INACTIVITY IS AN INDEPENDENT HEALTH RISK: OBJECTIVELY MEASURED MUSCLE ACTIVITY AND INACTIVITY DURING NORMAL DAILY LIFE OF ORDINARY PEOPLE

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ABSTRACT

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Today's society promotes oversitting, and physical inactivity appears to be an independent health risk. The continuum from total inactivity to vigorous intensity training contains different physiological actions and objective measurements are needed to find out associations between physical activity, inactivity and health. The purpose of this study was to describe muscle activity and inactivity during normal daily life of ordinary people measured objectively with sophisticated EMG-shorts. Activity and inactivity patterns were compared between the age groups and associations between EMG results and metabolic health markers were studied.

Eighty four healthy volunteers (20-30 yrs, n=27; 30-60 yrs, n=40; 60-76 yrs, n=17) were measured in the laboratory and during 1-6 days of their normal daily life with shorts measuring muscle activity (EMG). EMG was normalized to maximum voluntary contraction (EMG_{MVC}) and inactivity threshold was defined as an EMG level below that required during standing. Moderate and vigorous activity thresholds were defined as EMG values corresponding to 3 and 6 METs measured by indirect calorimetry during incremental treadmill walking test. The EMG results were compared between the age groups by One-way ANOVA with Tukey post-hoc test. Complete blood count, anthropometrics and blood pressure were measured in the morning in fasting condition and compared with the EMG results in a cross-sectional manner by bivariate correlation analyses (Pearson correlation coefficient, r) and forced-entry regression models.

Activity burst amplitude was 5.8±3.4% of EMG_{MVC} and was higher in the elderly (60-76 yrs) compared to the younger (p<.001). The subjects had 12600±4000 muscle activity bursts and the average duration was 1.4±1,4s. Regardless of age, thigh muscles were inactive for 67.5±11.9% of the waking hours. Corresponding times for low, moderate and vigorous activity were 16.7±9.9%, 8.5±3.4% and 7.3±4.2%, respectively. The elderly had more moderate activity compared to the younger (p<.01). The longest inactivity periods lasted for 13.9±7.3 minutes and were longer in the elderly compared to the younger (p<.01). The longest continuous inactivity period was positively associated with triglycerides and systolic and diastolic blood pressure independent of gender (P<.01), gender and age (P<.05), gender and waist circumference (P<.01) and gender and VO_2max (P<.05).

Only a minor part of muscle capacity is used in a normal daily life and the most of the time thigh muscles are totally inactive. The elderly had the same total inactivity time, but they had longer continuous inactivity periods compared to the younger. However, the elderly used a higher percentage of their muscle capacity during the day. The longest continuous inactivity period was positively and independently associated with elevated risk for metabolic diseases. Breaking prolonged periods of sitting would be a valuable and accessible way to easily promote metabolic health.

Key words: inactivity, sitting, muscle activity, objective measurement, metabolic diseases

TIIVISTELMÄ

Pesola, Arto 2011. Inaktiivisuus on itsenäinen terveysriski: objektiivisesti mitattu lihasten aktiivisuus ja inaktiivisuus terveiden ihmisten päivittäisen elämän aikana. Liikuntafysiologian Pro Gradu-tutkielma. Liikuntabiologian laitos, Jyväskylän yliopisto. 96 sivua.

Istumisen määrä on lisääntynyt yhteiskunnallisten muutosten seurauksena ennennäkemättömällä tavalla, vaikka lihasten inaktiivisuus vaikuttaa olevan itsenäinen terveysriski. Jatkumo täydellisestä inaktiivisuudesta kovatehoiseen harjoitteluun sisältää erilaisia fysiologisia vasteita, joiden yhteyksiä terveyteen täytyy tutkia objektiivisten aktiivisuusmittausten avulla. Tämän tutkimuksen tarkoituksena oli kuvailla EMG-shortseilla mitattua lihasten aktiivisuutta ja inaktiivisuutta terveiden ihmisten päivittäisen elämän aikana. Lihasten aktiivisuutta ja inaktiivisuutta verrattiin ikäryhmien välillä ja niiden yhteyksiä aineenvaihdunnallisiin terveysmuuttujiin tutkittiin.

