

Role of Low Energy Expenditure and Sitting in Obesity, Metabolic Syndrome, Type 2 Diabetes, and Cardiovascular Disease

Marc T. Hamilton,^{1,2} Deborah G. Hamilton,¹ and Theodore W. Zderic¹

It is not uncommon for people to spend one-half of their waking day sitting, with relatively idle muscles. The other half of the day includes the often large volume of nonexercise physical activity. Given the increasing pace of technological change in domestic, community, and workplace environments, modern humans may still not have reached the historical pinnacle of physical inactivity, even in cohorts where people already do not perform exercise. Our purpose here is to examine the role of sedentary behaviors, especially sitting, on mortality, cardiovascular disease, type 2 diabetes, metabolic syndrome risk factors, and obesity. Recent observational epidemiological studies strongly suggest that daily sitting time or low nonexercise activity levels may have a significant direct relationship with each of these medical concerns. There is now a need for studies to differentiate between the potentially unique molecular, physiologic, and clinical effects of too much sitting (inactivity physiology) separate from the responses caused by structured exercise (exercise physiology). In theory, this may be in part because nonexercise activity thermogenesis is generally a much greater component of total energy expenditure than exercise or because any type of brief, yet frequent, muscular contraction throughout the day may be necessary to short-circuit unhealthy molecular signals causing metabolic diseases. One of the first series of controlled laboratory studies providing translational evidence for a molecular reason to maintain high levels of daily low-intensity and intermittent activity came from examinations of the cellular regulation of skeletal muscle lipoprotein lipase (LPL) (a protein important for controlling plasma triglyceride catabolism, HDL cholesterol, and other metabolic risk factors). Experimentally reducing normal spontaneous standing and ambulatory time had a much greater effect on LPL regulation than adding vigorous exercise training on top of the normal level of nonexercise activity. Those studies also found that inactivity initiated unique cellular processes that were qualitatively different from the exercise responses. In summary, there is an emergence of inactivity physiology studies. These are beginning to raise a new concern with potentially major clinical and public health significance: the average nonexercising person may become even more metabolically unfit

in the coming years if they sit too much, thereby limiting the normally high volume of intermittent nonexercise physical activity in everyday life. Thus, if the inactivity physiology paradigm is proven to be true, the dire concern for the future may rest with growing numbers of people unaware of the potential insidious dangers of sitting too much and who are not taking advantage of the benefits of maintaining nonexercise activity throughout much of the day. *Diabetes* 56:2655–2667, 2007

Humans have been increasingly spending more time in sedentary behaviors involving prolonged sitting. This global trend is likely to continue, given the increasing availability and popularity of personal computers, TV, automation of chores at home, transportation trends, and further inventions in the future. The most direct effect of sitting idle is that the work performed by the large skeletal muscles in the legs, back, and trunk required for upright movement comes to a halt. Over the time course of 1 day, physical inactivity may induce negative effects on relatively fast-acting cellular processes in skeletal muscles or other tissues regulating risk factors like plasma triglycerides and HDL cholesterol (1–3). Sitting for prolonged periods would also cause the loss of opportunity for cumulative energy expenditure resulting from the thousands of intermittent muscular contractions throughout the 16-h period that people are awake. This may have chronic effects on the propensity to become overweight (4,5).

PARADIGM OF INACTIVITY PHYSIOLOGY

Research groups are beginning to focus on the physiological, medical, and public health impact of sitting too much. Relative to the large amount known about the acute and chronic effects of exercise (the discipline of exercise physiology), relatively little is known about the cellular signals, physiological responses, and disease outcomes caused by prolonged sitting and other ubiquitous sedentary behaviors (inactivity physiology) (2). There is enough information about exercise physiology to support the well-documented public health guidelines promoting at least 150 min/week of moderate-vigorous leisure-time physical activity aimed at decreasing risks for metabolic diseases (6,7). Many types of studies, including longitudinal interventional trials, have evaluated exercise training (6,8–10). University degree programs in exercise physiology and textbooks have been structured around disseminating information about how to exercise and the acute and chronic effects of exercise (11–14). However, we know much less about how alterations in the time engaged in sedentary behaviors (sitting) will impact the metabolic processes involved in the etiology of the metabolic syn-

From the ¹Department of Biomedical Sciences, University of Missouri-Columbia, Columbia, Missouri; and the ²Dalton Cardiovascular Research Center, University of Missouri-Columbia, Columbia, Missouri.

Address correspondence and reprint requests to Dr. Marc T. Hamilton, E102 VMB 1600 E. Rollins Rd., Department of Biomedical Sciences, University of Missouri-Columbia, Columbia, MO 65211. E-mail: hamiltonm@missouri.edu.

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CVD, cardiovascular disease; DVT, deep venous thrombosis; FTW, fast-twitch white; LPL, lipoprotein lipase; NEAT, nonexercise activity thermogenesis; PAL, physical activity level.

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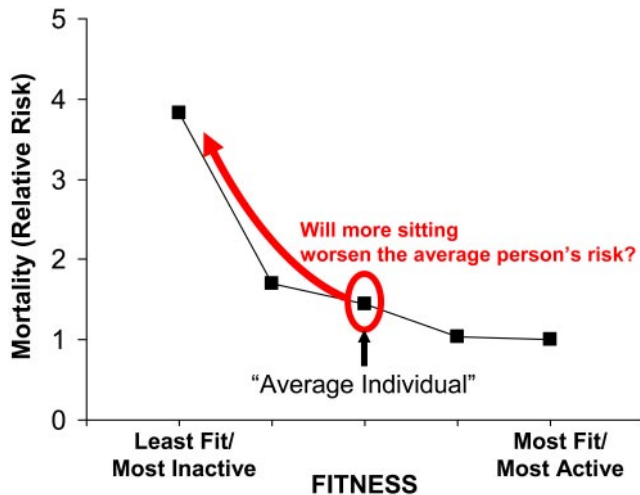


FIG. 1. A major question raised by the inactivity physiology paradigm is whether the typical person who already does not perform structured exercise regularly will have increased risks of metabolic diseases in the coming years as a result of too much sitting. The red circle shadows the median of 13,344 middle-aged men and women (adapted from ref. 86). As described in the text, the majority of people in the general population already do not follow the prescription for enough moderate-vigorous exercise. It logically follows that in people who already do not exercise, it is impossible for higher rates of age-adjusted metabolic syndrome, type 2 diabetes, obesity, and CVD over the coming years to be caused by further exercise deficiency. Inactivity physiology is a discipline concerned with the future of people who may be sitting too much. (Please see <http://dx.doi.org/10.2337/db07-0882> for a high-quality digital representation of this figure.)

drome, type 2 diabetes, obesity, and coronary artery disease. At this time, we are limited mostly to cross-sectional studies focused on inactivity (15–20), and even less has been done examining underlying biological mechanisms of action necessary to establish plausible cause-and-effect explanations for observational studies (2).

The first four tenets of inactivity physiology. The crux of the matter is that there is currently insufficient information about inactivity physiology to prompt new public health policies limiting sitting time and prescribing most forms of nonexercise activity to ameliorate specific risk factors related to metabolic diseases. From the limited amount that has been published, four tenets of inactivity physiology can be conceptualized to help guide further research. The significance of this issue is illustrated in Fig. 1. Conventionally, clinical and public health concerns focus on pushing the curve to the right with exercise prescriptions on top of the normal lifestyle. In contrast, the first tenet of a possible inactivity physiology paradigm shift already proposed (2) is that sitting more and performing less nonexercise activity could theoretically push this curve upward or shift it to the left (Fig. 1), where there is the most risk for disease (16–18,21,22). A standard practice in medicine and public health is to identify unhealthy behaviors and advocate that patients and populations limit those behaviors as much as possible. Thus, it is important to determine whether prolonged sitting time is a high-risk behavior for diseases like coronary artery disease or glucose metabolism in those with type 2 diabetes.

