactivity would increase chances of GDM. Physical activity is primary prevention.

### 42.3 Preeclampsia

**Definition**—A condition developing in late pregnancy that is characterized by a sudden rise in blood pressure, excessive weight gain, generalized edema, proteinuria, severe headache, and visual disturbances and that may result in eclampsia if untreated.

**Exercise outcomes**—Gavard and Artal (196) concluded that the balance of evidence still supports that exercise is the primary prevention against preeclampsia, with the effects being particularly strong for vigorous or intense exercise. No deleterious effects of exercise on preeclampsia were found, but Gavard and Artal caution that purposes of the investigations cited by them may not have been to report deleterious effects (196).

**Clinical outcomes**—Physical activity seems to be helpful in preventing preeclampsia from the limited numbers of studies on the topic.

### 42.4 Excessive weight gain during pregnancy

Gavard and Artal (196) conclude that prospective clinical trials are needed to establish exercise's effectiveness for lowering risk of maternal and fetal comorbidities during pregnancies with excessive weight-gain. Likewise, Shirazian and Raghavan (471) call for prospective interventional studies to demonstrate the benefits of weight limitation on pregnancy outcomes.

### 42.5 Polycystic ovarian syndrome (PCOS)

**Definition**—Accumulation of numerous cysts on the ovaries associated with high male hormone levels, chronic anovulation, and other metabolic disturbances. Classic symptoms include excess facial and body hair, acne, obesity, irregular menstrual cycles, and infertility.

**Exercise outcomes**—Limited information is available for the primary prevention of PCOS by physical activity. Exercise appears to provide secondary/tertiary prevention, so

studies of primary prevention seem justified. Thomson et al.'s review on treatment and management of PCOS conclude, "...few well-controlled randomized studies have been conducted evaluating the benefits of exercise training...Future research with rigorous study designs is needed to determine specific exercise guidelines..." (510).

#### 42.6 Female athlete triad (Triad)

**Definition**—A combination of disorders frequently found in female athletes that includes disordered eating, osteoporosis, and oligo- or amenorrhea.

The Triad is discussed in detail by an American College of Sports Medicine position stand (370). The position stand places emphasis on optimizing energy availability for primary prevention. The stand also states, "No pharmacological agent adequately restores bone loss or corrects metabolic abnormalities that impair health and performance in athletes with functional hypothalamic amenorrhea" (370). Eating disorders warrant psychotherapy.

#### 42.7 Dysmenorrhea

**Definition**—Painful cramps during menstruation.

**Exercise outcomes**—Physical exercise has been suggested as a non-medical approach to manage these symptoms, but Cochrane review (66) cautions their conclusion is limited to a single RCT with a small sample size of limited quality. Primary prevention by physical activity may be plausible but is not sufficiently proven.

### 43. Activity prevention of male reproductive disorders

#### 43.1 Erectile Dysfunction (ED)

**Definition**—Impotence, or erectile dysfunction (ED), is defined by the as the inability for a male to maintain erection of the penis sufficient for sexual performance.

**Etiology**—It is estimated that ED affects 30 million males in the United States. ED prevalence increases steadily with age, from 6.5% in men aged 20 to 29 years to 77.5% in those 75 years and older (453). In addition to physical inactivity, other risk factors are age, CVD, T2D, high cholesterol, smoking, recreational drug use, and depression are all risk factors. Erections are established through a set of well known events whereby neural stimulation (of various types) results in a release of nitric oxide, increased cGMP, and ultimately vasodilation of the smooth muscle in the arteries supplying the penis, which expands penile volume by increased blood flow into the corpora cavernosa. This process is reversed by phosphodiesterase type 5 (PDE5) breaking down cGMP; thus, pharmaceutical treatments of ED inhibit PDE5 activity.

**Cross-sectional evidence**—Several large cross sectional studies exist to suggest that physical inactivity is a cause of ED. In a cohort of over 31,000 men over the age of 50 one third of men had ED (19). Men engaged in at least 32.6 MET equivalent hours of exercise per week had a significantly lower relative risk (0.7) than those undergoing less than 2.7 MET activity hours/week, a similar reduction in risk as obesity increased risk (19). For instance in the Boston Area Community Health (BACH) Survey of 2031 males aged 30–79

lifestyle contributed to 12.2% of the total subject with clinically validated ED (295). However, when all covariates were considered, lifestyle alone could only explain 0.9% of the ED. In a prospective study from the same population those who went from no physical activity to some physical activity had a similar relative risk (OR of 0.5) as those that maintained high levels of physical activity (OR of 0.3) (131).

**Interventional evidence**—Utilizing a randomized-single blind design 110 obese men with ED, as defined by a International Index of Erectile Function (IIEF) less than 21, were either placed into an intervention group with the goal of 10% weight loss by walking 4 hours a week and reducing caloric intake or a control group. After 2 years, using an intent-to-treat analysis, the intervention group spent 195 min/wk doing physical activity and had a significant improvement in IIEF scores from 13.9 to 17, with no change in the control group. Furthermore, physical inactivity levels were independently associated with ED (170). In a follow up study using twice as many subjects this same group demonstrated that lifestyle intervention for two years reduced the prevalence of ED from 66% to 44% (169). Those within the lifestyle group that exercised more than 4 hours/wk were 1.9 times more likely to reverse ED than those in the lifestyle group that remained sedentary, correcting for changes in diet and other lifestyle habits. Using a higher intensity exercise of 75–80%  $\text{VO}_2\text{max}$  for 60 minutes, 3 times a week, previously sedentary, but otherwise healthy men, had significant improvements in subjective sexual experiences. The improved sexual experiences correlated with the improvement in fitness (557).

**Potential Mechanisms**—Since the underlying pathology of physical inactivity-induced impotence is similar to that of physical inactivity-induced endothelial dysfunction, many of the mechanisms through which exercise can be preventative are likely similar. However, the penile vasculature does not exhibit increased blood flow during treadmill running by Yucatan pigs (361). A few potential mediators of this are secreted factors from skeletal muscle (myokines), adipose tissue (adipokines), liver (hepatokines) or other changes in circulating factors, such as the physical activity-induced increase in testosterone in young, healthy men and adolescent boys (130, 326), an important regulator of vasculature health [reviewed in (344)]. Nevertheless, considerable evidence now suggests that chronic exercise training produces beneficial endothelial adaptations in vasculatures not recruited/active during exercise bouts. (Cross-reference: Effects of exercise on distribution of cardiac output in the peripheral circulation)

**Clinical significance of primary prevention** Physical inactivity is one cause of ED. Physical activity can be a primary preventer of ED.

### 43.2 Prostate Cancer (PCa)

The overall effects of physical activity on primary prevention of PCa are unclear. The NPAGCR concluded no association exists between physical activity and prostate cancer (412). On the other hand, the NPAGCR states a statistically significant trend towards decreasing prostate cancer risk was observed with increasing physical activity in several studies. Tertiary prevention may exist as Kenfield et al. (271) provided evidence that physical activity was associated with lower mortality and PCa mortality in men previously

diagnosed with PCa. Barnard et al. (23) noted that serum from subjects performing regular aerobic exercise led to reduced growth and increased apoptosis of lymph node cancer of the prostate tumor cells *in vitro*.

## 44. Pain

### 44.1 Definition

A basic bodily sensation that is induced by a noxious stimulus, received by free nerve endings, and characterized by physical discomfort.

### 44.2 Occurrence of low-back pain (LBP)

One-quarter of adults have at least 1 day of low back pain in a 3-month period and most adults suffer low back pain at some point during their lives (192). Well-trained individuals seem to exhibit higher pain tolerance to skeletal muscle biopsies and to skin suturing, but to our knowledge clinical trials testing the hypothesis are not available.

### 44.3 Clinical trials

Limited evidence exists according to a systemic review of 10 RCTs and 5 non-randomized clinical trials for the overall effectiveness of exercise to prevent LBP in humans (31).

### 44.4 Mechanisms

Moderate-intensity aerobic exercise reduced cutaneous and deep tissue hyperalgesia induced by acidic saline and stimulated neurotrophic factor-3 synthesis in gastrocnemius but not the soleus muscle (469). Sharma et al. (469) caution that their results are limited to animal models and cannot be generalized to chronic pain syndromes in humans.

### 44.5 Clinical significance

Exercise training has been long suggested to reduce pain, but not to be a cure to the source of the pain [see (469) for refs.], but sufficient publications to verify the claim do not exist. Bell and Burnett's review (31) concludes that future research is needed to clarify which exercises are effective and the dose-response relationships regarding exercise and low-back-pain outcomes.

## 45. Digestive tract diseases

### 45.1 Definition

The digestive tract begins in the mouth, ends in the anus, and includes accessory organs of digestion. Scores of digestive tract clinical conditions exist (368). Inactivity increases digestive system disorders. Some (cancers, non-alcoholic liver disease, and diabetic pancreas) are considered in elsewhere in the article.

### 45.2 Diverticulitis

**Definition**—Diverticulitis is an inflammatory swelling of an abnormal pouch (diverticulum) in the intestinal wall, usually in the large intestine (colon).

**Physical activity is a primary preventer**—Physical activity lowered the risk of diverticulitis and diverticular bleeding during an 18-yr of follow-up of 47,228 US males in the Health Professionals Study (492). Vigorous-intensity activity subjects largely explained the association, a conclusion verified by Williams (562).

### 45.3 Gallbladder disease

**Definition**—Gallbladder disease includes inflammation, infection, stones, or blockage (obstruction) of the gallbladder.

**Physical activity is a primary preventer**—Physical activity levels are inversely related to prevalence of gallbladder disease in an American Indian population (285).

**Mechanism**—Treadmill running promoted changes in hepatic gene expression that increased cholesterol uptake by the liver while simultaneously increasing the catabolism of cholesterol to bile acids, thus effectively reducing cholesterol saturation in the bile. Wilund et al. (566) suggest their results describe a potential mechanism by which exercise improves cholesterol clearance from the circulation while simultaneously inhibiting gallstone formation.

### 45.4 Clinical significance

Observational studies suggest that diverticulitis, constipation, and gallbladder disease can be caused by physical inactivity and primarily prevented by increased activity. Physical activity may reduce the risk of gastrointestinal hemorrhage and inflammatory bowel disease although this cannot be substantiated firmly (409).

## 46. Chronic respiratory diseases

### 46.1 Definition

Chronic diseases of the airways and other structures of the lung constitute chronic respiratory diseases. Some of the most common are asthma, chronic obstructive pulmonary disease (COPD), respiratory allergies, sleep apnea, occupational lung diseases and pulmonary hypertension. (Cross-reference: Chronic lung disease)

### 46.2 Etiology

Causes of these respiratory diseases are varied and include behavioral (smoking), environmental (air pollution and occupational hazards), and suppression of the immune system.