Kahdeksankymmenenneljän terveen vapaaehtoisen (20-30 -vuotiaat, n=27; 30-60 -vuotiaat, n=40; 60-76 -vuotiaat, n=17) lihasaktiivisuutta mitattiin EMG-shortsien avulla laboratoriossa sekä 1-6 normaalin päivän aikana. EMG normalisoitiin maksimaaliseen tahdonalaiseen lihassupistukseen (EMG_{MVC}) ja inaktiivisuuskynnys määritettiin seisomisen aikaisen EMG-aktiivisuuden alapuolelle. Keski- ja kovatehoinen aktiivisuuskynnys määritettiin EMG-arvoiksi, jotka vastasivat epäsuoralla kalorimetrialla nousujohteisen mattotestin aikana mitattuja 3:a ja 6:a lepoaineenvaihdunnan kerrannaista (MET). EMG-tuloksia verrattiin ikäryhmien välillä yksisuuntaisella varianssianalyysillä ja Tukeyn post-hoc testillä. Täysi verenkuva, kehonkoostumus sekä verenpaine mitattiin aamulla paastotilassa ja niitä verrattiin EMG-tuloksiin Pearsonin korrelaatiokertoimilla sekä regressiomalleilla.

Keskimääräinen lihasaktiivisuusjakson suuruus oli 5.8±3.4% EMG_{MVC}:stä, ja arvo oli korkeampi ikääntyneillä (60-76 -vuotiaat) nuorempiin verrattuna (p<.001). Päivän aikana oli 12600±4000 lihasaktiivisuusjaksoa, joiden kesto oli keskimäärin 1.4±1,4s. Lihakset olivat inaktiivisena 67.5±11.9% hereilläoloajasta kaikilla ikäryhmillä, ja vastaavat lukemat kevyt-, keski-, ja kovatehoiselle aktiivisuudelle olivat 16.7±9.9%, 8.5±3.4% ja 7.3±4.2%. Ikääntyneillä oli enemmän keskitehoista aktiivisuutta nuoriin verrattuna (p<.01). Pisimmät yhtämittaiset inaktiivisuujaksot kestivät 13.9±7.3 minuuttia ollen pidempiä ikääntyneillä nuoriin verrattuna (p<.01). Pisin yhtämittainen inaktiivisuusjakso oli positiivisesti yhteydessä triglyserideihin ja systoliseen ja diastoliseen verenpaineeseen itsenäisesti sukupuolen (P<.01), sukupuolen ja iän (P<.05), sukupuolen ja vyötärönympäryksen (P<.01) ja sukupuolen ja aerobisen kunnon (P<.05) vaikutuksesta.

Vain pieni osa lihaskapasiteetista on käytössä päivittäisen elämän aikana ja suurimman osan ajasta lihakset ovat täysin inaktiivisena. Ikääntyneiden kokonaisinaktiivisuusaika oli sama, mutta heillä oli pidemmät yhtämittaiset inaktiivisuusjaksot nuoriin verrattuna. Ikääntyneet kuitenkin käyttivät suurempaa osaa lihaskapasiteetistaan päivän aikana. Pisin yhtämittainen inaktiivisuusjakso oli positiivisesti ja itsenäisesti yhteydessä kohonneeseen aineenvaihduntasairausriskiin. Pitkien istumisjaksojen välttäminen voisi olla arvokas ja helposti toteutettava tapa aineenvaihdunnallisen terveyden ylläpitämiseksi ja edistämiseksi.

Avainsanat: inaktiivisuus, istuminen, lihasaktiivisuus, objektiivinen mittaaminen, aineenvaihduntasairaudet

CONTENTS

1 INTRODUCTION

Since the beginning of the industrial revolution, there has been an ever growing difference between the conditions under which our genome evolved and the way we live today. Modern environment not only limits physical activity, but requires prolonged sitting at work, at school and at home. Estimated physical activity energy expenditure was up to 24.7kcal/kg per day for men and 14.6kcal/kg per day for women in hunter-gatherer societies, while estimates for modern sedentary office workers are 4.4 kcal/kg and 4.2kcal/kg per day for men and women, respectively. Our genome has not changed as rapidly as social evolution and trends of physical inactivity, meaning that human genome requires physical activity to maintain its normal function and preventing the incidence of many chronic diseases. (Hill et al. 2003, Cordain et al. 1997.)