The second tenet of inactivity physiology is that the various times that people spend sitting or participating in exercise-based leisure-time physical activity are distinct classes of behavior, with distinct determinants (5) and independent effects on risk for disease (19,20,23–26). The third, and central, tenet for the paradigm of inactivity

physiology is that some of the specific cellular and molecular processes explaining the responses during inactivity physiology versus exercise physiology are qualitatively different from each other. Because sitting and other sedentary behaviors, as well as nonexercise physical activity, may be quite distinct sets of behaviors and not simply the bottom end of a continuum through to structured exercise, an axiomatic corollary based on the accepted specificity principle is that sitting too much may affect the cellular processes responsible for metabolic risk factors for type 2 diabetes and coronary heart disease differently than structured exercise as previously studied in the field of exercise physiology. Simply put, the hypothesis is that signals harming the human body during too much inactivity are not always the same signals boosting health above normal with a bolus of exercise several times per week on top of nonexercise activity. Furthermore, in one example, the most potent mechanism determining risk factors is gained by maintaining a high volume of daily intermittent low-intensity postural and ambulatory activity (1–3).

The fourth tenet is that in cohorts of people who do not exercise, further increases in age-adjusted rates for coronary artery disease, type 2 diabetes, metabolic syndrome, and obesity cannot be caused by additional exercise deficiency. Thus, if the inactivity physiology paradigm is proven true (it is arguably still a hypothesis at this time), the dire concern for the future may rest with growing numbers of people unaware of the potential insidious dangers of sitting too much or the possible benefits of at least maintaining daily low-intensity intermittent nonexercise activity throughout most of the day. Support for these concepts will require translational studies ranging from observational epidemiology to insights on cellular regulatory mechanisms in animal models and humans. The following review summarizes the current evidence leading to this conceptual framework.

A NEW CONCERN FOR FUTURE PUBLIC HEALTH PROBLEMS?

Have humans reached the pinnacle for physical inactivity? One misimpression some laypersons may have is that most people do not engage in substantial physical activity unless they make a conscious effort to exercise. Even with more automation than in the past century, self-professed couch potatoes who never exercise stand and ambulate ~9 h/day during incidental movements (15). People such as homemakers who do not get much time to rest while awake are believed to stand and perform at least light-intensity activity about 12 h/day (27). Accelerometry estimated that sedentary young adults moved their body an equivalent of walking 9 miles/day (28). Even obese-sedentary adults have been found to stand and ambulate an average of 6.5 h/day (15). More than 90% of the calories expended in all forms of physical activity were due to this pattern of standing and nonexercise ambulatory movements because individuals did not exercise and because the energy expenditure associated with nonexercise activity thermogenesis (NEAT) while sitting was small (15). Obviously, 6–12 h/day of nonexercise activity is beyond what anyone would exercise regularly. Laboratory rats housed in standard cages without running wheels also recruit postural leg muscles for >8 h/day (29); the local contractile activity in the legs is not without significant consequence for regulatory mechanisms important for risk factors, as will be explained below. Thus, it is important to

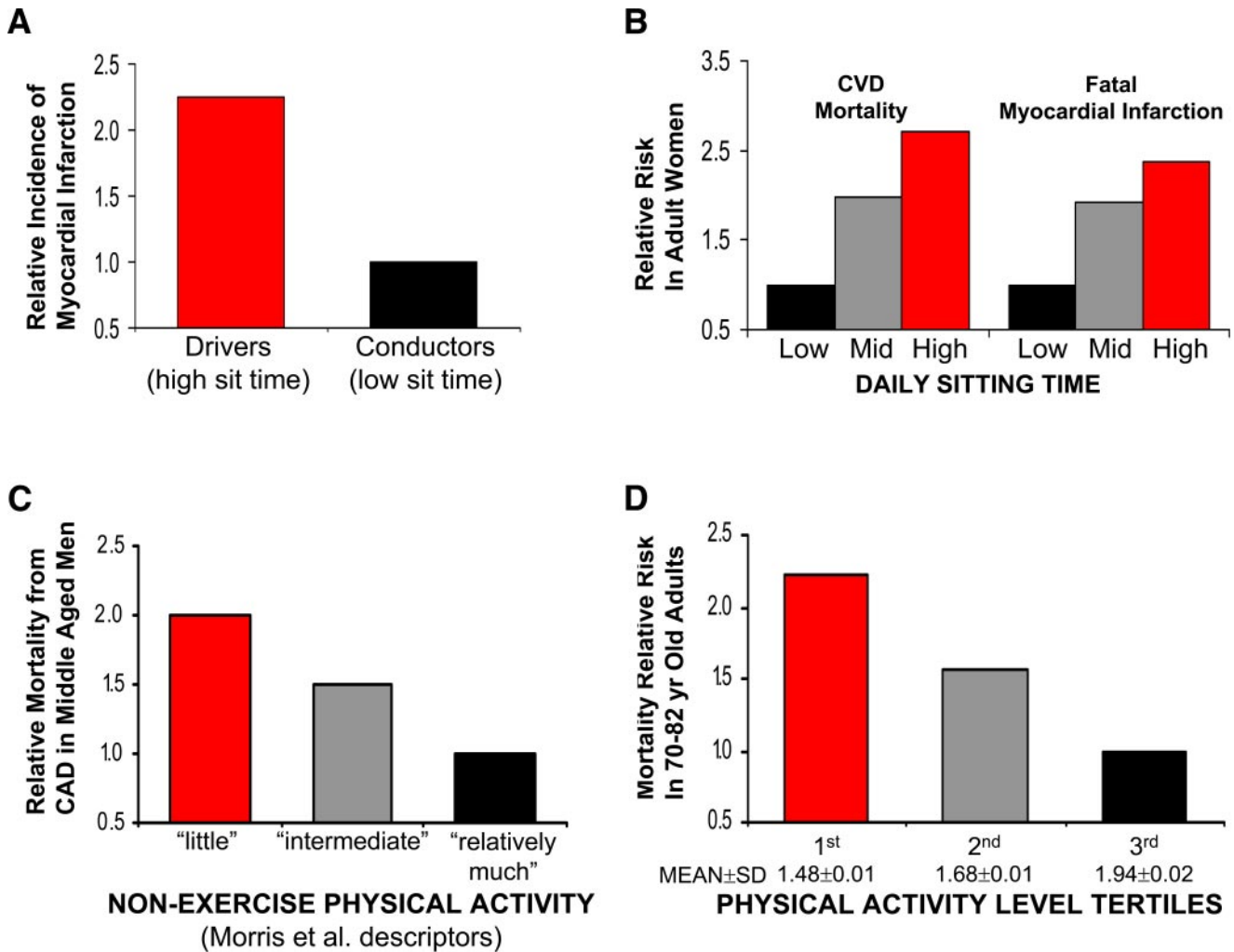


FIG. 2. Middle-aged men who had to sit many more hours per week and obtain less physical activity had greater risk for premature myocardial infarction (A) and mortality from coronary artery disease (C) (ref. 17). These general findings were subsequently confirmed in studies in middle-aged women (B) (ref. 18) and an elderly group (D) (ref. 21). (Please see <http://dx.doi.org/10.2337/db07-0882> for a high-quality digital representation of this figure.)

seek an answer to the question illustrated in Fig. 1; i.e., can the average adult who already does not follow the public health policy prescribing regular moderate-vigorous exercise become even more unhealthy in the coming years if they sit too much and do not maintain sufficient daily nonexercise physical activity? Changes in the technological environments of people's homes, workplaces, and communities, together with societal trends that are contributing to the progression of human inactivity, are continually appearing worldwide, and it is naïve to assume new developments will not appear in the future that will foster a continuation of this trend. Thus, it is unreasonable to assume that humans have necessarily reached the pinnacle of physical inactivity. Creative strategies could hopefully curb this potential problem of inactivity in homes, schools, communities, and workplaces (4).

Consideration of physical inactivity as a distinct behavioral concern independent of exercise habits.