### 46.3 Physical inactivity

There are no studies to our knowledge showing that physical inactivity is associated with an increase in most chronic obstructive pulmonary diseases. With sleep apnea it is difficult to determine whether physical inactivity is a cause or a result of the sleep apnea resulting in a viscous cycle of less sleep coupled with less activity (549). With asthma, an interaction of an increased environmental pollution with physical activity may be the factor for more recent studies finding higher asthma in athletes. In two cross-sectional studies, asthma was more



prevalent in swimmers [Odds ratio (OR) = 10], long distance runners (OR = 6), and power athletes (OR = 3–4), than in less active individuals (232, 233). However, in contrast, an older study of Finnish athletes that died between 1936 and 1985 showed that they were no more likely to have asthma and about 50% less likely to die of any pulmonary disease than non-athletes (291). Our suggestion is that increased environmental pollution interacting with physical inactivity, rather than physical activity *per se*, is a major cause for increased asthma rates in athletes. The conclusion is consistent with an increase in asthma in the general population as well in the last several decades.

The sum of data suggests that a “J-shaped” curve exists where physical inactivity and extreme physical activity increase the risk the greatest for acquiring upper respiratory tract infections (URTI). While some prospective studies suggest a greater risk for URTI after a competitive event (381, 382), with increasing amount of training (229, 408), and higher in faster finishers (487) others show no difference after an event (159) and lower UTRI with 6–7 METs/day of any activity (331). A decreased prevalence of UTI existed in two intervention studies utilizing lower levels of physical activity [one involving elderly women (380) and the other mildly obese females (383)] However, many of these studies contain methodological problems including, failure to report bouts of physical activity, UTRI are only reported never verified by virus analysis, higher medical awareness during high intensity training, contact with other infections (large marathon), stress, nutrition, supplements, and all the studies are focused on exercise not physical inactivity.

#### 46.4 Mechanisms

There are several excellent reviews that the reader is directed to on immunosuppression following high levels of physical activity (64, 199, 401). The changes in immune function include low levels of lymphocytes and lymphocyte function (301), impaired phagocytosis, impaired neutrophilic function with prolonged exercise (401), neutrophil degranulation (400), reduced monocyte function (302), reduced oxidative burst activity, and potentially lower mucosal immunoglobulin levels (201).

#### 46.5 Clinical significance

While regular moderate exercise reduces susceptibility to infection compared to sedentary, prolonged bouts of strenuous exercise cause a temporary depression of various aspects of immune function (e.g., neutrophil respiratory burst, lymphocyte proliferation, monocyte antigen presentation) for ~3–24 hr, e.g., after prolonged (>1.5 h), of moderate to high intensity (55–75% maximum O<sub>2</sub> uptake) without food intake (199, 200). Periods of intensified training (overreaching) lasting 1 wk or more may result in longer lasting immune dysfunction (199, 200)

### 47. Chronic kidney disease (CKD)

CKDs damage the kidneys so that they are no longer capable of adequately removing fluids and wastes from the body or of maintaining the proper level of certain kidney-regulated chemicals in the bloodstream. (Cross-reference: Chronic renal failure). CKD is a secondary consequence of physical inactivity's increasing hypertension and T2D prevalence. Albumin

to creatine ratio (ACR) is a marker of kidney function. The U.S. DPP found no change in ACR despite reductions in diabetes development with lifestyle reduction of T2D (136). In contrast, the Australian Diabetes, Obesity, and Lifestyle Study found that increased television watching or low self-reported leisure-time physical activity were associated with increased odds ratio of albuminuria and low estimated glomerular filtration rate in 6,000 subjects (325, 558). Physical inactivity was one of multiple covariants accounting for early decline in renal function in 1400 U.S. diabetic blacks (287). Norwegians (n = 65,000) undergoing no or little physical activity were twice as likely to have a low estimated glomerular filtration rate (215). In summary, physical inactivity contributes to development of CKD.

## **48. Clinical significance of physical inactivity as one cause of 35 chronic conditions**

### **48.1 Volume of evidence**

Much of the article has presented evidence to prove that physical inactivity is a primary, upstream event that causes substantial increases in risk factors for 30 chronic diseases/conditions (Table 11; Fig. 3). The volume of evidence in itself is overwhelming. The clinical significance of physical activity itself is underappreciated as specific disease risk factors, themselves are often the prime objective of research and clinical care, rather than emphasis being placed on one major cause (physical inactivity) that is upstream of these risk factors.

### **48.2 Levels of evidence**

Levels of evidence-based medicine vary in strength among the 30 chronic conditions caused by physical inactivity. Pressure toward evidence-based medicine has come from public and private health insurance providers, which refuse coverage of practices lacking in systematic evidence of usefulness. Levels of evidence are ranked for policy decision-making for health care distribution. The highest level of evidence is that there is a systemic review of RCT trials (Level 1) (94). The lowest level is based on mechanisms. However, models of extreme physical inactivity are so dramatic in the magnitude of health detriment that Human Institutional Research Boards (IRB), for ethical reasons if side effects were to be muscle atrophy, for example, the IRB would consider the risk and then review what arrangements have been made to mitigate this risk. Our speculation is that IRBs would likely be hesitant, for ethical reasons, to approve RCTs lasting years if irreversible overt chronic disease were to occur because of physical inactivity. Therefore, RCTs to prove long-term physical inactivity causes a chronic disease are unlikely to occur.

In 2008 the DPP Research Group commented,

“Debate prevails about whether resources (human and financial) would be better spent on T2DM prevention or on its early detection and treatment. Early detection is feasible through use of the same simple tests used in prevention programs, and could be done much more economically than attempting to prevent diabetes at the population level. Allocation of resources to intensive management of patients with newly diagnosed diabetes could be preferable to prevention. A major drawback of

this approach, however, is that many people will have already developed macrovascular disease (and, rarely, microvascular disease) before diagnosis. Nonetheless, no data from clinical trials that have specifically compared prevention with early detection and intensive treatment have yet been reported” (116).

Narayan et al. already predicted in 2003 that 50% of U.S. births in 2000 would have diabetes in their lifetime (366). Seven years later, the CDC has made a similar statement that diabetes prevalence could increase to 33% of the population in 2050 in the worse case scenario (61). Boyle et al. (61) predict that focusing on high-risk subgroups of the population the widespread implementation of reasonably effective preventive interventions could considerably reduce, but not eliminate, future increases in diabetes prevalence. Nonetheless, physical activity as primary prevention remains largely not reimbursable and mostly absent from evidence-based medical discussions.

**Clinical significance**—The primary prevention of physical inactivity is underappreciated.

## 49. Effectiveness of drug therapy for simultaneous primary prevention of 35 physical inactivity conditions

### 49.1 Inability to mimic adaptive health benefits of physical activity

The natural adaptations to exercise provide a higher therapeutic index (benefits/side effects) than any drug therapy could exceed (Fig. 3). The high therapeutic index of exercise is in part due to its systemic complexity. It requires the integration of almost every physiological system (brain, neural, vascular, liver, adipose, muscle, etc.) to accomplish several basic physiological tasks such as movement and energy utilization. Since physical activity results in the whole body disruption of homeostasis in multiple organ systems, a drug therapy alone cannot replicate the entire ensemble its effects, without actually increasing physical activity. The complexity of physical activity is highlighted by comparison to other traits such as obesity. For instance, Reed et al. (431) estimate that 31% (extrapolated to 6000 genes) of all viable knockout mice have altered body weights. Such physiological complexity has been difficult to pharmacologically address with no FDA approved obesity drugs since 1999. Since the relative contribution of BMI for CVD and CHD has been estimated to be 10% and 7%, respectively (349), more than obesity is responsible for these diseases, making an “exercise pill” even less likely than obesity pill. We have published scientific criteria that must be met to legitimately use the terms ‘exercise pill’ and ‘exercise mimetic’ (53).

### 49.2 Clinical significance

Drugs will not substitute for all health benefits from physical activity in individuals medically capable of exercise.

## 50. Risk factors worsen over 6–12 months in RCTs

### 50.1 RCTs

The definition of chronic diseases contains the word “ongoing”. Slentz, Houmard, and Kraus (481) cite evidence to support the notion, “continued sedentary lifestyle in overweight or obese individuals—particularly those who already have some metabolic abnormalities—

comes at a high metabolic cost, as numerous health-related variables worsen over relatively short time periods” (51, 123, 218, 257). Examples from their own studies are given. Twelve markers that increase the risk of chronic diseases became worse in the 6-month inactive “control group”, including increases in body weight, waist circumference, waist-to-hip ratio, VAT, total abdominal fat, fasting insulin, LDL particle number, small dense LDL and LDL-cholesterol; and decreases in insulin sensitivity, and fitness (35, 153, 246, 257, 284, 481).

Hunter et al. (251) have published similar decrements for inactive “control” groups. Aerobic- and resistance-exercise adherence for 1 yr prevented regain of VAT in healthy, overweight, premenopausal women following a weight loss of 12 kg (251). Specifically, aerobic or resistance exercise adherers did not change in visceral adipose tissue mass (1.6% and 0%, respectively) (80 min/wk), contrary to a 38% increased VAT in the non-exercise adherers. While aerobic and resistance exercise adherers still regained 3.1 and 3.9 kg of body weight, respectively, it was significantly less than the 6.2 kg regain in exercise non-adherers, which was similar to the 6.4 kg gained in the group that did not exercise (251). Thus, sedentary “controls” became less healthy by increasing risk factors for chronic diseases, compared to exercising groups in both the Slentz et al. (481) and the Hunter et al. (251) studies. Together the two studies illustrate contemporary inactive “control” groups have a progressive worsening for risk factors of chronic diseases that physical activity can be a primary prevention against. A similar theme was apparent for osteoporosis, presented earlier in this article, i.e., bones in non-bone loading group lose mass and density over a period of months. Importantly, the above studies fit the definition of “slow in its progress and of long continuance” for chronic diseases (551). The pathological events from sedentary lifestyle are slow in progress.

## **51. Primary prevention of physical inactivity: childhood developing adult disorders**

### **51.1 Prevalence of physical inactivity in youth**

58% and 92% of American children aged 6–11 and 12–19 yrs-old, respectively, do not meet the recommended 60 min of daily physical activity (527). 73%–91% of Canadian children do not accomplish sufficient daily step numbers (76). A study was performed to compare lifestyle of children reminiscent of 100 yrs ago vs. modern children. 11-yr old accelerometer values were found the following progressive declines in physical activity in weekday minutes of activity/day: Old-Order-Amish (90 min) > Old-Order-Mennonite (69 min) > rural Saskatchewan (58 min) > urban Saskatchewan (49 min) (168). Tremblay et al. have commented, “Groups that preserve a traditional lifestyle, with significant incidental, lifestyle-embedded, physical activities, appear to achieve high levels of daily physical activity and fitness and resist obesity (525).