There is a broad agreement among health and exercise experts that moderate- to vigorous intensity physical activity has a major preventive role in cardiovascular disease, type 2 diabetes, obesity and some cancers. A curvilinear risk reduction occurs across volume of activity the steepest gradient being at the lowest end of the activity scale (Physical Activity Guidelines Advisory Committee 2008, Powell et al. 2011.) In U.S. the amount of people reporting adequate activity as defined by physical activity guidelines has risen from 21.0% in 1996 to 50.6% in 2009 (National Center for Chronic Disease Prevention and Health Promotion, http://apps.nccd.cdc.gov/brfss/index.asp, accessed 25.1.2011). At the same time, despite the higher prevalence of people engaging in moderate-to-vigorous intensity physical activities, the prevalence of chronic diseases and obesity are rising dramatically (Centers for Disease Control and Prevention, http://www.cdc.gov/obesity/downloads/obesity_trends_2009.pdf, accessed 22.2.2011).

This clear gap between the dose and response could be named as an "activity paradox", a justified question about the minimum threshold for recommended physical activity. Due to the research focus and physical activity recommendations the inactive person is usually defined as a person who does not participate in moderate-to-vigorous intensity physical activities (Bennett et al. 2006, Powell et al. 2011). This definition ignores the high and highly variable amount of light intensity activities performed during normal

daily tasks (Hamilton et al. 2007). Indeed, objective measurement of daily physical activity has revealed that people are most of the day literally inactive, with minimal muscle activity (Klein et al. 2010). People spent on average 54.9% of their daytime (or 7.7 hours) in sedentary behaviors in U.S. (Matthews et al. 2007). In Europe, on average 40.6% of people sit more than 6h/day. The highest percentage of people sitting >6h/day was found in Denmark (women 56.1%, men 55.0%) and in Finland (women 46.4%, men 50.8%). (Sjöström et al. 2006.) Recent epidemiological findings suggest that not only the lack of physical activity, but also prolonged times of sedentary behavior, particularly sitting, increase significantly the risk of chronic diseases. The association persists even if people participate in moderate-to-vigorous intensity physical activities. (Hu et al. 2001; Hu et al. 2003, Dunstan et al. 2004, Dunstan et al. 2007, Bertrais et al. 2005, Ford et al. 2005, Dunstan et al. 2005, Jakes et al. 2003, Kronenberg et al. 2000). The recommended half an hour a day of moderate to vigorous physical activity may thus not compensate for the community level decrease for every day physical activities, which is a consequence of industrial and technological development.

The continuum from total inactivity to vigorous-intensity training contains different physiological actions. Similarly, to carry out physical activity for health and fitness, one needs to meet a portion from every phase of this continuum. Still the existing scientific literature does not tell the exact pattern of optimal physical activity. It is still unknown, what is the activity threshold that triggers the healthy signals. According to recent findings, physical inactivity is not only lack of activity, but may contain individual physiological effects that on excess doses may disturb health, regardless of recommended doses of more intensive physical activity (Hamilton et al. 2007).

The purpose of this thesis is firstly to discuss the entirety of physical activities and their associations to health, and secondly to find out whether the inactive ending of physical activity continuum would have independent detrimental consequences on individual and public health. Muscle activity during normal daily life of ordinary people was measured objectively with sophisticated shorts measuring electromyographic (EMG) activity, and associations between activity, inactivity and health related variables were studied.

2 PHYSICAL ACTIVITY AND DAILY ENERGY EXPENDITURE

Physical activity can be defined as "bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level" (U.S. Department of Health and Human Services 1996). Previously physical activity and exercise were considered to be synonyms and their main objective was to improve cardiorespiratory fitness. In 1990 official recommendations stated for the first time that the quantity and quality of exercise to gain health benefits may differ from what is recommended for enhancing fitness (ACSM 1990.) Physical activity can today be defined as "Both exertion during routine daily activities and exercise for the sake of enhancing fitness" (Jacobson et al. 2005). Thus, exercise is nowadays generally considered one of the subcategories of physical activity (U.S. Department of Health and Human Services 1996).