As described above and in more detail later, the total amount of time and energy expended during exercise is less than that during nonexercise activity. Recent National Health and Nutrition Examination Survey data (as reported by Kruger et al. [30]) reveal that only 28% of Americans are "regularly active" by meeting the current

minimal exercise recommendation for ~30 min/day for ~5 days/week of at least moderate activity. For minority racial groups and less educated people, the numbers are one-half that (30). It logically follows that in people who already do not exercise, it is absolutely impossible for further rates of age-adjusted overweight/obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease (CVD) over the coming years to be caused by further exercise deficiency. In contrast, nonexercise activity deficiency can still increase profoundly because nearly all people stand and move at least 1 h/day and generally for many hours each day. Thus, in keeping with the first tenet of inactivity physiology, many people are potentially at greater risk for disease in the future by sitting more. Part of the rationale for this concept is based on studies such as those shown in Fig. 2. Furthermore, the specific act of TV viewing as an index of sitting has been studied extensively in cross-sectional studies for both adults and children (5). TV viewing, a highly prevalent leisure-time sedentary behavior, may have detrimental effects on overweight and obesity that can be independent of leisure-time physical activity (5). Interestingly, emerging evidence also indicates that maintaining a high level of daily low-intensity activity may be important independently of moderate-vigorous

TABLE 1
Characteristics of inactivity physiology and nonexercise physical activity

Inactivity physiology	
Inactivity physiology defined	Acute and chronic physiological effects of sedentary behaviors (nonexercise activity deficiency)
Modality	An emphasis on sedentary behaviors while not standing (mostly sitting in humans)
Reference comparison	Nonexercise physical activity (NEAT-producing behaviors)
Energetics	Activity energy expenditure is low during most types of sitting compared with even light-intensity movements when standing
Potential outcomes of prolonged sitting	Cardiovascular disease (Fig. 2), mortality (Fig. 2), metabolic syndrome (refs. 21–24), obesity (refs. 4,5), and deep venous thrombosis (refs. 48–53)
Cellular mechanisms	Largely understudied, potentially distinct from exercise (example in Table 2; Figs. 5 and 6)
Nonexercise physical activity	
Frequency	Up to dozens/hundreds of bouts of nonexercise activity per day; always 7 days/week
Intensity	Highly variable but often low (<3 METS or <25–50% Vo_{2max})
Duration	Prolonged, often >8 h/day; highly variable (Fig. 3)
Modality	Primarily involving movements while standing; leisure or non-leisure time physical activity
Prescription	Currently, more vague than the exercise prescription; “limit sitting time” is the most direct; the specific interactions between frequency, intensity, duration, and modality of nonexercise activity to replace sedentary time are largely unknown

The defining characteristics of inactivity physiology and the unique patterns of nonexercise physical activity are listed. This can be contrasted to exercise physiology guidelines.

physical activity for at least a limited number of metabolic risk factors for coronary artery disease, like elevated glucose (31), type 2 diabetes (20), and lipids such as triglyceride and HDL (1,2). Thus, both in the vast numbers of people who do not exercise and even in the people who do, arguments have been made that time spent in sedentary behavior should be considered a distinct entity from exercise.

The question of the role of sitting and nonexercise physical activity on disease has been raised. In a review of the landmark Institute of Medicine report on human energy expenditure for control of body weight, Brooks et al. (32) eloquently stated a critical proposition related to physical activity level (PAL):

“Any physical activity, be that occupational, recreational, intentional, or spontaneous, that raises energy expenditure over basal contributes to the PAL. The PAL reflects summation of all accumulated physical activity in a 24 h period. It is important to note, however, that substantial fidgeting and other spontaneous activities may contribute to PAL, but may not produce the health benefits of sustained, vigorous exercise.”

In 1995, a letter to the editor criticized the then new American College of Sport Medicine/Centers for Disease Control and Prevention physical activity guidelines as “the promotion of interrupted lifestyle activities as a matter of faith” (33). A theme of this review is that the most compelling arguments will require a careful examination of the old and new observational studies that may shed light on the role of inactivity on disease (Fig. 2). Second, there needs to be a newfound application of the specificity principle in physiological studies geared toward determining whether the unique patterns of nonexercise activity (Figs. 3 and 4; Table 1) have sufficient potency to significantly regulate specific physiological processes controlling risk factors (Fig. 5).

The 1995 public health recommendation focused on adding at least 30 min/day of leisure-time physical activity

on top of whatever else people do when they are awake for 16 h/day. While this document was well conceived given the large body of information available about structured leisure-time exercise, the question left open is, Are there possible insidious effects of sitting idle throughout the waking day, as hypothesized in Fig. 1? Interestingly, circa 1950, when Morris and colleagues performed their classical occupational studies (Fig. 2), the medical profession viewed their work with skepticism (34), and the research subjects were unaware that there would be a consequence on morbidity and mortality as a result of the inactivity in their vocation. Those seminal findings still raise critical questions. Would a shift in lifestyles toward more sitting and less nonexercise activity significantly impact coronary artery disease, type 2 diabetes, hypertension, and premature death? How would experimentally altering sitting time and nonexercise physical activity in either the most immobile or most active quintiles of the population change specific metabolic risk factors? Would providing more opportunities to avoid prolonged sitting in conference rooms, offices, schools, living rooms of homes, and public meeting places help lower the disease burden of people who are currently constrained to sit for much of their waking day?

EPIDEMIOLOGICAL OBSERVATIONS

CVD and mortality. Some occupations put limits on standing (e.g., bus drivers) (Fig. 2A) or sitting (e.g., conductors of subway trains, buses, and trolleys). People with jobs that involve much sitting such as bus drivers and telephonists have about twice the rate of CVD as those with more standing and ambulatory activities such as bus conductors and mail carriers (17). A summary of this work by Paffenbarger et al. (34) provided interesting historical insights. While there was an approximately twofold difference in CVD, bus drivers and conductors had a slight difference in average heart rate during work shifts (91 vs.

106 bpm). When the conductors were not balancing themselves in a moving vehicle, they spent time ambulating intermittently. In the subgroup of men who were conductors on double-decker buses, they moved up stairs briefly throughout the day, and this would include more intense contractions. Even after accounting for trouser waist size as a measure of central body fat, the drivers still had higher rates of death from CVD (34). The most distinguishing characteristic was that drivers sat throughout almost the entirety of their 5.5-h shift.

Another fascinating finding (Fig. 2B) comes from studies of a more recent cohort study by Weller et al. (18). They related their estimation of daily sitting time to CVD mortality (Fig. 2B). Risk for CVD mortality was 2.7-fold greater in high sitters relative to that in low sitters. Manson et al. (16) concluded that prolonged sitting predicted increased cardiovascular risk in 73,743 women independently of age or recreational energy expenditure. Manini et al. (21) quantified total activity energy expenditure in elderly individuals with a PAL <1.5 to >2 and found a graded decrease in mortality across the three tertiles (Fig. 2D). Their questionnaires included both nonexercise and exercise types of activity. Since the amounts of vigorous exercise and walking for exercise were not different between tertiles (21), then by default, the difference in mortality risk was associated with nonexercise physical activity. Most recently, Matthews et al. (22) reported that there was a progressive inverse relationship between risk for all-cause mortality and nonexercise activity in Chinese women. That study also indicated a benefit of nonexercise activity independent of exercise. Taken together, these studies support the first, second, and fourth tenets stated above and demonstrate a significant impact of inactivity on par with relative risk of smoking and other concerns aggressively managed, like hypercholesterolemia (7). We suspect that historically we are just now at the inception for many more studies appearing in the literature testing the hypotheses raised by the inactivity physiology paradigm. If confirmed consistently in additional studies, the dire concern for people who do not exercise, or perhaps even if they do, is that they may develop more disease if they sit more and move less in everyday nonexercise activity in the future than they do now. Thus, it is plausible that the public health burden could expand because of the insidious effects of inactivity (NEAT deficiency). However, it is also important to emphasize that these were observational studies and that there have been too few translational studies in humans and animals providing mechanistic support or interventional evidence to support a stronger case for the cause-and-effect relationships.