### **51.2 Obesity in children and adolescents**

Between the mid-1960's and mid-1980's, childhood and adolescent obesity ranged between 4%–6% (Fig. 14). About 25 yrs later (mid-1980's to 2008), obesity (>95% BMI percentile for children in the 1960's) in children (6–11 yrs) had risen 5-fold from ~4% in 1963–1974 to 20% in 2007–2008, and in adolescents (12–19 yrs) rose 3-fold from ~5%–6% in between

1966–1980 to 18% in 2007–2008 (Fig. 14) (386, 387). Even with a more liberal cutoff for overweight and obesity, 36% of children and 34% of adolescents, rather than 15% were above the 85<sup>th</sup> percentile of the 1960's (386). Higher BMI during childhood is associated with an increased risk of CHD in adulthood (20).

### 51.3 Fasting blood glucose

The number of youth with elevated fasting blood sugar increased 87% from 1999–2000 to 2005–2006 (318). The children with high fasting blood glucose have 49% lower glucose deposition index (504). More importantly, children with elevated fasting blood glucose were 3.4 and 2.1 times more likely to develop prediabetes and diabetes, respectively, as adults (378).

### 51.4 Prediabetes in children and adolescents

The number of US adolescents with elevated fasting glucose reached ~2,769,000 in 1999–2002 (147). Within this population, adolescents of Mexican Americans decent are overrepresented (15.3% of all Mexican American adolescents) relative to non-Hispanic whites (11.3%) and non-Hispanic black adolescents (7.4%).

### 51.5 Adult-onset diabetes in our adolescents

Once considered a disease of adults, T2D is becoming increasingly common among adolescents (376) with ~39,005 U.S. adolescents having T2D in 1999–2002, and now almost as common as T1D in some pediatric populations (147). Children in whom T2D develops are at earlier risks for complications as adults from the disease, including retinopathy, neuropathy, and cardiovascular and renal disease that may require decades of treatment (188). Primary prevention of T2D is essential in children and adolescents (327).

The estimated lifetime risk of developing diabetes for children born in 2000 is 32.8% for males and 38.5% for females, about 10–15% higher than current prevalence (366). This risk is higher for Hispanics, at 45.4% for males and 52.5% for females. In addition to developing complications, adolescents diagnosed as having diabetes have large reductions in life expectancy. For example, Narayan et al. (366) estimated that if diagnosed with T2D at age 20 yrs, males and females would die 17 and 18 years before normal, with a reduction of 27 and 30 quality-life adjusted years.

### 51.6 Metabolic syndrome in adolescents

A major problem with identifying the metabolic syndrome in children and adolescents is that there are no established criteria in this population (315). According to Cook et al., “In obese adolescents only, the prevalence rates were 44.2% using the definition of Cook/Ford (113), 26.2% using the adult criteria, 14.1% using the definition of Caprio, and 12.4% using the definition of Cruz” [As different modifications of adult criteria for the metabolic syndrome were applied, the specific criteria can be located in Table 1 of and Table 1 of (315)]. Children with BMI and waist circumference values greater than normal values are at increased risk for the adult metabolic syndrome (500). Morrison et al. (356) contend that evaluating 5- to 19-year-old children for metabolic syndrome and family history of diabetes

could identify children at increased risk of adult metabolic syndrome and T2D, allowing prospective primary prevention of these outcomes.

### 51.7 Atherosclerosis

Atherosclerosis is a consequence of lifetime accumulation of vascular lesions and plaques. Expectedly, Gillman indicates that the extent of coronary lesions in adolescents is associated with risk factors including lipids, smoking, blood pressure, obesity, and hyperglycemia (we add inactivity as a risk factor). Reversibility of childhood metabolic syndrome is rare, thus leading to high risk of adulthood cardiovascular disease” (197, 548).

### 51.8 Non-alcoholic fatty liver disease (NAFLD) in children

The prevalence of NAFLD among normal-weight children is 3–10%, rising up to 40–70% among obese children (32, 33).

### 51.9 Cognitive function

Children and adolescents who are physically inactive will develop less cognitive skills than more active cohorts, as discussed in Cognitive Function section.

### 51.10 Peak lifetime value determines years to reach clinical disease

Increases in bone mineral mass, skeletal muscle mass, and CRF occur throughout childhood and adolescence peaking and have their greatest lifetime values in the third decade of life. Thereafter with aging, their respective values progressively decline to lower values, at some age reaching a threshold past which an overt clinical condition has an increased probability of existing (osteoporosis, sarcopenia, and endurance frailty).

**Bone: less weight-bearing activity by children/adolescents results in earlier osteoporosis**—After the age of ~25 yrs, bone mineral density (BMD) is progressively lost. As some age, BMD passes a threshold of an overt clinical event (osteoporosis). For example, a 25-yr old individual with a BMD that is 90% of the mean peak BMD be osteoporotic ~30 yrs earlier than if they had a BMD 110% of the mean peak BMD (Fig. 13).

The positive effect of mechanical loading on bone growth is greatest pre- and early-puberty in girls (25) and pre-puberty in boys (146). Thus, less load-bearing activity by children during skeletal growth is associated with smaller bone mass than in load-bearing children (438, 463). For example, girls starting at ages 9–15 had substantially greater increases in bone mineral content at lumbar spine and femoral neck if they had the highest physical activity levels during the 7-year follow-up as compared with those having the lowest physical activity levels (424). Thus, Rizzoli et al. (438) assert that childhood and adolescence is a key determinant of bone health and future fracture risk during adulthood.

**Skeletal muscle: less weight-bearing activity by children/adolescents results in earlier sarcopenia**—In an earlier section (Inactivity accelerates loss of functional capacities with chronological aging leading to premature death), Skeletal muscle power peaks about the third decade of life, and then declines thereafter (Fig. 6). However,



physically inactive individuals reached skeletal muscle frailty 24 yrs younger in age than masters' weight lifters.

**CRF: less endurance-type play in children/adolescents increases risk of earlier death at old age**—Fig. 4 in the earlier section (Inactivity accelerates loss of functional capacities with chronological aging leading to premature death), showed that  $\text{VO}_2\text{max}$  peaks at the third decade of life, and thereafter declines. However, physically inactive individuals passed below the threshold of aerobic frailty 30 yrs earlier in age than masters' aerobically trained individuals.

### 51.11 Summary

Physical inactivity is a cause of chronic disease in children and adolescents. Documented health benefits by prevention of physical inactivity in children and adolescents (412, 494) include increased physical fitness (both CRF and muscular strength), reduced body fatness, favorable cardiovascular and metabolic disease risk profiles, enhanced bone health, and reduced symptoms of depression and anxiety.

## 52. Public policy

### 52.1 Underappreciated cost

The NPAGCR (412) indicates that physical activity diminishes mortality by 30% in the U.S. Stated alternatively, physical inactivity increases mortality by 30%, or by 720,000 annual deaths (one death every 44 seconds). Our estimations are that U.S. health care costs of inactivity will range from \$2.2–3.8 trillion in the first decade of the 21<sup>st</sup> century, or \$700 yearly (\$7000 for the next decade) from each U.S. resident. Our estimate of physical inactivity's cost is in line with a) the Society of Actuaries estimate that overweight and obesity cost the U.S. \$270 billion/year (cost includes increased need for medical care, and loss of economic productivity resulting from excess mortality and disability) (485) and b) the estimated nationwide cost of for physical inactivity and obesity of \$507 billion with projected costs exceeding \$708 billion in 2008 (98). We estimate that if every U.S. individual had 30 min of moderate physical activity/day obesity, annual U.S. health costs would be reduced ~4% (\$100 billion out of \$2.4 trillion), and additionally we speculate that if all U.S. individuals would approach the physical activity levels of U.S. Amish, obesity would be reduced ~8% (\$200 billion out of \$2.4 trillion). Further, physical activity reduces prevalence of many conditions that are not obesity co-morbidities, so we contend our estimates of physical inactivity are conservative and underestimates.

### 52.2 Role of exercise scientists in public policy

According to Kersh and Morone, “Public health crusades are typically built on a scientific base...In any event, medical knowledge in itself is rarely enough to stimulate a political response. Rather, the key to its impact lies in the policy entrepreneurs who spread the medical findings” (272). Scientists enable the enablers. Exercise and chronic diseases are complex polygenic conditions. The scientific and technical expertise to appreciate the complexity of exercise/inactivity and chronic diseases is limited within the scientific community. Thus, policy entrepreneurs must be careful in their selection of scientists to



enable their public policy. The information in this article was presented both to enable both scientists and policy entrepreneurs to reduce physical inactivity-caused diseases.

### 53. Conclusion

Physical activity, food, and reproduction are some of the minimal requirements for life. They evolved not as choices, but as requirements for individual and species survival. Modern humans have been able to engineer most physical activity out of daily life. Humans now have a choice not to be physically active. Conclusive and overwhelming scientific evidence, largely ignored and prioritized as low, exists for physical inactivity as a primary and actual cause of most chronic diseases. Thus, longer-term health was also engineered out with the successful removal of physical activity as a necessity for immediate survival. The comprehensive evidence herein clearly establishes that lack of physical activity affects almost every cell, organ, and system in the body causing sedentary dysfunction and accelerated death. The massive multifactorial nature of dysfunction caused by sedentarism means that just as food and reproduction remain as requirements for long-term continued human existence, physical activity is also a requirement to maximize health span and lifespan. The only valid scientific therapeutic approach to completely counter sedentary dysfunction is primary prevention with physical activity itself.