The practical context where physical activity takes place is often used for more specific categorization. The most common categories are household, transportation, occupational or leisure time. Leisure time physical activity (LTPA) can further be divided for example to competitive sports, recreational activities and exercise training. (U.S. Department of Health and Human Services 1996).

2.1 Daily energy expenditure

2.1.1 Components of total daily energy expenditure

Human daily energy expenditure is classically divided in three components: basal metabolic rate (BMR), thermic effect of food (TEF) and activity thermogenesis (figure 1A). Also other factors such as medication and emotion may contribute to energy expenditure to a smaller degree. Lean body mass, skeletal muscle mass and body mass are best predictors of BMR (Dériaz 1992). Between individuals, ¾ of variability in BMR is predicted by lean body mass (Ford 1984). In sedentary individuals, BMR accounts for approximately 60% of total daily energy expenditure. Thermic effect of food (TEF) is the

energy expenditure associated with the digestion, absorption and storage of food. TEF accounts for approximately 10–15% of total daily energy expenditure.

The last component of daily energy expenditure, activity thermogenesis, is separated into two components: exercise-related activity thermogenesis and non-exercise activity thermogenesis (NEAT), also called lifestyle physical activity. (Levine 2002.) Non-exercise activity thermogenesis can be further divided into two categories. First of these, sedentary behavior, may be defined as an activity expending very little energy (approximately 1.0–1.5 metabolic equivalents (METs)), such as sitting and lying down. The other one, light-intensity activity, requires low energy expenditure (approximately 1.6–2.9 METs), and includes activities such as standing, self-care activities, and slow walking. (Ainsworth et al. 2000). Another way to divide NEAT into components is based on volition, such that a spontaneous component includes actions like fidgeting, sitting, standing, and walking, and an obligatory component includes occupation, household, and daily living activities (Levine et al. 2000).

2.1.2   Variation in total daily energy expenditure

Daily energy expenditure can vary as much as 2000 kcal/day between two people of similar size. Because BMR is largely predicted by body size and TEF is a small component of total daily energy expenditure, the variance in total daily energy expenditure between people of similar size can be explained by differences in activity thermogenesis due to different occupations and leisure-time activities. Energy expenditure during sedentary behaviors is very close to resting energy expenditure, but supporting the body mass when stood up in combination with spontaneous fidgeting-like movements or very slow ambulation raises whole body energy expenditure 2,5-fold more (Levine et al. 2000, Levine 2007.) The cumulative effect of non-exercise activities can be very high. When comparing the average of the lowest and highest quartiles in total energy expenditure, NEAT typically ranges from ~300 to ~2000kcal/day (figure 1B, Hamilton et al. 2007.)
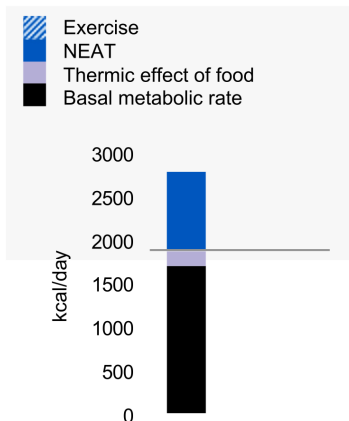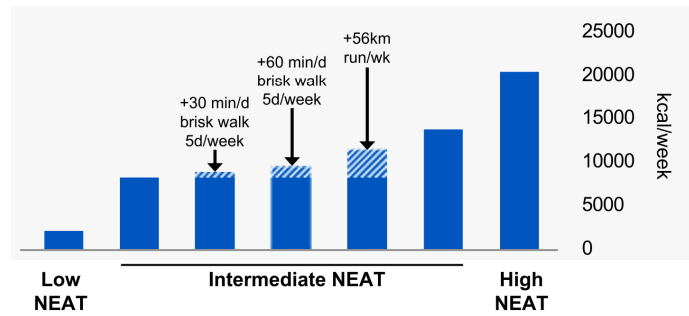
FIGURE 1. A: Human daily energy expenditure is divided in three components. In sedentary individuals, basal metabolic rate accounts for almost 60% of total daily energy expenditure. (Adapted from Levine 2002.) **B:** Variance in total daily energy expenditure between people can be explained by differences in NEAT (adapted from Hamilton et al. 2007).