Metabolic syndrome risk factors and type 2 diabetes are associated with indexes of sedentary time. Metabolic syndrome is a constellation of risk factors for CVD and type 2 diabetes, including plasma triglycerides, HDL cholesterol, plasma glucose, blood pressure, and central adiposity or waist girth. Studies have shown that the classification of people with metabolic syndrome (19,23–25) and related metabolic risk factors (31,35–40), excessive adiposity or weight gain (5,15,41–46), poor glucose management in children with type 1 diabetes (47), and type 2 diabetes risk (20,26,35) have all been directly related to sitting time and/or inversely to low nonexercise activity. Estimations from prolonged TV and computer time led to the conclusion that too much sitting can more than double the risk for metabolic syndrome (19,23,24). Dunstan et al. (19) found that for each 1-h increase of TV

viewing per day, there was a 26% increase in the prevalence of metabolic syndrome in women. The magnitude of this negative effect per 1 h of sedentary TV time was about the same as the positive effect derived from 30 min of extra physical activity aimed at boosting health (19). TV time presumably involved sitting, because study participants were specifically asked about the duration of viewing the TV as the primary activity. Simultaneous house cleaning, cooking, or performing other physical activity while watching TV were excluded. It is important to point out that detriments in metabolic risk factors and disease outcomes due to physical inactivity are often independent of BMI or other markers for excess adiposity (19,20,25,31,36–39). This latter point of independence with BMI is suggestive that specific effects of sitting may be caused by inactivity per se and are not just due to chronic changes in body composition (see LPL ACTIVITY, PLASMA TRIGLYCERIDE CLEARANCE BY SKELETAL MUSCLE, AND HDL CHOLESTEROL RESPONSES DURING INACTIVITY).

Interactions between sedentary time and physical activity. Correlation analysis revealed that a negligible amount of variance in leisure-time physical activity could be explained by the indexes of sedentary time (23,38,40). Independent from exercise, sedentary time predicts metabolic syndrome (19,23–25) and its components (19,20,23,25,26,31,35–40). A recent study by Healy et al. (31) used accelerometry to more objectively assess movements throughout most of the day. Standing and sitting time were not measured directly with inclinometers. However, from their accelerometry analysis, there was evidence that their study cohort performed low-intensity nonexercise activity for at least 5–6 h/day. The effect of low-intensity activity on postprandial glucose concentration was independent of moderate-vigorous activity. Most interesting, the postprandial glucose concentration at 2 h appeared to have a direct and almost linear relationship across quartiles of sedentary time and an equally strong inverse relationship with the amount of low-intensity activity.

Taken together, the epidemiological studies reviewed above regarding mortality, coronary heart disease, diabetes, and specific metabolic risk factors are suggestive that inactivity (sitting) and low nonexercise activity may produce serious health problems, and this cannot simply be explained by exercise deficiency. The most direct evidence in the future for this important area could come from experimentation inducing more sitting time to directly determine mechanisms and whether there are plausible cause-and-effect relationships between inactivity (sitting) and metabolic risk factors.

DISTINCTIVE CHARACTERISTICS OF INACTIVITY PHYSIOLOGY

Patterns of nonexercise physical activity and sitting time. There are many modalities of nonexercise activity (housework, puttering, shopping, vocational movements, etc.), but there are some common features (Table 1). The frequency and cumulative duration of nonexercise activity throughout the day is extremely high. People perform intermittent bouts of nonexercise activity throughout most of the waking day, 7 days/week, 365 days/year. In contrast, the frequency of exercise is more limited, generally to <150 min/week (30). In a fabulously comprehensive review by Bennett et al. (48), “sedentary” was defined in the physical activity literature as <20 to <150 min/week. As described above, almost everyone obtains much more

than 20–150 min/week of nonexercise activity, and thus physical activity trials testing health benefits do not pertain to the effects of inactivity (sitting too much) and nonexercise activity. While the term “sedentary behavior” (5) helps capture this distinction, we aim to make this distinction even more explicit. Because the word sedentary has more frequently come to mean lack of exercise instead of the original Latin meaning of *sedere* (sit), we have moved toward using the word “inactivity” and have coined the term inactivity physiology (2) to minimize confusion and emphasize the distinctive characteristics between sitting too much or exercising too little.

Distinctive characteristics of nonexercise activity are illustrated with electromyogram patterns as an index of local contractile activity of skeletal muscle in the leg (Fig. 3A), inclinometers and accelerometers (Fig. 3B), and energy expenditure (Fig. 4). In the example shown (Fig. 3A), the subject took four steps in 1 min. Contractions were also required during standing while not stepping and for standing up from a chair. Nonexercise activity is required throughout much of the day (Fig. 3B). The patterns of inactivity (high sitting day) and high muscle fiber recruitment during nonexercise activity (high standing day) may potentially produce specific cellular signals regulating risk factors for disease. Translational studies seeking to identify a molecular reason to maintain a relatively high level of daily activity (1,2) have experimentally identified the specific role of local contractile activity in postural skeletal muscles on lipoprotein metabolism during periods of intermittent low-intensity ambulation and standing.

These pervasive patterns of sedentary behaviors and irregular nonexercise activity raise critical questions for research, but do not currently fit easily into existing public health recommendations. In clarifying the original 1995 guidelines (7), the recently updated American College of Sports Medicine/American Heart Association recommendation (49) explicitly addressed the concept of accumulating short bouts of physical activity because “there was confusion how short these bouts could be. For consistency and clarity, the minimum length of these short bouts is clarified as being 10 min.” The recommendation currently states that the recommended minimum of aerobic activity is “in addition to” the frequent and routine nonexercise activities such as “taking out the trash,” “walking to parking lot at store or office,” and “walking around the home or office.” The minimal intensity (“at least moderate”) was also clarified. Defining moderate in relative terms to aerobic fitness, especially in older adults, was clarified as a noticeable increase in heart rate and breathing along with a perceived exertion of 5 or 6 on a 10-point scale (50). Importantly, the amount of nonexercise activity or sitting patterns is not addressed in any detail by the recommendation, and we believe this will be a critical issue for further research. However, the clarifications do help in separating how the public can distinguish between exercise and the distinctive sedentary and nonexercise activity behaviors illustrated in Fig. 3.

A major reason for our knowing less about inactivity and nonexercise activity than about structured exercise has been the practical hurdle of quantifying sitting time and patterns of spontaneous nonexercise movements. This is being overcome in part with better use of accelerometers and inclinometers. When people are standing up, there are generally movements, or at least light fidgeting-like movements (15,28). Critical for any confusion about