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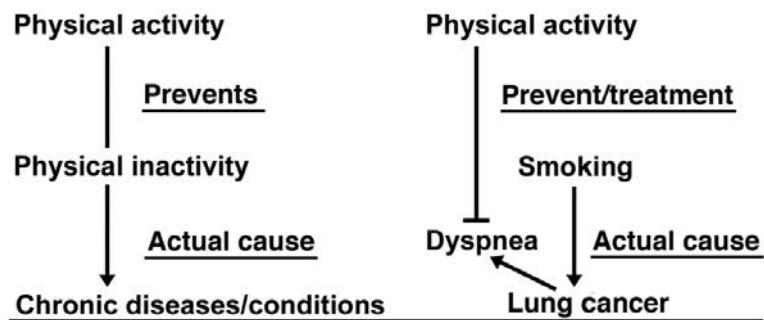


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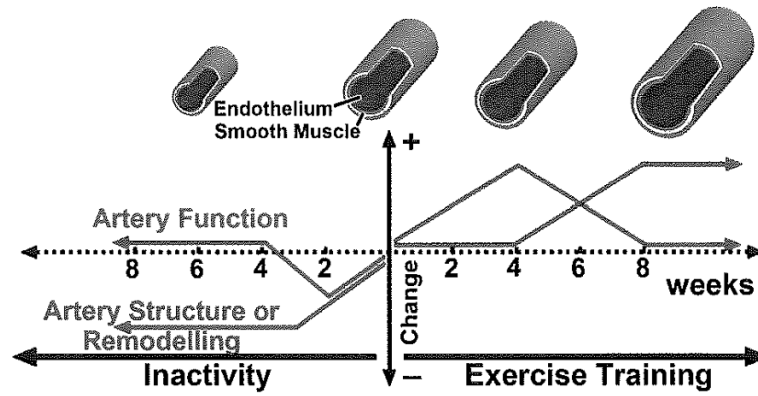
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**Figure 1.**

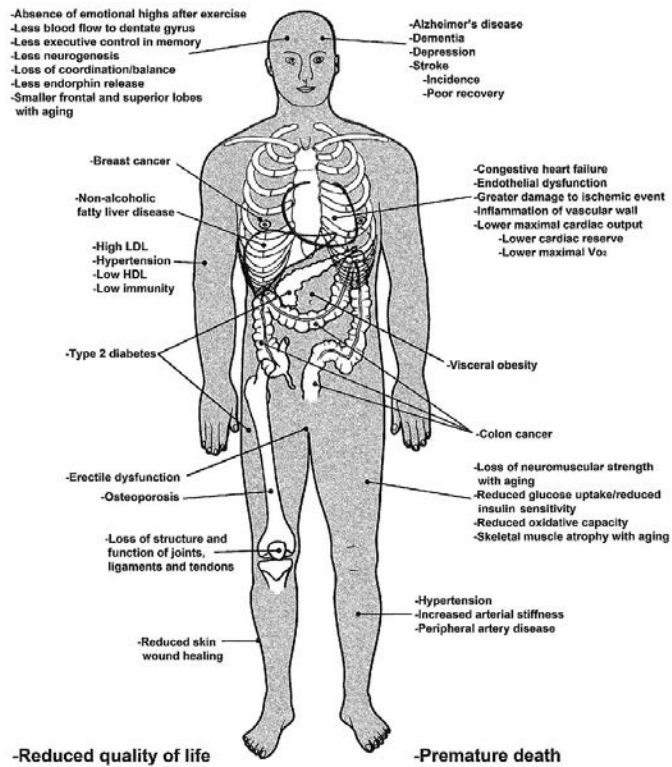
Physical activity produces primary and tertiary preventive health benefits for chronic diseases. *Left panel.* Physical inactivity is an actual initiating cause of a chronic disease/condition. Restoration of physical activity (primary prevention) removes the actual cause (physical inactivity) that produced the health deficiency. *Right panel.* Physical inactivity is not the cause of lung cancer. Smoking is an actual cause of lung cancer. Addition of aerobic exercise training compensates (tertiary prevention) for loss of lung function after surgical removal of a portion of lung by strengthening respiratory skeletal muscles for remaining lung (179). Exercise does not cure lung cancer.



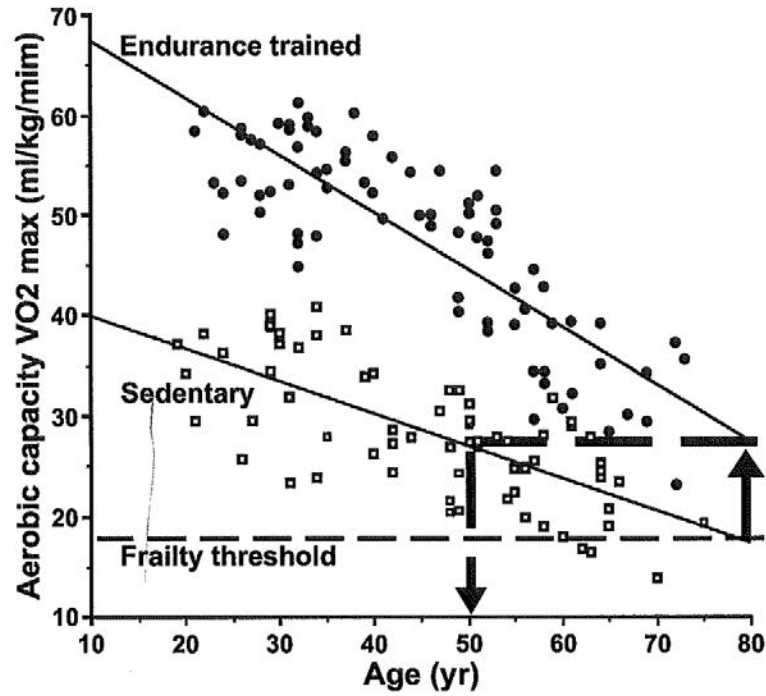
**Figure 2.**

Changes in artery function and structure (remodeling) show differential time courses in response to increasing or decreasing human physical activity as hypothesized by Thijssen et al. (506). Exercise training (right side) produces early, rapid increases of arterial function (blue line), which is followed weeks later by arterial remodeling (red line and larger diameter vessel) that returns arterial function to pre-exercise training levels. Physical inactivity (left side) is associated with immediate, rapid decreases in arterial diameter after spinal cord injury (decreased size in top far left blood vessels and red line). Function immediately decreases and then returns to pre-injury value. [Reproduced with permission from Figure 2 in ref. (506)].



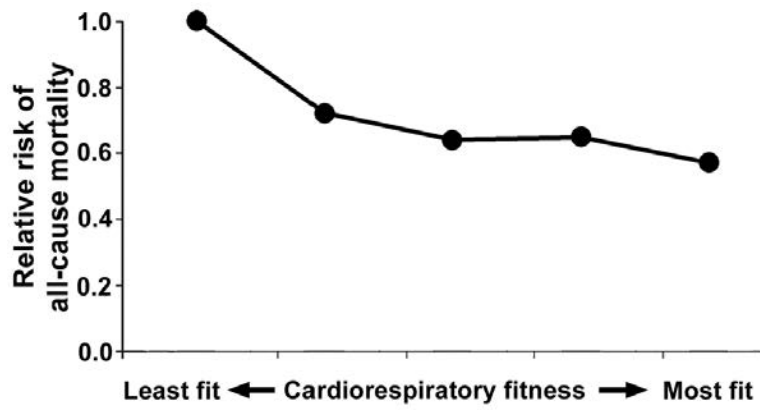


**Figure 3.** Health deficiencies accelerated by decreasing physical activity from higher to lower levels. Gheorghe Constantinescu generously made original drawing. [Reproduced with permission from (53)].



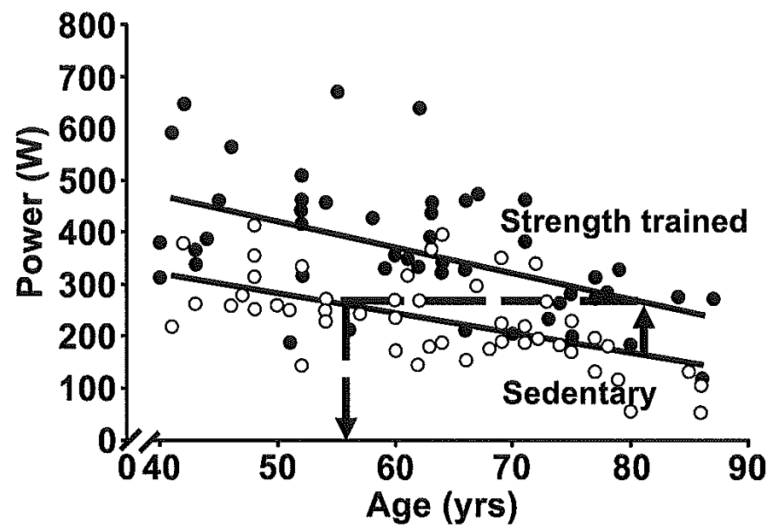
**Figure 4.**

Best-fit linear lines are shown for aerobic capacities of two cross-sectional groups (aerobic trained and sedentary) as a function of their increasing chronological age. At the chronological age of 80 yrs, a horizontal line is extended from the endurance trained line to the left where it intersects the sedentary line at age 50 yrs. Subjects were women who had been aerobically trained for at least 2 yrs with road-racing competition (closed circles) vs. women who were sedentary (open squares) who performed no regular exercise and had BMI's  $<35 \text{ kg/m}^2$  (aerobic-trained women were matched across the entire age range for age-adjusted world-best 10-km running times to ensure homogeneity relative competitiveness). [Reproduced with permission from (503)].



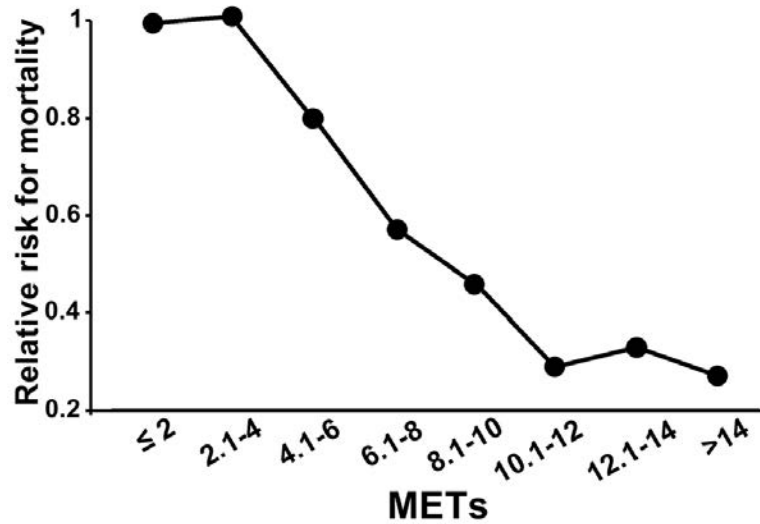
**Figure 5.**

Relative risk of death as a function of cardiorespiratory fitness (CRF) or change in CRF. Relative risks of all-cause mortality by (CRF) quintiles for 12,831 women aged 20–100 years without cardiovascular disease (CVD) or cancer in the Aerobics Center Longitudinal Study. Relative risks were adjusted for age, year of examination, body mass index, smoking status, abnormal electrocardiogram, hypertension, diabetes, hypercholesterolemia, and family history of CVD. [Reproduced with permission from (312)].