Overweight and obesity are preventable causes of death and many comorbidities including type 2 diabetes, hypertension, stroke, cholelithiasis, degenerative arthritis, sleep apnea and cancer (WHO 1991). Obesity epidemic has arisen from gradual weight gain in the population produced by very small degrees of energy imbalance. In the study of Brown et al. (2005) over 8000 middle-aged Australian women was followed for more than 5 years, during which the women gained weight an average of 0.5kg/year. The authors estimated, that this weight gain was accomplished by a positive energy balance, that was only 10 kcal/d. (Brown et al. 2005.) In U.S. adults the weight gain is about 0.45–0.91 kg each year, which equals to an accumulation of 15kcal/d. Given the larger positive energy balance in some individuals (90% U.S. population are gaining <50kcal/d) and metabolic costs of storing energy (efficiency at least 50%), a decrease by about 100kcal/d in energy balance by any combination of reducing energy intake and increasing energy expenditure would prevent weight gain in 90% of the U.S. adults. (Hill et al. 2003.) Since there is evidence that energy intake appears to have decreased during the past decades, the role of energy expenditure in obesity epidemic has got more attention (Levine et al. 2006).

2.2 Physical activity during normal daily life

Despite clear evidence of health benefits of regular physical activity, only 29% of Europeans and 32.5% of Finns can be defined to be physically active (figure 2, Sjöström et al. 2006, Tudor-Locke & Bassett 2004). The prevalence of people not engaging in any physical activity above basal levels (up to an hour of low grade movement), considered as sedentary, is in general the mirror image of the prevalence of sufficient activity in Europe. The average prevalence of sedentary people in Europe is 31% the highest prevalence being found in France (women 46.3%, men 39.7%, figure 2). (Sjöström et al. 2006.)
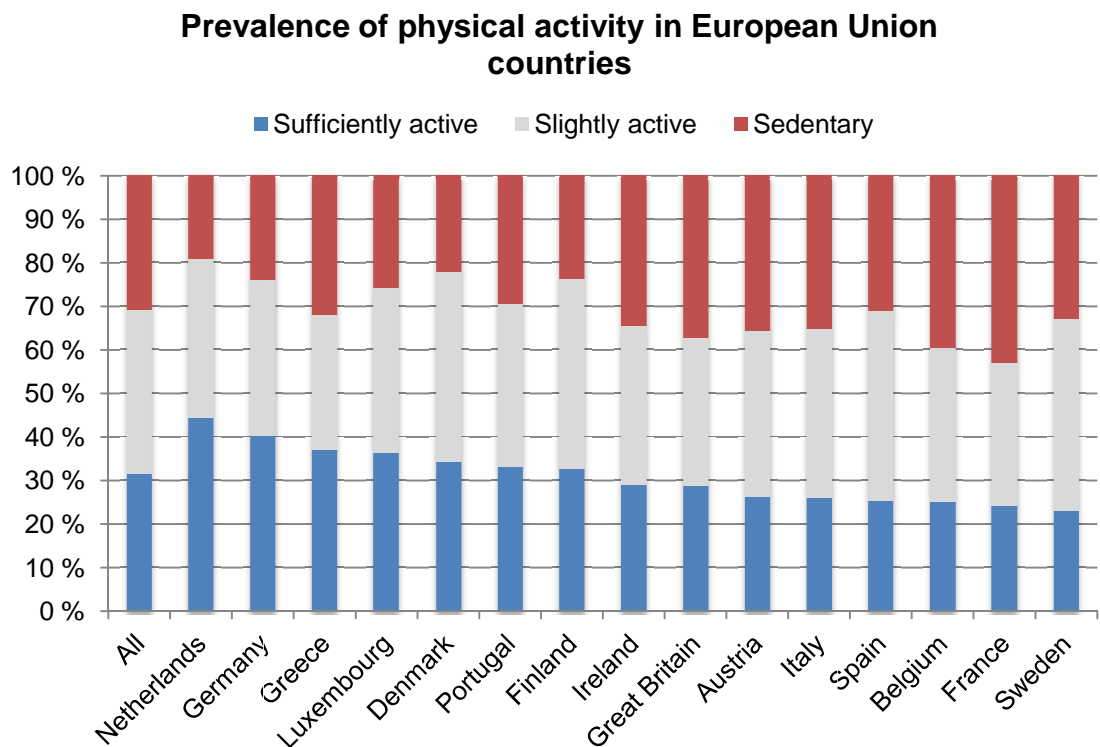
FIGURE 2. Prevalence of physically active (an approximate to at least 10000 steps of walking per day) and sedentary people across European Union countries (adapted from Sjöström et al. 2006).