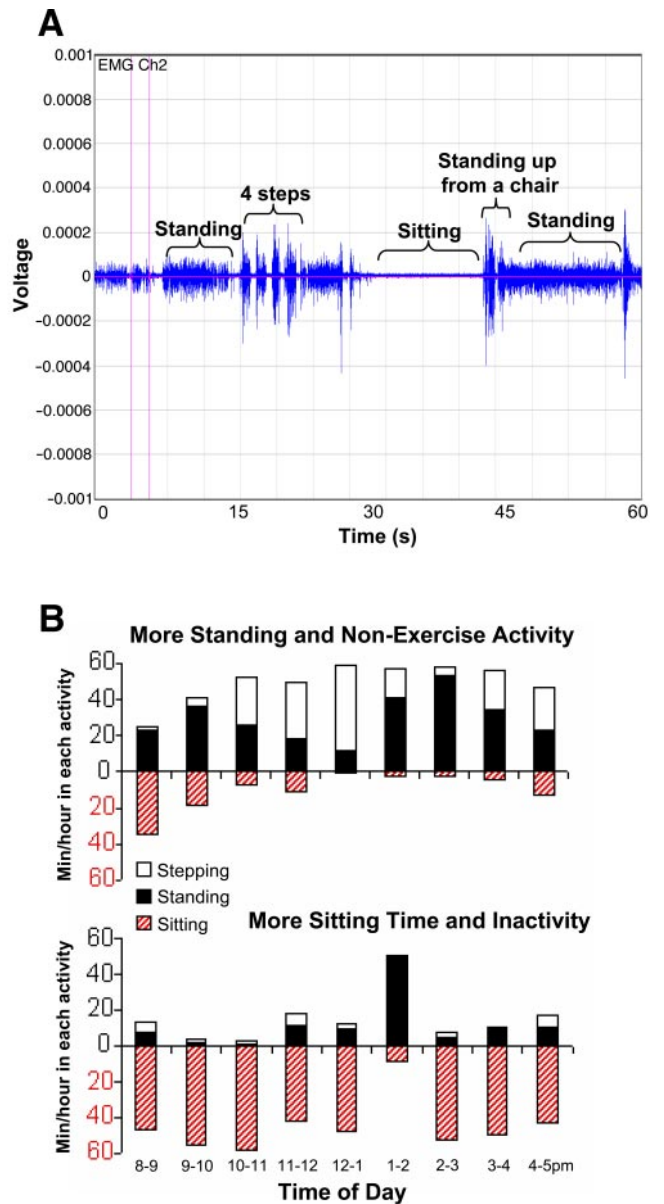


FIG. 3. Distinctive characteristics of patterns of inactivity and nonexercise physical activity (M.T.H., unpublished observations) are shown over a 1-min epoch (A) and during the workday (B). A: Skeletal muscle recruitment during nonexercise physical activity by using electromyogram signals of a leg muscle during intermittent standing, brief stepping, sitting, and rising from a chair. This person took four steps and stood intermittently during this minute while at work and would not have been categorized as exercising. There was a silent signal while sitting, and this was quickly interrupted to stand up again to greet a visitor. B: Quantification of postural allocation with inclinometer technology and ambulation with accelerometry averaged over hourly epochs within the same individual on two different days. The sensitivity of the accelerometer was arbitrarily set to accurately record stepping time above 1.0 mph. (Please see <http://dx.doi.org/10.2337/db07-0882> for a high-quality digital representation of this figure.)

dose-response issues is the fact that there is great variability within (Fig. 3B) and between individuals in patterns of sitting time and nonexercise movements (15,28,31,43–46). Biological determinants contribute to this (15,28). Lean and obese people stand and ambulate ~9 and ~6.5 h/day, respectively (15). Supporting the mass of the body in combination with spontaneous movement or very slow ambulation (1 mph) raises whole-body energy expenditure 2.5-fold more than when seated still (51). Nonexercise

movements decrease significantly as people age and become more sedentary (28). Thus, given the small differences in daily energy balance necessary to explain weight gain over many years (52), it is plausible that postural allocation plays a role in human obesity. A major question raised by the inactivity physiology paradigm is whether the typical person who already does not perform structured exercise regularly will have increased risks of diseases in the coming years as a result of too much sitting. If so, then a secondary question relates to the minimal and optimal patterns of nonexercise physical activity necessary to prevent specific metabolic concerns for specific cohorts, such as controlling glucose metabolism in people with diabetes or controlling triglycerides and HDL cholesterol in people with dyslipidemia. Understandably, there is no public campaign to limit sitting because inactivity physiology is still an emerging area of research and because insufficient evidence may exist to justify sounding the alarm at this point.

Specificity principle. A cornerstone paradigm from years of exercise research has been the specificity principle; namely, that the magnitude and qualitative type of adaptive responses depend on the type of exercise training. It is axiomatic that the low resistances associated with aerobic endurance training will not produce the same responses as high-resistance weight training. Thus, people who desire to maximize strength will lift heavy weights and those who want to maximize endurance performance will run or bicycle long distances with a much lower resistance and greater duration. The stimulus to skeletal muscles, cardiovascular system, and other organs is vastly different when comparing different exercises. Thus, the corollary is that the underlying cellular regulatory mechanisms responsible for causing the adaptation must also be different. Although the cumulative weekly energy expenditure in people who exercise regularly is a small slice of the pie for total energy expenditure (Fig. 4A), there are nonetheless healthy benefits of exercise (7). Except for maybe weight control, most exercise physiologists would probably agree that there is something special about an exercise deficiency that may not necessarily be substituted for by any factor raising total body energy expenditure. For example, a drug or hormone raising basal metabolic rate 200–300 kcal/day would unlikely cause many of the exercise-like benefits such as increased maximal cardiac stroke volume and fatigue resistance. If one accepts this specificity principle for exercise deficiency, the logical corollary would be that a deficiency in the larger slice of the pie because of too little nonexercise physical activity (Fig. 4A) may also cause specific biological problems. Exercise of relatively shorter duration and greater intensity may or may not be able to substitute for a NEAT deficiency since nonexercise activity takes place over a far greater time span every day and continually interrupts sedentary time. This hypothesis is still largely untested, and further research is much needed. In summary, both exercise and nonexercise physical activity patterns may be healthy, but if one accepts the specificity principle, then one should not assume that people can simply replace nonexercise physical activity deficiency with a bolus of exercise a few times per week.

The cumulative number of the thousands of daily muscular contractions during nonexercise activity requires a greater energy demand than a bolus of continuous exercise (Fig. 4B). There is a wide range in the energy demand of NEAT (Fig. 4B). Even brisk walking 5 days/week or

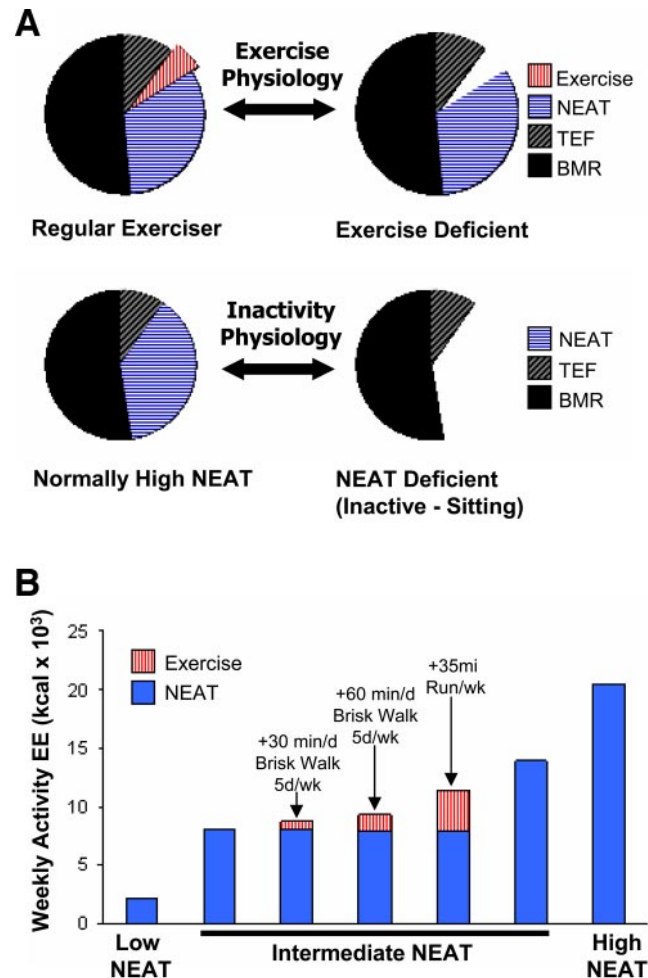


FIG. 4. Comparison of exercise physiology and inactivity physiology in relation to energy expenditure. Components of total energy expenditure (A) and the energy expended from exercise on top of NEAT (B). Exercise physiology examines responses to exercise and effects of stopping training. Exercise does not typically constitute the majority of activity energy expenditure even in regular exercisers. Nevertheless, consistent with the specificity principle, the slice of the energy demand in the pie graph (A) due to exercise (brisk walking at 4 mph for 60 min/day, 5 days/week) can be a significant supplement for boosting health above levels in untrained people by stimulating multiple specific cellular signals uniquely activated by acute or chronic exercise. It thus follows logically that the specificity principle also predicts that some physiological and biochemical responses induced by physical inactivity (shown as NEAT deficiency in A) are not simply the opposite of the exercise responses. Activity energy expenditure (B) is the energy required above basal metabolic rate for exercise or other movement. Energy expenditure was derived from normative values for a reference person weighing 70 kg using a PAL of 1.85 (refs. 27, 87, and 88). NEAT is the most variable component of the total energy expenditure, typically ranging from ~300 to 2,000 kcal/day when comparing the average of the estimate for the lowest and highest quartiles in total energy expenditure (refs. 27 and 32). (Please see <http://dx.doi.org/10.2337/db07-0882> for a high-quality digital representation of this figure.)

running 35 miles/week produces less energy expenditure (and fewer muscle contractions) than intermediate amounts of NEAT (Fig. 4B). The energy expenditure of “standing workers” was ~1,400 kcal/day for shop assistants or homemakers, ~2,300 kcal/day for higher levels of intermittent daily activity involving some manual labor, and even higher values have been reported for strenuous professions requiring very high levels of effort such as lumberjacks (53). In contrast, seated workers with little option for muscular activity during weight-bearing movements expended ~700 kcal/day in activity, and chair-

bound individuals with less option for using muscles in normal life expend as little as 300 kcal/day in NEAT (27). Efforts are beginning to appear in the medical literature for practical strategies to encourage NEAT-enhancing behaviors (4).