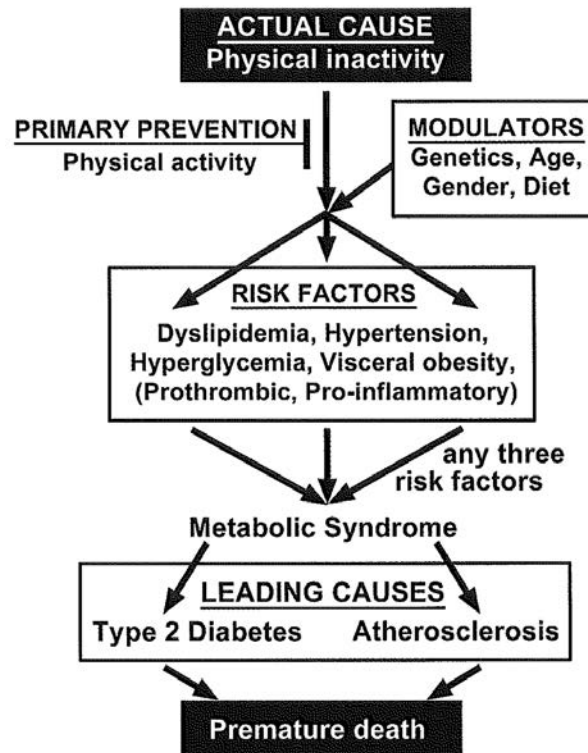
**Figure 6.**

Best-fit linear lines are shown for power of two cross-sectional groups (strength trained and sedentary) as a function of their increasing chronological age. At the chronological age of 80 yrs, a horizontal line is extended from the power-trained line to the left where it intersects the sedentary line at age 56 yrs. The cross-sectional strength-trained subjects are shown in closed circles and sedentary in open circles. [Reproduced with permission from (402)].



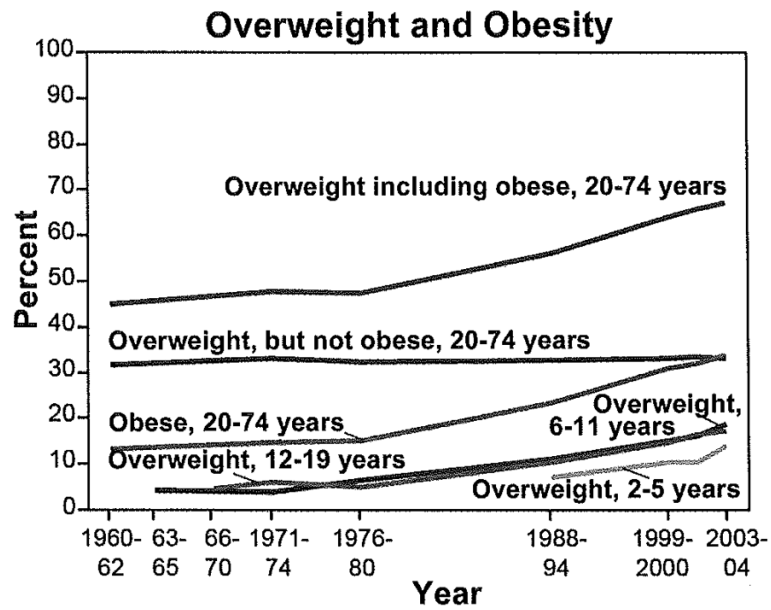
**Figure 7.**

Mortality risk at different exercise capacities. Significant reductions in mortality do not occur <4 metabolic equivalents of resting metabolism (METs), become less at ~4 to 6 METs and an asymptote occurring at ~10 METs in 15,000 U.S. veterans of wars. [Reproduced with permission from (278, 280)].

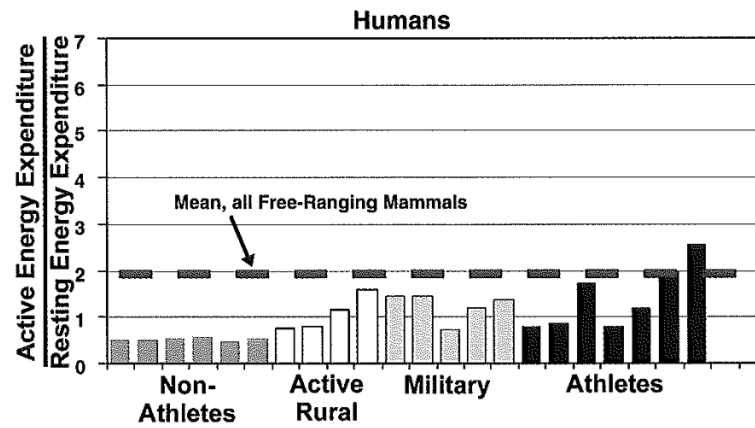


**Figure 8.** Physical inactivity is an actual cause of premature death by interacting with other environmental factors to increase risk factors for metabolic syndrome, which, in turn produces two “leading causes” of “premature death” (type 2 diabetes and atherosclerosis). Primary prevention of physical inactivity is shown by physical activity inhibiting physical inactivity.



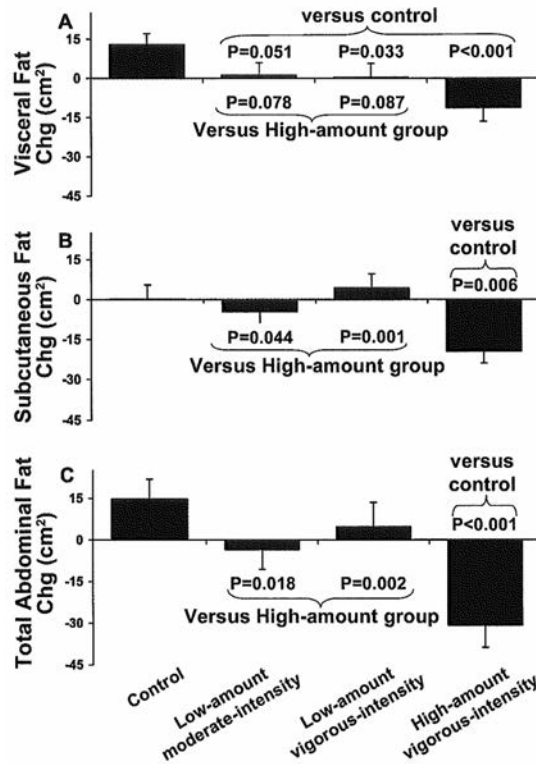


**Figure 9.** Overweight and obese, by age from 1960–2006. Modified from CDC website (87).



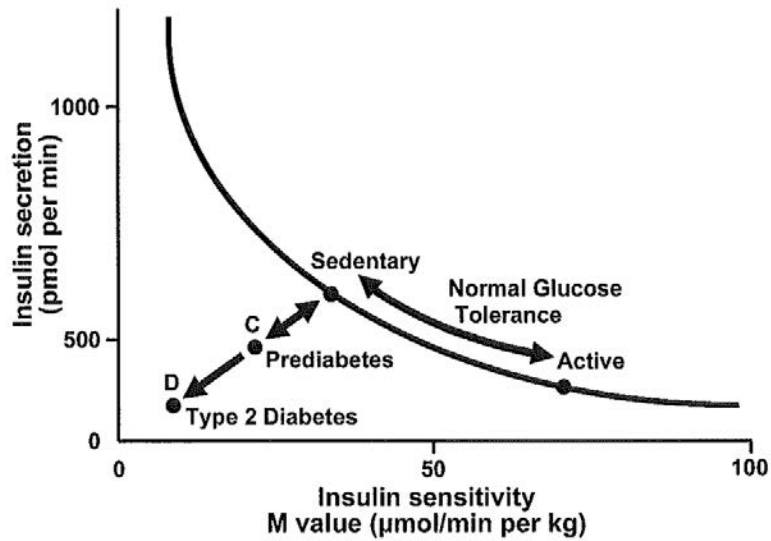
**Figure 10.**

Human caloric expenditure for physical activity in non-athletes is much lower than physically active populations. The y axis is the ratio of Activity Energy Expenditure (AEE) / Resting Energy Expenditure (REE). AEE = free-living energy expenditure – (diet-induced energy expenditure + REE). Data are presented for various human groups (non-athletes living in developed nations, military trainees, individuals from rural areas engaged in high levels of physical activity, and athletes in training) on the x axis. Each bar is a single subject. Non-athletes in developed nations have AEE/REE ratio of  $\approx 0.5$ , which is equivalent to PAL of  $\approx 1.67$ . [Reproduced with permission from (225)].



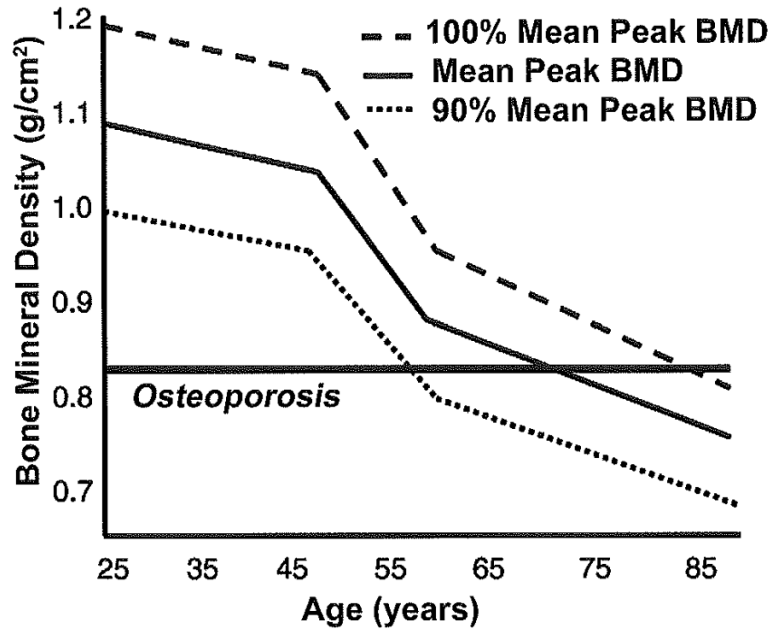
**Fig. 11.**

Gain by visceral and abdominal fat depots in non-exercising group while 6 months of exercise training produced loss in these fat depots. Data are presented as change in A) visceral abdominal fat, B) subcutaneous abdominal fat, and C) total abdominal fat on the y axis. Four exercise levels are given on the x axis; they are 1) Control (no exercise); 2) Low-amount, moderate-intensity exercise (caloric equivalent of walking ~12 miles/wk at 40–55% of peak oxygen consumption); 3) low-amount, vigorous-intensity exercise (same amount of exercise as group 2, but at 65–80% of peak oxygen consumption); and 4) high-amount, vigorous-intensity exercise (caloric equivalent of jogging ~20 miles/wk at 65–80% of oxygen consumption). [Reproduced with permission from (479)].