In addition to prevalence of physical activity, objective measurements by accelerometers showed that people spent on average 54.9% of their daytime (7.7 hours) in sedentary behaviors in U.S. (figure 3, Matthews et al. 2007). In Europe, on average 40.6% of people sit more than 6h/day based on questionnaire surveys. The highest percentage of

people sitting >6h/day was found in Denmark (women 56.1%, men 55.0%) and in Finland (women 46.4%, men 50.8%). (Sjöström et al. 2006.)
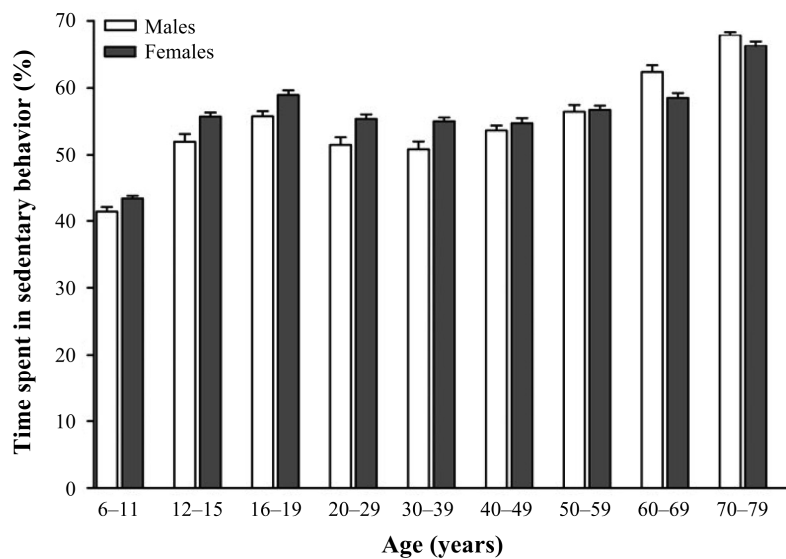
FIGURE 3. Percentage of time spent in sedentary behaviors by age and gender in United States in 2003–2004. Threshold for sedentary behavior was set to <100 counts/min measured by Actigraph accelerometer, equivalent to sitting, reclining and lying down. (Adapted from Matthews et al. 2008.)

Because every movement is produced in the muscle, the most direct approach to characterize daily physical activity is to measure long-term electromyographic (EMG) activity. Klein et al. (2010) studied EMG duration and mean IEMG in the human vastus lateralis muscle (subjects aged 20–48 years) during a 24-hour period. Total EMG duration ranged from 1h to 3 hours and average IEMG from 3.2% to 12.1% of MVC suggesting that only a fraction of muscle capacity is used during normal daily life. On average 66±6% of the total EMG duration occurred at 5% of MVC IEMG or less. Only 6.2±1.8% of the total EMG duration occurred above 20% of MVC IEMG. The results did not differ between the genders. (Klein et al. 2010.)

The authors also delineated the importance of setting the EMG threshold for inactive behavior with caution because of methodological factors. The application of progressively higher threshold from baseline to 4% of MVC reduced the EMG duration in a

curvilinear manner. In two subjects out of ten the EMG duration was 95min and 50min shorter when threshold was lifted from 1% of MVC to 2% of MVC. (Klein et al. 2010.)