CONTRASTING EXERCISE PHYSIOLOGY AND INACTIVITY PHYSIOLOGY

Molecular responses during inactivity. It is easy to forget when studying behaviors (e.g., prolonged sitting) that statistical correlations with risk factors does not prove causation and that interventional studies are required to identify the actual stimuli causing a cellular regulatory mechanism to raise metabolic risk factors. If sitting really does cause disease, then specific cells within the muscles or other parts of the body must somehow sense and respond to stimuli triggered by prolonged sitting. We already know that when compared to a day of normal spontaneous standing/light ambulation, short periods of immobility either repress or stimulate the expression of dozens of genes (54). From global transcriptional analysis of the expression of thousands of genes, the expression of many genes were “switched on” and dozens of genes “switched off” during local contractile inactivity in postural muscles in the leg. Inactivity physiology research is only beginning to identify the molecules responsible for the aforementioned metabolic risk factors for coronary artery disease, such as the control of plasma lipoprotein metabolism (2).

Deep venous thrombosis: a medical condition uniquely caused by too much acute sitting and not just lack of exercise. Deep venous thrombosis (DVT) is an example for how too much sitting, not just too little structured exercise, can induce medical problems. DVT is a serious and potentially life-threatening condition where blood clots develop in the veins deep within idle leg muscles (55). The problem has long been known to be caused by prolonged sitting, as in the air raid shelters in London during World War II (55), in the 1950s when people began taking extended automobile journeys and flying on airplanes (56), and even during excessive TV viewing (57) or computer and video game use (58–60). Global transcriptional analysis in combination with biochemical information may reveal specific molecular responses within the legs explaining the risk for DVT during physical inactivity (T.W.Z., unpublished observations). Thus, DVT is a clear example for why limiting sitting time is a reasonable prescription for some medical conditions (Table 1). DVT prevention is also an example where light, intermittent, and frequent local muscle contractions in the legs might be an optimal physical activity recommendation for preventing this disorder unique to inactivity physiology.

Human bed rest and prolonged inactivity in animals. Current practice often attempts to limit bed rest following surgeries or injuries when medically possible. Three weeks of bed rest in otherwise healthy men (61) had a more profound impact on physical work capacity than did three decades of aging in the same men (62). Interestingly, the mechanism responsible for the decrease in maximal oxygen consumption during bed rest was due to stroke volume and cardiac output (61), whereas during aging the decrease was due to maximal oxygen extraction (62). Thus, bed rest studies reveal that routine nonexercise physical activity and/or standing in everyday life are

obviously important in human physiology. It may be tempting to infer from this that bed rest studies also offer insights about sitting too much because when people sit they are also immobile and have reduced NEAT. However, great caution is warranted because bed rest studies typically investigate the effects of lying down for several or more days (63,64). While we are unaware of evidence that 1 day of lying down would cause secondary physiological effects impinging upon metabolic events, several days of lying down uninterrupted may have widespread consequences. Others have reviewed the many physiological responses of bed rest, including a host of neural-humoral changes, orthostatic intolerance, skeletal muscle atrophy, disturbances in fluid balance, etc. (65). Application of the rat hindlimb unloading model over an 11-day period to identify mechanisms of lipid dysregulation during reduced standing/nonexercise ambulation have also had this concern (1) and thus have employed an intermittent phase each day where the rat is returned to the standing position. At least in rats, intermittent reloading was able to successfully prevent skeletal muscle atrophy (1) and adverse changes in both myocardial contractility (66) and the cerebral vasculature (67).

Lipoprotein lipase function. Lipoprotein lipase (LPL) regulation has served as the prototype both for understanding how skeletal muscle metabolism contributes directly to lipoprotein risk factors and for insights about how exercise and physical inactivity may impact disease outcomes, though for different cellular reasons. As far as we know, LPL is the first protein directly interacting with and regulating lipoproteins to be studied at the cellular level during physical inactivity (1–3,68,69), raising the possibility for other metabolic processes to be impaired during inactivity as well. Many studies have evaluated the metabolic consequences of altered LPL function. Low LPL has been associated with blunted plasma triglyceride uptake (1,70,71) and reduced plasma HDL levels (1,70). LPL may also have some effects on hypertension (72), diabetes-induced dyslipidemia (73), metabolic problems in aging (68), human metabolic syndrome (74,75), and coronary artery disease severity and incidence in many human studies (76,77). Positive effects of LPL on preventing diet-induced adiposity (78,79) and insulin resistance (78,80) have been reported but not in all models (81,82). Experimental elevations in LPL have been reported to reduce diabetic dyslipidemia and limit diet-induced atherosclerosis in transgenic rabbits (83).

LPL responses during exercise. Increased skeletal muscle LPL has been frequently reported following short-term exercise training (84,85). LPL activity was measured in six muscles after intensive training for 2 weeks. Exercise increased LPL activity 2- to 2.5-fold in the least oxidative regions of leg muscle (fast-twitch white [FTW] muscle type). This increase after run training was on top of the normal level present in nonexercising control rats with spontaneous standing/light ambulatory activity. The most oxidative postural leg muscles that already had high LPL due to nonexercise activity did not display any further increase in LPL after training. LPL mRNA gene expression and LPL protein levels were increased in tandem with the same patterns as for LPL activity. Furthermore, intense continuous electrical stimulation of the motor nerve to a predominantly FTW muscle for 1 month also increased LPL mRNA expression, protein, and activity approximately threefold. In both rats (85) and humans (84), the transient temporal pattern for LPL expression after stop-