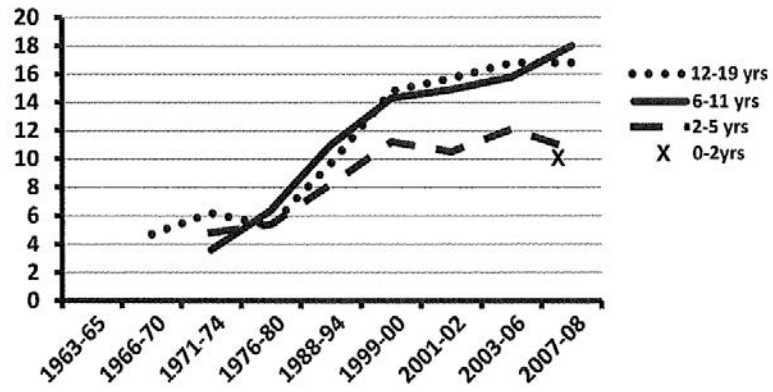


**Fig. 12.**

Insulin secretion is presented as a function of insulin sensitivity. Insulin secretion rises as insulin sensitivity falls when physically active individual (point A) becomes sedentary (point B). A failure of insulin secretion to compensate for fall in insulin sensitivity is noted when both insulin secretion and insulin sensitivity decline from point B to point C, indicating prediabetes. The upper axis for increased and decreased levels of physical activity implies bidirectionality of the two arrows for glucose intolerance and insulin resistance. The leftward enlarging two arrows illustrate increasing glucose intolerance and insulin resistance with 2–3 days of decreased physical activity. The clinical significant is that low levels of physical activity produce a permissive environment for prediabetes. In opposite direction, high levels of daily physical activity markedly diminish the permission state to develop prediabetes. The distinction between the two arrows is based upon variability in Masters athlete's responses to stopping training as shown in figure 2 of ref (443) in which 4 subjects had lesser increases in blood insulin (insulin resistance arrow) at 30 min into an oral glucose tolerance test as compared to 10 other subjects (glucose intolerance arrow). A continued decline in both insulin secretion and insulin sensitivity at point D is where overt type 2 diabetes is present. Reproduced with permission from Bergman's original figure (ref 36).



**Figure 13.** Peak value for bone mineral density (BMD) in third decade of life contributes to the age in later life at which threshold for osteoporosis is passed. The higher the peak value for BMD, the later age in life delays age at which BMD reaches the osteoporosis threshold, below which osteoporosis is diagnosed. The upper line reflects a population that had high bone-loading physical activities throughout lifespan with genes predisposing to high bone strength in contrast to the lower line reflecting low lifetime bone loading with genes predisposing to low bone strength. Adapted from Rizzoli et al. (438) who modified original figure of Hernandez et al. (235). [Reproduced with permission from (438)].



**Figure 14.**

Rise in childhood and adolescent obesity in U.S. From 1980's to 2007–2008 obesity in 2–5, 6–11, and 12–19-yr-old U.S. females increased 3–5-fold. [Tabular data is converted from graphic from (386, 387)]



**Table 1**

Estimated historical reductions in daily steps by humans.

<b>Population</b>	<b>Year</b>	<b>Steps per day</b>		<b>References</b>
Paleolithic	(~20,000 BC)	~13,200–21,120 (men)	~10,560 (women)	(385)
Amish	(2002)	18,425 (men)	14,196 (women)	(27)
Mean of 26 studies	(1966–2007)		7,473 (mainly women)	(63)
Colorado	(2002)	6,733 (men)	6,384 (women)	(573)
US adults	(2010)	5,340 (men)	4,912 (women)	(26)

**Table 2**

Tendency for dose-response between higher physical activity level and lower mortality in Swedish monozygotic twins [modified from (77)].

Sex	Physical activity level	All-cause mortality		Cardiovascular mortality	
		Hazard ratio	95% confidence intervals	Hazard ratio	95% confidence intervals
Men	Low	1		1	
	Moderate	0.84	0.72, 0.98	0.86	0.68, 1.08
	High	0.64	0.50, 0.83	0.55	0.36, 0.85
Women	Low	1		1	
	Moderate	0.82	0.70, 0.96	0.85	0.64, 1.13
	High	0.75	0.50, 1.14	0.34	0.1, 0.95

Questionnaire used with 7 items: low physical activity (“almost never” and “hardly ever”) level; moderate (“very little”, “not much”, and “quite much”); and high (“a lot” and “very much”)

**Table 3**

Studies with Twin Discordant for Physical Activity Levels.

Outcomes	Physical Inactivity Effect	MZ (n)	Other (n)	Sex	PA Measurement	Comments	Ref
MRI Visceral Fat	↑ 50% in inactive Twin	16		B	Questionnaire	Age 50–74 years and Followed for over 32 years. Subset for Finnish twin study.	(316)
MRI Liver Fat Score	↑ 170% in inactive Twin						
MRI Intramuscular Fat	↑ 54% in Inactive Twin						
BW changes from 1975 to 2005	↑ 5.4 kg for the inactive twin		42 twins MZ to DZ proportions unclear	B	Phone Interview	Unclear about proportion of MZ vs. DZ, but states no differences between MZ and DZ. Subset of Finnish twin study. Twins not discordant for PA had no difference in BW.	(545)
WC changes from 1975 to 2005	↑ 8.4 cm in inactive twin						
BMI	↑ 0.33 BMI in non-vigorously active twin	614		M	Self Reported Vigorous Activity	All males (mean age 41.1) that fought in Vietnam war. When looking at all twins modeling predicted no genetic effect on the relationship between vigorous activity and BMI.	(335)
Weight Gain	↑ 5.4 kg inactive twin	42		B	Questionnaire showing Discordant PA in 1975, 1981, and 2005	Finnish twin study	(545)
Waist Circumference	↑ 8.4 cm in inactive twin						
Total Body fat in women with similar weight	↑ 1.0 kg& 1.4 kg fat for 1-hr or 2-hr less activity/wk	156		W	Questionnaire Home, sport, sweating activities	Discordant for physical activity. Age of 55.5 yr/old  Also showed increased physical activity increased muscle mass and strength (not analyzed in discordant twins)	(455)
Total and regional Body fat in women with discordant weight	↑ 3.96 kg lower BF & 0.53kg central						
BMI	↑ 2.12 in inactive twin (p<0.001)	35			Healthy Runners Survey – high PA = 40km/wk > than low PA (male), 32km/wk (female)	Subjects recruited from the National Healthy Runners Survey. No active twins with overweight twin were themselves overweight.	(563)
HDL	↓ 0.14 in inactive (p=0.004)						
HDL2	↑ 2.71 in inactive (p=0.001)						
Apo A-1	↑ 0.10 in inactive (p=0.004)						
Lipid profile before and after 40% fat or 20% fat diet (cross over study): LDL and sybfractions, apolipoprotein A-1	N.S.	28		M	Survey. One twin running >50km/wk than other twin	Subjects recruited from the National Healthy Runners study. A diet low in fat independent of high amounts of exercise modifies circulating lipids.	(564)

Outcomes	Physical Inactivity Effect	MZ (n)	Other (n)	Sex	PA Measurement	Comments	Ref
Adiposity	↑ Sig lower in inactive twin	21		F	9 months of 3xwk high intensity weight bearing activity	Girls were prepubertal aged 8.7. Did not tell the control group that they could no longer participate in sports.	(534)
BMD	N.S.	12			Lifetime leisure high-impact sports	Subgroup from the original group.	
aBMC	↓ Sig in inactive twin						
Femoral neck and lumbar BMD	E = 1% & G = 73% of lumbar variance	105		M	Questionnaire for endurance and balls sports	Finnish men (35–69yr/old) Calcium supplements also explained 1% of difference in BMD.	(541)
Spinal MRI	N.S. disk degeneration	22		M	Questionnaire between 1975 and 1981 showing discordant endurance PA (3.9 v 1.1 time/wk)	Finnish Twin Cohort aged 35–69	(542)
	↓T6-T12 disk degeneration in low strength PA twin	12			Questionnaire between 1975 and 1981 showing discordant strength PA (2300 v 200 hrs)		
Psychomotor reaction times	↓ Sig slower choice reaction for hand & contra foot in inactive	38			Lifetime exercise histories	Finnish twin cohort. Average age of discordant PA twins is 50. PA data collected in 1972, 81, 92	(475)
Psychological functioning (mood, optimism, control)	↓ Sig in inactive twin	63		B	Questionnaire for discordant vigorous activity	From US National Survey of Midlife Development	(258)
Survey based Anxiety and Depression symptoms	N.S.	?	?	B	Leisure time PA only	Article is unclear how many MZ twins were discordant for PA in their models. Only current levels of PA and not PA history used. Used Dutch population, but excluded cycling to work as PA (non-leisure)	(126)
Dementia	↑ P = 0.07 for inactive PA twin	90		B	Twin registry reported 31 years before follow-up	Swedish twin registry. Data on all twins showed significant correlation of increased PA and decreased dementia	(12)
Life satisfaction	N.S.	161	172	2842	Survey	Data in MZ and related family members showed an OR>1.0 for active pair of an unrelated paired of people.	(498)
Life Happiness	N.S.						
Lactate threshold	E is 25–30% & G is 50–60%	9		M	6 months of anaerobic threshold training	Aged 11–14. Change in VO2max was more due to the	(119)
VO2max	E is 35% & G is 45%						

Outcomes	Physical Inactivity Effect	MZ (n)	Other (n)	Sex	PA Measurement	Comments	Ref
Total Body Fat	E is 20% & G is 70%					less weight gain in trained twin. Used analysis of variance to estimate the genetic and training effects.	
Myocardial infusion at rest, during adenosine, and cold-pressor test	N.S.	9		M	Separated by VO2max and physical activity levels	Young males with a 18% difference in VO2max (ml/kg/min) of (43.7 vs 50.7)	(221)
Endothelial function via ultrasound of brachial and LAD coronary artery	N.S.						
Oxygen extraction fraction	↑ in low fit (p=0.06)						
Hepatic FFA uptake at rest	↑Sig in less fit group					Same subjects as above.	(222)
Myocardial FFA uptake at rest and during exercise	N.S.						
Skeletal muscle perfusion and free fatty acid uptake	N.S.					Same subjects as previous study.	(223)
Cornell voltage (electrical measurement of LV hypertrophy)	↓Sig in inactive						(36)
Right-side hypertrophy index							
LV mass index							
Type 2 Diabetes	18 inactive v 2 active twins acquired T2DM	5	15 DZ	B	Leisure time PA	Twins discordant for PA and discordant for Type 2 diabetes. For MZs it was the inactive twin that developed type 2 diabetes.	(288)
Mortality from 1975–1981	↑Sig in inactive DZ twins, but not inactive MZ twins	157	517	B	Questionnaires for vigorous PA and estimates of >2MET wk/day/wk	Finnish twin cohort aged 24–60. Low level of leisure physical activity in early life was associated with increased risks of death in dizygotic twin pairs, but monozygotic co-twins.	(289, 546)

B = both sexes; DZ = dizygotic; E = exercise component; G = genomic component; M = men; MZ = monozygotic; N.S. = non-significant; PA = physically active; W = women; ↑ = increase; ↓ = decrease