2.3 Factors affecting total amount of physical activity and daily energy expenditure

Many biological, psychological, behavioral, social, cultural and environmental factors affect whether an individual is or chooses to be physically active (Trost et al. 2002). Exercise is chosen physical activity, but spontaneous physical activity (SPA), which is a part of non-exercise activity thermogenesis (NEAT), is mostly not chosen and thus bypasses higher cortical function. The result of these both actions is locomotion and rise in energy expenditure (Teske et al. 2008). In addition to NEAT-increasing or -reducing factors in our environment, there may be genetically determined mechanism that integrates SPA and NEAT to energy intake and energy stores. The cooperative or complementary action of biology and environment may thus determine whether an individual is obese or at high risk for chronic diseases. (Levine & Kotz 2005.) In this thesis, only the biological factors affecting NEAT and complementary nature of activity energy expenditure components are examined more closely.

2.3.1 Biological factors

Genetics. According to family and twin studies, genetic factors explain a small (29%, Pérusse et al. 1989) or a moderately large (78%, Joosen et al. 2005) part of the variation in physical activity level. The energy expenditure of these activities has also a genetic component because of different total and lean body mass, but also additional genetic factors are involved (Joosen et al. 2005). Also the effects of physical activity on the body mass index vary with genotype (Rankinen et al. 2010).

Age. Exercise and NEAT decrease significantly as people age (Sjöström et al. 2006, Harris et al. 2007). Compared with sedentary young people, active elderly people perform one third less nonexercise movement, because they walk almost 5km a day less

than young controls. Authors suggested, that with aging the biological drive to be active may be lower (Harris et al. 2007.)

The reason for NEAT decline may be found from dysregulation of central mechanism that regulate activity (Inoue et al. 2001). Dysfunction in large muscle fiber peripheral nerves (Resnick et al. 2001) or decline in muscle mitochondrial content and oxidative capacity also limit the activity that a subject is able to perform (Petersen et al. 2003, Conley et al. 2000). Also the perceived exertion is elevated leading to earlier cessation of activity (Allman & Rice 2003). Skeletal muscle mass begins to gradually decline at about the age of 45 (Janssen et al. 2000), and elderly people have lower maximal force and power levels compared to younger ones (Yamauchi et al. 2010). Thus the elderly need a higher muscular effort in performing daily tasks (Landers et al. 2001).

Gender. According to the 2006 Eurobarometer study, prevalence of physically active men was higher than that of women in all European Union countries. Conversely, in all countries except Denmark and Germany, the prevalence of people engaging in no physical activity was higher among men than women. In only three of the 15 countries (Austria, Denmark and Great Britain) the prevalence of sitting more than 6 hours per day was higher among women than men. (Sjöström et al. 2006.) In agricultural countries the work burden of women may be much higher than that of men because women work both in the public domain and in the home (Levine et al. 2001).

Obesity. Energy expenditure in physical activity is related to body size, such that it requires more energy to move a large body than a smaller one (Passmore 1956). Thus, after weight loss the energy cost of weight-bearing activities decreases (Foster et al. 1995).

Amount of daily activity energy expenditure seems to be closely coupled with regulation of body mass. Prolonged caloric restriction reduces activity levels (de Groot et al. 1989, Martin et al. 2007), and overfeeding increases activity levels (Levine et al. 1999) in lean individuals. Conversely, in the study of Levine et al. (2005a) obese individuals sit on average 2 hours longer per day than lean individuals, and posture allocation did not change after obese individuals lost or lean individuals gained weight (figure 4). If the obese subjects had had the same posture allocation as lean subjects, they would have

expended an additional 350kcal/day because of the energy cost of standing/ambulating. These findings suggest, that posture allocation may be biologically determined, such that obesity is associated with a NEAT-defect that predisposes obese people to sit. (Levine et al 2005a.)