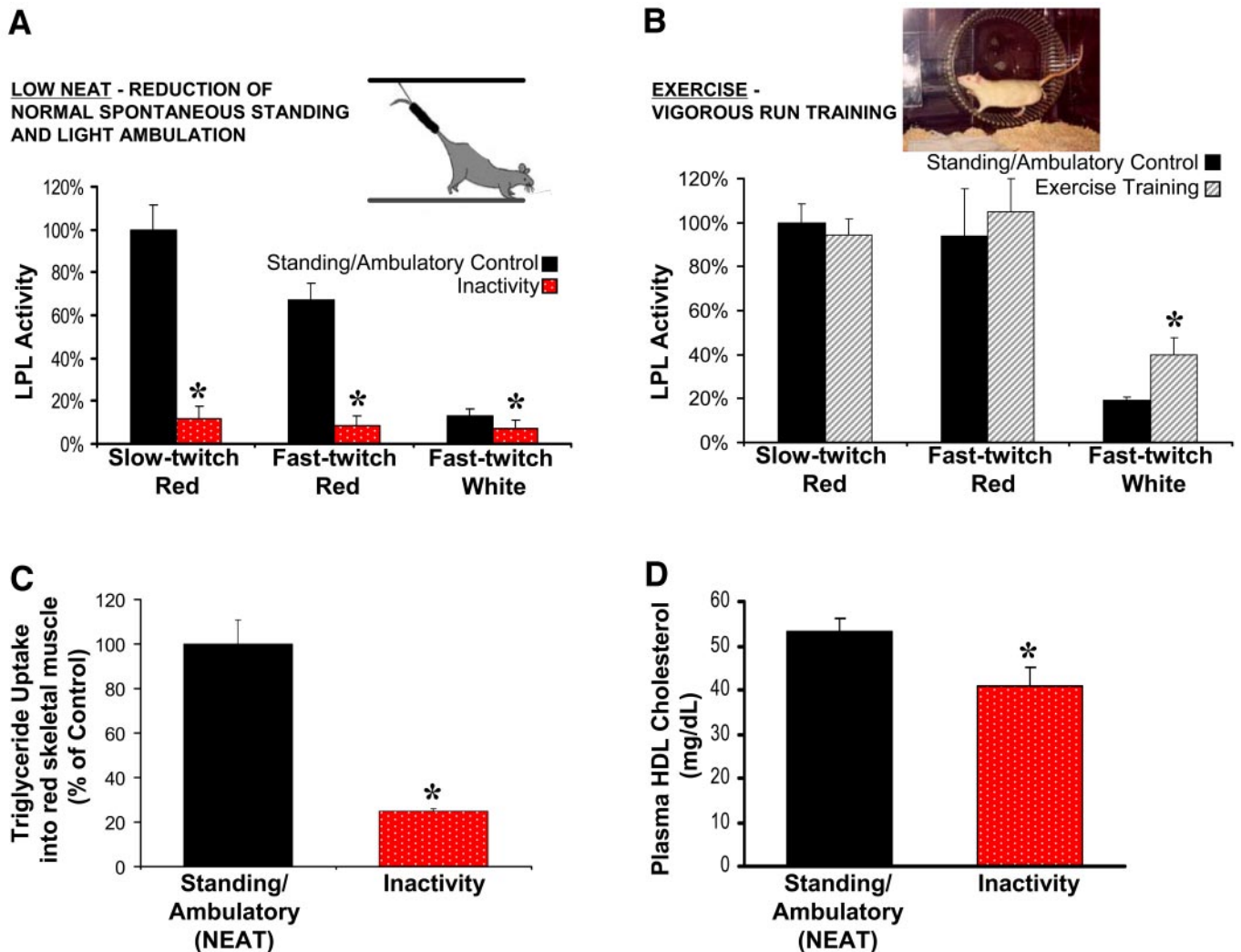


FIG. 5. LPL activity in studies of inactivity (A) and exercise (B) physiology is summarized for three skeletal muscles (refs. 1 and 85). C and D: Effects of reducing normal spontaneous standing/low-intensity ambulation on plasma triglyceride clearance by the fast-twitch red quadriceps muscle (C) and plasma HDL cholesterol (D). A, C, and D: * $P < 0.05$ between standing/ambulatory control and inactivity. B: * $P < 0.05$ between standing/ambulatory control and exercise. (Please see <http://dx.doi.org/10.2337/db07-0882> for a high-quality digital representation of this figure.)

ping exercise is consistent with a role for pretranslational regulation.

LPL activity, plasma triglyceride clearance by skeletal muscle, and HDL cholesterol responses during inactivity. Studies that have prevented standing and ambulatory activity of one or both of the hindlimbs of rats (1,3) have been reviewed in more detail elsewhere (2). The physical activity for the referent control group in these studies was limited to the normal spontaneous patterns of standing and intermittent light ambulating of rats in the cage (no running wheels). Laboratory rats may perform standing activity as much as most humans (15), based on electromyogram studies revealing activity of ~8 h/day in the motor units required in the leg of nonexercised rats (29). The acute (1–18 h) and chronic (11 days) responses to inactivity were studied (1). Atrophy of skeletal muscle mass and alterations in food intake or body mass caused by complete loss of mobility were avoided because the chronic inactivity was intermittent for only one-half of each day (1). Remarkably, most of the LPL activity associated with microvasculature of the most oxidative muscles was lost within 1 day of inactivity (Fig. 5). The finding of a rapid loss of functional LPL activity was consistent in

both male and female rats and also in mice. LPL activity started to decrease after ~4 h of inactivity, and effects were apparently complete within ~18 h. The 12- and 6-h data are shown for hindlimb muscles in Figs. 5A and 6A, respectively. Consistent with LPL function, the clearance of plasma triglyceride by skeletal muscle was decreased significantly (Fig. 5C). Plasma HDL cholesterol concentration was ~20% lower in the inactive condition compared with that in the normally standing/ambulatory group after both 1 (Fig. 5D) and 11 (1) days.

The cellular mechanism for the loss of LPL is being studied in detail (1–3), and some of those findings are summarized here to illustrate the contrast between cellular reasons for an increase in LPL that can occur during exercise and the decrease in LPL during contractile inactivity. First, notice the type of muscle cells associated with changes in LPL in Fig. 5A and B. With inactivity, there was a profound decrease in LPL in the more oxidative types of muscle. On average, LPL activity decreased to only 10% that of controls (spontaneous standing and light ambulation associated with nonexercise activity of normally caged rats) after 12 h in the type of muscle recruited most frequently in everyday life (29). During normal physical