**Table 4**

## Studies with Twin Response to Exercise

PA Intervention	Outcomes	H-effect	MZ (n)	DZ (n)	Sex	Comments	Ref
Submaximal supine bicycle at HR of 110bpm	End-diastolic mean wall thickness (rest)	H = 53%	21	12	M	Similar results when adjusted for body fat. Non-genetic component is made up of both shared and non-shared environmental components.	(40)
	LV diameter (rest)	N.S					
	Fractional shortening (rest)	H = 13% (N.S)					
	Change in End-diastolic mean wall thickness w/ exercise	H = 0% (N.S.)					
	Change LV diameter w/ exercise	H = 24%					
	Change in Fractional shortening w/exercise	H = 47%					
	Cycling Power output	H = 53%					
	Cycling VO2max	H = 46%					
20-wk endurance training	LV wall, posterior wall, septal wall, LV mass,	Minimal H effect	20	20 (not related)	M	Training effect in all subjects.	(303)
Supine bicycle at 60W (submaximal)	SBP (rest)	Sig H	32	21	M	Less effect on heritability during exercise than at rest (conclusions based only on abstract; unable to obtain full article)	(41)
	DBP (rest)						
	Change in SBP w/exercise						
	Change in DBP w/exercise						
Graded Cycle test to "exhaustion"	Peak VO2	H = 77%, 66% when PA and skinfolds adjusted	29	19	M	Testing was done on a max test and also collected with HR was at 150bpm.	(176)
	O2 uptake at HR of 150bpm	H = 61%, 16% when PA and skinfolds adjusted					
	Mechanical Efficiency	N.S. H Correlation					
	Anaerobic energy generation	H = 78%, 58% when PA and skinfolds adjusted					
	Respiratory exchange ratio	H = 6% only					
30 minutes of treadmill at anaerobic threshold	GH and PRL response to exercise and cortisol at rest	Sig H Correlation	9		M	Athletes	(135)
	ACTH and cortisol response to exercise and beta-endorphin at rest	N.S. H Correlation					
93 days of negative energy balance (diet and exercise)	euglycemic-hyperinsuliemic clamp before and after intervention	N.S. H Correlation	7		M		(390)
	Fasting and postprandial insulin						
	dehydroepiandrosterone sulfate & androsterone glucuronide	Sig. H effect	7		M	Healthy Young Males.	(419)
	Cortisol levels						
Wingate test, max progressive test	Max 5 s Wingate power	H = 74%	8	8		Not correlated were measures in the ergojump test. Had	(75)
	Max Lactate Wingate	H = 82%					



PA Intervention	Outcomes	H-effect	MZ (n)	DZ (n)	Sex	Comments	Ref
	Delta Lactate during maximal test	H = 84%				different heritability's with different tests measuring same performance measure. Homogenous subject group.	
10-wk isokinetic strength training (5d/wk)	HK, MDH, B-HAD	N.S. H	5	5 (unrelated)	M		(505)
	oxoglutarate dehydrogenase activity (OGDH)	Sig H					
Maximal and submaximal treadmill running	running economy	N.S. H Correlation	8	8		No significant differences in references to MZ v DZ twins.	(440)
	VO2 max	N.S. H Correlation					
	Maximal lactate	H = 75%					
15 weeks of endurance training	Skeletal Muscle HKII, (31%), PFK (37%), LDH (21%), MDH (31%), & B-HAD (60%)	Sig H	12		M		(217)
	fiber-type, CK activity,	N.S. H					
15 weeks of high intensity supramaximal exercise (4-5 times/wk)	ALC, CK, HK, LDH, MDH, OGDH activity & PFK:OGDH activity ratio	Sig H	28			Exercise bouts of 15-90s all out.	(474)
	fiber type & anaerobic capacity						
A single 90 minute bout of exercise	Rest v Ex Adipose LPL activity following exercise	Sig difference btw MZ and DZ	11	10	M	Aged 18-27	(458)
Cycle exercise	Rest v Ex metabolic rate(VO2)	H = 46% at low power. N.S. H at > 6xRMR	37	21 + 31 parent child	B		(60)
Cycle exercise to max	Absolute and BW adjust VO2max	Sig H	12	12	M	18-31 years old	(177)
	Rest v Ex LV internal diameter	N.S. H					
	Rest v Ex Fractional Shortening	N.S. H					
	LV Mass	N.S. H when adjusted for BW					
165 min submax treadmill test before & after 22 days of 1000 kcal/day overfeeding	Pre v Post change in VO2max	Sig H	12		M		(524)
93 days of supervised 60min/d exercise	Loss in B.W., fat mass, skinfold, visceral fat	Sig H	7		M	Healthy young males	(59)
	Change in fasting TAGs and Cholesterol						
	Change in VO2max, RER during exercise						
1000 kcal of vigorous exercise per day for 22 days	Pre v Post fasting insulin	Sig H	12		M	Healthy young males.	(522)
	Pre v Post delta insulin during OGTT	N.S. H					
93 days of supervised 60min/d exercise	Pre v post fasting insulin and glucose disposal	N.S. H, but Sig improvement	7				(390)
116min/day of cycle ergometer for 22days at 58% max	Pre v Post fat mass	N.S. H	12		M	Healthy males aged 19.1 yr old.	(414)
	basal lipogenesis	Sig H					

PA Intervention	Outcomes	H-effect	MZ (n)	DZ (n)	Sex	Comments	Ref
	Pre v Post insulin stimulated lipogenesis	N.S. H					
	Pre v Post epinephrine and basal lipolysis	N.S. H					
	Pre v Post LPL activity	N.S. H					
	Fat Free Mass	Sig H					
20-wk cycle ergometer endurance training	Pre vs. Post epinephrine lipolysis	Sig H.	8		B	4 male and 4 female.	(133)
	Basal lipolysis	N.S. H					
Single 90 min bout of exercise	LPL activity	More Sig in MZ than DZ	11	10	M		(458)
116 min/day of cycle ergometer for 22days at 58% max	Total Cholesterol	Sig H	12		M		(134)
	LDL Cholesterol						
	HDL Cholesterol						
93 days of supervised 60min/d exercise	Total cholesterol	Sig H	7		M	Male, young and healthy. ~93000 total calorie deficit. Significant within twin effects.	(298)
	LDL Cholesterol						
	Cholesterol to HDL ratio						
116min/day of cycle ergometer for 22days at 58% max	Baseline RMR	Sig H	12		M		(415)
	Baseline thermic effect of food						
	Pre v Post plasma T3, T4, and FT4	Sig H (except for T3)					
93 days of supervised 60min/d exercise	Pre v post RMR, Thermic effect of food,	Sig H	7		M	Healthy young males	(523)
	Thyroid hormones						
14 weeks of exercise training	Cardiac Size	N.S. H	28	10 + 12 siblings	B	No genetic effect on heart size pre or post exercise training.	(3)

B = both; DZ= dizygotic; H = heredity effect; M = male; monozygotic; N.S. = non-significant; n = number of subjects

**Table 5**

Studies with Twin Correlations that are corrected for PA levels or Unique Environmental Effects (twins may not be discordant for PA).

Outcomes	H-effect	PA Effect	MZ (n)	DZ(n)	Sex	PA Measurement	Comments	Ref
Weight gain	↓ correlation in inactive		1571	3029	B	Questionnaire of Physical activity levels at baseline	Finnish twin study. At all activity levels MZ twins had greater heritability than DZ twins.	(231)
Waist Circumference		↑ 2.5 cm in low PA twin					No analysis for discordant PA. If twins had large genetic susceptibility then low PA resulted in larger increase in WC	(266)
BMI		N.S.	287	189		Questionnaire in 1998 and 2002. Only looking at leisure and occupational PA		
Waist Circumference	76(M)–77(F)%	21(M)–22(F)%					African Americans aged 22–88 from Carolina African American Twin Study of Aging. All effects are unique environmental not just PA levels.	(374)
Waist-Hip Ratio	59(M)–56(F)%	36(M)–38(F)%						
BMI	89(M)–73(F)%	11(M)–27(F)%	71	75	B	Questionnaire		
Discordant for BMI by at least 3.		N.S.	23		B	Interviews and Questionnaire for PA	No significant effects of PA on the discordance of overweight prevalence.	(214)
Discordant for obesity		↓ fitness (8%) and activity (15%) in Obese twin	14		M	VO <sub>2</sub> max and Baecke leisure time PA	From FinnTwin study – obese also had lower adipose mitochondrial gene expression	(362)
Subscapulartrice ps BF ratio	24%						PA was inversely related to adjusted waist circumference	(468)
waist circumference	46%		265		M	“crude” measure of PA		
Diastolic BP	35%	5%					Aerobic exercise in adolescence lifetime high intensity aerobic associated with low diastolic BP throughout life (mean age of 50 at study time).	(236)
Aerobic exercise amount	44%	N.S.	71	104	B	Interview: Lifetime exercise divided into power, aerobic, or other		

Outcomes	H-effect	PA Effect	MZ (n)	DZ(n)	Sex	PA Measurement	Comments	Ref
“Augmentation index”, or systemic arterial stiffness		↑ Sig in high genetic risk group when inactive	53	262 + 54 singletons	F	Questionnaires		(209)
MZ subjects that are discordant for hypertension		Hypertensive twin ↑being inactive (after military service)	281		M	Survey from the National Heart, Lung, and Blood Institute (NIH)	Twins whom are veterans of WWII aged 55–66. Surveyed at time of entry to military and time of study.	(78)
HDL cholesterol	Correcting for genetics prevent correlation	↑correlation btw exercise and HDL	179	255	F	Questionnaire (one question about PA)	Kaiser Twin Registry in Oakland, CA, aged 18–85.	(105)
Lumbar spine disk degeneration	74%	N.S.	172	154	B	Interviewed about weight bearing exercise	No effect of adjustment for exercise on lumbar or cervical disk degeneration	(456)
Lumbar spine disk degeneration	73%	N.S.						
total body BMC (DEXA)		1.2% less in inactive twin/hour of less exercise	30	26		Questionnaire for weight bearing exercise	Associated was not present in pre-pubescent twins	(254)
leg BMC		↓ 1.4% in inactive						
Spine BMC		↓ Sig in inactive						
BMD		N.S.	122	93	F	12 month recall questionnaire for sport activity	10–26 yr old from Australian twin registry.	(577)
Smoking Likelihood at follow up (about 4 yrs)		↑ 3.36x for inactive twin to be regular smokers	97	339	B	Survey for twins discordant for PA (3 categories used) at baseline	Adolescents from a Finnish Twin Registry. Did not analyze by zygosity.	(290)
Discordant Prevalence of non-Alzheimer dementias		↑Risk Correlated with Physical inactivity	106			Questionnaire administered 30 years before	Swedish twin registry average age of first questionnaire was 48	(195)
Twins discordant for chronic fatigue syndrome – cognitive functioning tests pre-post max test	Cognitive tests did were N.S.	No relationship to chronic PA was made	21		B (19 M, 2F)	Acute Cycle ergometer to max	Exercise caused no change in cognitive functioning acutely.	(103)
Various Cognitive Functions	>15%	<80%	1,432	1,715 + 268,496 siblings	M	Cycle W max/kg	PA effect for all non-shared environmental effects.	(1)

B = both;

DZ= dizygotic;

F = female;

H = heredity effect;

M = male; monozygotic;

N.S. = non-significant;

n = number of subjects.