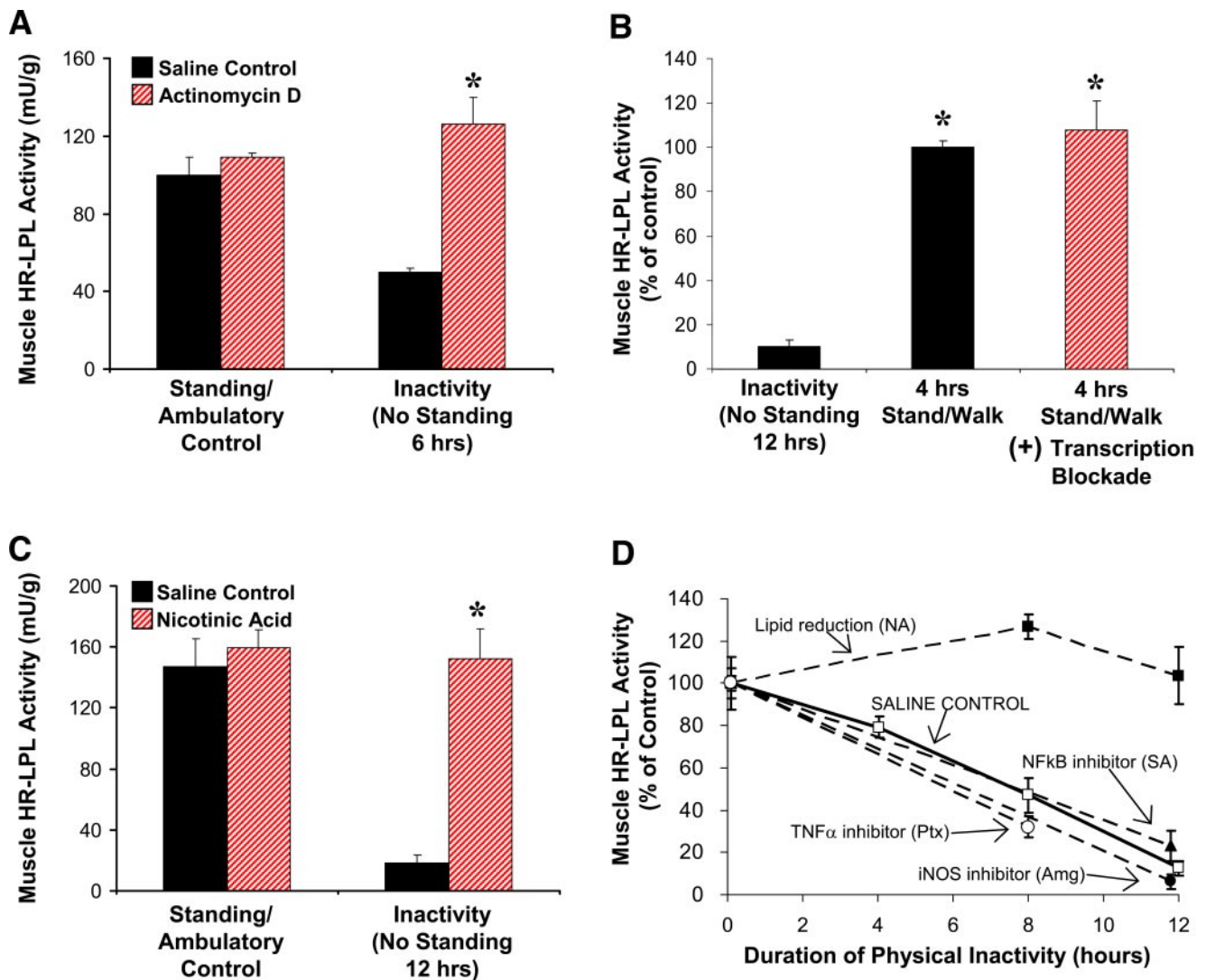


FIG. 6. Studies identifying unique cellular responses to physical inactivity when standing/ambulatory time is limited. Acute administration of the transcription blocker actinomycin D was without effect on LPL in rats with a normally higher amount of nonexercise physical activity. Administering the transcription blocker at the initiation of acute inactivity prevented the fall in LPL activity, indicating that a gene is switched on, which is responsible for the lowering of LPL activity (A). Re-initiation of intermittent standing and very slow ambulation (0.3 mph) following 12 h of inactivity restored muscle LPL completely (B). Blocking transcription did not impair this process. Lowering of plasma triglyceride and free fatty acid during inactivity with nicotinic acid (NA) completely prevented the decrease in LPL caused by physical inactivity, while having no effect on LPL activity in muscles with normal spontaneous cage activity (C). Inhibition of several signaling pathways known previously to suppress LPL activity had no effect on the decrease in LPL activity caused by physical inactivity (D). Amg, aminoguanidine; HR-LPL, heparin-releasable LPL activity, which is the functional fraction of LPL activity residing on the surface of the capillary endothelium; iNOS, inducible nitric oxide synthase; NF κ B, nuclear factor- κ B; Ptx, SA, pentoxifylline/salicylic acid; TNF- α , tumor necrosis factor- α . (Please see <http://dx.doi.org/10.2337/db07-0882> for a high-quality digital representation of this figure.)

activity, when rats stood on the hindlimbs, LPL activity was significantly greater in the oxidative red muscle regions than in the FTW muscle regions. The lower levels of LPL in FTW muscle of control animals and the less impressive decrease during inactivity could be explained by the normally low level of recruitment (29) in this type of muscle.

The importance of local contractile activity was experimentally demonstrated in another model of inactivity where only one leg was prevented from bearing weight and where the expected decrease in LPL activity to only 5% that in controls in the most oxidative muscle regions was observed in the unloaded leg but not in the contralateral leg that still performed work (1). LPL also was not affected by changes in physical activity in continuously working skeletal muscle (diaphragm) and cardiac muscle. Thus, differential regulation of lipoproteins by LPL during

experimentally induced inactivity and normal nonexercise physical activity is linked to local contractile activity and not a generalized response to the systemic energy demands.

Stimuli signaling for suppression of LPL activity. Studies with the transcriptional inhibitor actinomycin D (1) indicate that the process decreasing LPL during inactivity may be due to upregulation of a gene other than LPL that quickly switches off the functional LPL activity found on the capillary endothelium (Fig. 6A). The effects of the transcriptional blockade were specific to the inactive group because there was no effect on LPL in standing/ambulatory rats. LPL was rapidly restored to normal within 4 h of intermittent standing and slow walking (Fig. 6B). This rapid increase in LPL activity was not limited by blockade of gene transcription. In seeking to begin to identify signaling events (Fig. 6C and D), nicotinic acid

TABLE 2

LPL studies indicate that the underlying cellular events during inactivity (NEAT deficiency) are distinct from the cellular events after exercise training

	Inactivity mechanisms	Exercise mechanisms
Comparison studied for LPL	Inactivity (not standing) vs. normal spontaneous intermittent standing/ambulation during nonexercise physical activity	Exercise vs. normal nonexercise physical activity (spontaneous intermittent standing/ambulation)
Fiber type mostly affected	Red oxidative muscle fibers have ≥ 10 -fold lower LPL activity during inactivity	White glycolytic muscle fibers have 2.5-fold greater LPL activity after exercise
LPL mRNA involvement	No difference in LPL mRNA between inactive and control	LPL mRNA expression increases 2.5-fold in multiple glycolytic muscles after exercise
Evidence of inhibitory pathway	Transcription of an inhibitory gene suppresses LPL by a posttranslational mechanism	No evidence for inhibitory gene

The mechanisms regulating LPL during physical inactivity ("Inactivity mechanisms" column) and during exercise training ("Exercise mechanisms" column) were studied in comparison with the same referent control group (i.e., normal Sprague-Dawley rats with only intermittent and spontaneous nonexercise physical activity). Table is redrawn from refs. 1,2,85.

(niacin) was a pharmacological compound particularly effective in completely preventing the loss of LPL activity. This and other findings with high-fat feeding led to the interpretation that there was an increased sensitivity to plasma lipids during physical inactivity, tending to decrease LPL activity in skeletal muscle (3). This has practical implications for understanding one reason why nicotinic acid has been so effective in lowering plasma triglycerides and raising HDL cholesterol in clinical cardiology for decades, and it supports a rationale for paying closer attention to unique aspects of inactivity physiology. **Contrast in LPL regulation during inactivity and exercise studies.** A central question to this whole issue of inactivity physiology and nonexercise activity deficiency is whether exercise operates by a different set of cellular mechanisms or simply that all effects of changes in physical activity operate along a continuum. Studies are beginning to appear in the literature (1–3) that are important for determining whether the regulation of the lipoprotein risk factors most commonly associated with metabolic syndrome and type 2 diabetes (plasma triglyceride and HDL cholesterol) in exercise physiology studies are not merely the mirror image of effects of the inactivity physiology studies (Fig. 5). Those studies are the first steps of research for the third tenet of the paradigm of inactivity physiology; i.e., inactivity is not the same as lack of exercise. This concept, proposed earlier (2), is that some of the specific cellular and molecular processes explaining the responses during inactivity physiology and exercise physiology are qualitatively different from each other and that sometimes the most potency is gained by maintaining daily low-intensity postural and ambulatory activity.

Table 2 lists examples for how the mechanisms driving LPL responses differ between inactivity physiology and exercise physiology. One day of inactivity had a several-fold greater change in LPL activity than the exercise training response. The effects of inactivity on LPL suppression were greatest in the most oxidative muscle regions. In contrast to inactivity, exercise by running the same type of rats increased LPL gene expression and LPL activity in the most glycolytic skeletal muscles and not in oxidative muscles (Fig. 5B). Both in studies of rats (85) and humans (84), vigorous exercise has consistently been shown to produce parallel increases in LPL mRNA expression and LPL protein. These two studies showed LPL gene expres-

sion rising within the hours after exercise and then falling transiently to normal levels by the next day. This temporal association is consistent with pretranslational regulation of LPL gene expression. LPL mRNA increased consistently by ~ 2.5 fold in four muscles after running and quickly returned to control levels by the next day after not running anymore (85). In contrast, neither acute (Fig. 5A) nor chronic (1) inactivity altered LPL mRNA gene expression (1,54) despite the marked decrease in LPL activity. Furthermore, the rapid restoration of LPL activity during 4 h of intermittent standing and very slow ambulation was not impaired during blockade of gene transcription (Fig. 6B). In summary, the magnitude of LPL suppression during inactivity after reducing standing/low-intensity ambulation was much greater than the increase after adding exercise on top of normal nonexercise physical activity. These studies support the specificity principle and the third tenet of inactivity physiology because the cellular responses to inactivity and exercise are qualitatively different.

CONCLUSIONS

People spend too many hours in a waking day sitting for the scientific community to neglect the existing yet limited evidence that these behaviors may matter for metabolic diseases. Furthermore, there are too many hours of nonexercise physical activity in most people's lives to neglect the consequences of reducing this time or to not encourage efforts seeking to determine how this large volume of nonexercise physical activity should fit into public health recommendations in the near future. Sitting time and nonexercise activity have been linked in epidemiological studies to rates of metabolic syndrome, type 2 diabetes, obesity, and CVD. This obviously raises the pressing need for interventional studies to more conclusively test for specific negative metabolic effects of prolonged sitting or to compare and contrast the potential benefits of daily nonexercise physical activity and structured exercise. Translational studies are needed at multiple levels, ranging from cellular research determining whether there are plausible mechanisms regulating risk factors to more epidemiological research identifying clinical outcomes in diverse populations. As one example, the limited existing evidence indicates that inactivity quickly engages signals for specific molecular responses contributing to poor lipid metabolism by suppression of skeletal muscle LPL activ-

ity. Given the ubiquitous and strong support for the specificity principle that various forms of physical activity produce unique cellular signals and physiological responses, it is reasonable to suspect that studies elucidating the qualitative and quantitative biochemical and clinical effects of sitting too much will yield fascinating insights.

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