↑ = increase;

↓ = decrease

**Table 6**

Genetic Influence on Physical Activity, Exercise Levels, and Exercise Capacity. B = both; DZ= dizygotic; F = female; H = heredity effect; M = male; monozygotic; N.D. = not determined; n = number of subjects; Y = young

PA Measurement	H-effect	Unique Environmental Effect (unless noted)	MZ (n)	DZ (n)	Sex	Comments	Ref
Isometric knee extensor strength	56%	42%	206	228	F	PA effect is non-shared environmental effects. All older women subjects (63–76 yr/old). New non-shared environmental effects responsible for differences at follow up.	(515)
leg extensor power	67%	33%					
isometric knee extensor strength (at 3 years follow up)	58%	15%	149	164			
leg extensor power (at 3 years follow up)	48%	11%					
Elbow flexor muscle cross sectional area	43%	6%	25	16	M	Subjects were young (22.4 yr old) Caucasians from Belgium. Remaining variation accounted for by MCSA and environmental effects.	(125)
Elbow flexor eccentric strength	47%	20%					
Elbow flexor isometric strength	32%	1%					
Leg extensor power	32%	4%	101	116	F	Finnish Twin Study on Aging. Subjects 63–73 yr old.	(514)
Leg extensor strength	48%	52%					
Isokinetic lifting	60%	35%	122	131	M	Finnish twin study.	(446)
Psychophysical lifting	33%	49%					
Isometric trunk extensor endurance	5%	61%					
Questionnaires based on country. >60min of 4 MET activity = exerciser	26.5–70.5%	29.2–51.9%	13676	23375	B	Twins from 7 different countries. Australia had lowest genetic – highest unique environmental. UK females had highest genetic.	(497)
SportsMET (>4MET activity in last 3 months)	79% in Y, 41% Mid	21% in Y 57% Mid	69Y, 93M	88Y, 105M	B	Young and middle age subjects	(122)
Questionnaire Physical activity amount = 60–150 minutes a week	MZ = 45% DZ = 30%	MZ = 55%	1003	386	B	Twins from the Washington State twin registry. The more PA you undergo the less the genetic influence there is.	(148)
Questionnaire Physical activity amount > 150 minutes a week (current guidelines)	MZH=31% DZ= 25%	MZ = 69%					
Baecke and exercise Questionnaire	40–65%	60–35%	359	232	M	Nationwide Swedish twins. No shared environmental effect.	(166)
Sport participation between ages of 13–16	0%	16–22%	1095	1533	B	Dutch population. Does not include common environmental	(496)
Sport participation between ages of 17–18	36%	17%					

PA Measurement	H-effect	Unique Environmental Effect (unless noted)	MZ (n)	DZ (n)	Sex	Comments	Ref
Sport participation after age of 18	85%	15%					
Adulthood exercise	43%	26% from competitive sports	121		M	Finnish twin study. Also found that sports from ages 12–18 was a predictor of adulthood exercise.	(476)
Respiration chamber (doubly labeled H <sub>2</sub> O) activity-induced energy expenditure	8%	30%	12	8	B	Aged 17–39 yr old. Univariate analysis using the additive genetic, but excluding the common environmental component.	(259)
Respiration chamber physical activity by accelerometer	0%	59%					
Doubly labeled H <sub>2</sub> O Free living activity induced energy expenditure	72%	29%					
Free living PA by accelerometer	78%	22%					
RMR	3%	38%	62	38	B	Aged 4–10. Correlations are corrected for body weight and do not include common environmental	(189)
Total EE by Doubly labeled H <sub>2</sub> O	19%	23%					
Physical Activity energy expenditure	0%	31%					
VO <sub>2</sub> max, V <sub>max</sub> , HR <sub>max</sub>	40, 50, 60%	N.D.	106	66	B	Also 42 brothers included in the study	(57)
Fiber Type	N.S.	N.D.	35	26	B	32 brothers also included MZ twins had inter-pair correlation, but DZ and brothers suggested strong (but not quantified) environmental component.	(58)
Skeletal muscle mitochondrial activities	N.S.						
Oxidative to glycolytic ratio	25–50%						

Abbreviations: B, both; DZ, dizygotic; F, female; H, heredity effect; M, male; monozygotic; N.D., not determined; n, number of subjects; Y, young



**Table 7**

Calories expended by physical activity: Hunter-gatherer vs. Moderns

Species	Sex	Weight (kg)	RMR (kcal)	TEE (kcal)	Ratio (TEE/RMR)	EE PA (kcal)	Day range (km)
Fossil hominids							
<i>Homo habitus</i>		48.0	1404	2387	1.70	983	
<i>Homo erectus</i>		53.0	1517	2731	1.80	1214	
<i>Homo sapiens</i>		57.0	1605	2880	1.80	1284	
Modern hunter-gatherers							
Kung	M	46.0	1275	2178	1.71	903	10
	F	41.0	1170	1770	1.51	600	8
Ache	M	59.6	1549	3327	2.15	1778	16
Acculturated modern humans							
<i>Homo sapiens</i> (sedentary)	M	70.0	1694	2000	1.18	306	2.4
office worker	F	55.0	1448	1679	1.16	231	2.4
<i>Homo sapiens</i> (runner)		70.0	1694	2888	1.70	1194	11

RMR = resting metabolic rate; TEE = total energy expenditure; EE PA = energy expenditure attributed to physical activity; Runner was running 12.1 km/h. Table modified from (115, 385).

**Table 8**

Estimation of caloric cost of mechanization of daily living

Active activity	Calories used	Sedentary activity	Calories used
Hand clothes washing	45	Machine clothes washing	27
Hand dish washing	80	Machine dish washing	54
Walk to work	83	Drive to work	25
Stair climbing	11	Elevator	3
Total for active	219	Total for sedentary	109

Modified from (304)

**Table 9**

Estimation of caloric cost of removing walking/standing from daily living

Active activity	Calories used	Sedentary activity	Calories used
Walk up one flight of stairs	4	Take escalator up one flight	0.1
Park and walk into fast food restaurant	23	Sit in car for 10 min in a drive-through lane at restaurant	5
Walk dog for 30 min	125	Let the dog out the back door	2
Stand for 30 min of phone calls	20	Recline for 30 min of phone calls	4
Walk into gas station to pay	5	Pay at pump	0.6
Walk 1 min to colleague & stand to talk to them for 4 min	6	Send e-mail to colleague	2
Walk length of two football fields parking away from store	10	Drive around until a parking space opens near store's entrance	3
Total for active	193	Total for sedentary	16.7

**Table 10**

Prospective studies implicating physical inactivity as a risk factor in the development of T2D

Comments	Sample size	Country of study	Reference
↓ Age-adjusted risk of 6% every 500 kcal of leisure time physical activity	5990 men	US	(234)
↓ Relative risk of 60% between moderately active men and inactive men	7735 men	UK	(248)
↓ Relative risk of 26% between upper and lower quintile of physical activity	70102 women	US	(406)
↓ Adjusted relative risk of 59% between upper and lower quintile of physical activity	2924 men	Japan	(365)
↓ Adjusted relative risk of 15 and 57% between moderate and high compared to low physical activity	2017 men 2352 women	Finland	(249)
↓ Adjusted relative risk of 13, 30 and 76% between low, moderate and high compared to no physical activity	4069 men 4034 women	Germany	(338)

Modified from Table 1 in Ref (539)

**Table 11**

Estimations of the incubation durations to overt clinical conditions for diseases/conditions caused by physical inactivity and of the percentage reductions in diseases primarily prevented by physical activity (where sufficient information exists in healthy humans aged 20–65 yrs of age).

<b>Disease/condition</b>	<b>Inactivity causes (Longer-term most days of the week implies years or decades while short-term is weeks to months)</b>	<b>Exercise primarily prevents\delays * Just meet guidelines for moderate activity (30 min/day), not intent-treat. ** Our speculated asymptote for maximum in dose-response ~ Indicates our speculated percentage</b>
Premature death	Long-term increase	Yes, 30% reduction
VO <sub>2max</sub> (CRF)	30-yr acceleration in loss	Yes, **Aerobic activity delays 30 yrs
Sarcopenia	24-yr acceleration to reach	Yes, **Resistance activity delays 24 yrs
Metabolic syndrome	Long-term increase	Yes, *20–30%; **80%
Obesity	Long-term increase	Yes, *20–30%; **~80%
Insulin resistance	Increase in 2–3 days	Yes, * ~80%; **~95%
Prediabetes	Intermediate-term increase	Yes, * ~80%; **~95%
Type 2 diabetes mellitus	Long-term increase	Yes, * ~80%; **~95% (<60 yrs old)
Non-alcoholic fatty liver disease	Long-term increase	Yes, * ~80%; **~95%
Coronary heart disease	Long-term increase	Yes, *20%; **50%
Peripheral artery disease	Long-term increase	Yes, *20%; **50%
Hypertension	Long-term increase	Yes, 2.3-mm Hg lower diastolic blood pressure in hypertension translates into an estimated 12% and 24% increased risks for CHD and stroke, respectively
Stroke	Long-term increase	Yes, *25%; **35%
Congestive heart failure	Long-term increase	Yes, ~Should be major percentage
Endothelial dysfunction	Increase in hours	Yes, Asymptote should approach 90%
Atherogenic dysfunction	Long-term increase	Yes, ~Should be major percentage
Hemostasis	Shorter-term increase	Yes, ~Should be minor percentage
Deep vein thrombosis	Increase in hours	Yes, close to 100%
Dementia	Long-term increase	Yes, *35%
Depression and anxiety	Shorter-term increase	Yes, *20–30% (depression); *30% (anxiety)
Osteoporosis	Long-term maintenance	Yes, ~Should be major percentage
Balance	Shorter-term loss	Yes, ~Should be major percentage
Bone fracture/falls	Long-term increase in old	Yes, *35–60% (hip fractures) *30% (falls)
Colon cancer	Long-term increase	Yes, *40%
Breast cancer	Long-term increase	Yes, *25%
Endometrial cancer	Long-term increase	Yes, *30%
Gestational diabetes	Increase in weeks	Yes, ~ occurrence strengthens with predisposing genes
Preeclampsia	Increase in weeks	Yes, insufficient information
Erectile dysfunction	Long-term increase	Yes, Asymptote should approach 90%
Diverticulitis	Long-term increase	Yes. Insufficient information
Constipation	Increase in days	Yes, Asymptote should approach 100%

Disease/condition	Inactivity causes (Longer-term most days of the week implies years or decades while short-term is weeks to months)	Exercise primarily prevents\delays * Just meet guidelines for moderate activity (30 min/day), not intent-treat. ** Our speculated asymptote for maximum in dose-response ~ Indicates our speculated percentage
Gallbladder diseases	Long-term increase	Yes, insufficient information