Overweight or obesity is also consistently negatively associated with leisure time physical activity (Trost et al. 2002). After controlling for several confounding factors, individuals in the highest quintile for leisure time physical activity were approximately 50% less likely to be obese than those in the lowest quintile (Martínez-González et al. 1999).
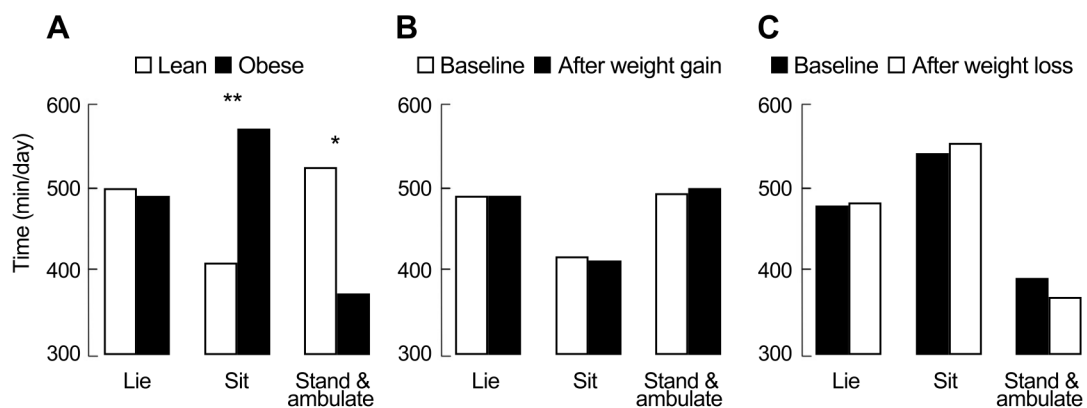
FIGURE 4. A. Time allocation for different postures for 10 obese and 10 lean sedentary subjects. **B.** Posture allocation in seven obese sedentary subjects who underwent caloric restriction. **C.** Posture allocation in 10 lean sedentary subjects who underwent experimental weight gain. Statistically significant difference was found between lean and obese subjects at baseline. (Adapted from Levine et al. 2005a.)

Central and humoral factors. NEAT, more specifically spontaneous physical activity, is likely to be affected through a central mechanism that regulates energy balance. Hypothalamic nuclei and the associated neurotransmitters are associated with body weight regulation. (Friedman & Halaas 1998.) In addition, more primitive brain areas may also affect SPA and NEAT. There may be so called master motor cells in medulla, that may initiate signals that are intended to produce locomotion for hunting, eating and reproduction (McAllen et al. 1995, Borday et al. 2004, Levine et al. 2007).

Many neurotransmitters have been shown to effect energy balance. These include cholecystokinin, corticotropin-releasing hormone, neuromedin U, neuropeptide Y, leptin, agouti-related protein, orexins and ghrelin. Especially orexin has shown to influence

especially spontaneous physical activity and is studied in detail. (Garland et al. 2011.) Orexin A is synthesized in the lateral hypothalamic area and its receptors are distributed throughout the brain (Sakurai et al. 1998). When orexin A is injected into specific brain areas, SPA and NEAT are stimulated significantly in rats (Kotz et al. 2008). Mice that don't have orexin perform much less SPA and weight significantly more than wild-type littermates, despite their reduced feeding behavior (Hara et al. 2001). In addition, rats that are obesity resistant remain lean despite enhanced food intake (Teske et al. 2006). Finally, humans that lack brain orexin due to autoimmunity to orexin in narcolepsy, have increased body mass index (Kotagal et al. 2004).

White adipocytes secrete a multitude of proteins and factors, termed adipokines, which are closely integrated into overall physiological and metabolic control (Trayhurn et al. 2006). For example, leptin secreted by adipocytes stimulates the sympathetic activity in several organs, and both of these signals affect hypothalamus decreasing food intake and increasing energy expenditure. Correspondingly sympathetic stimulation provides negative feedback to limit leptin production. (Rayner & Trayhurn 2001.) Also other adipokines, such as IL-6 and adiponectin, play a direct role in the regulation of energy balance (Trayhurn et al. 2006). Adipokine production may increase in obesity due to increased fat mass (Harris et al. 2007).

2.3.2 Environmental factors

Occupation. Different occupations explain the most of the variance in NEAT between people, such that a person working seated may have PAL (physical activity level) as low as 1.4 compared to a person doing strenuous work, who may gain a PAL of 2.4 (table 1, Black et al. 1996).

Urban environment. In high- and middle-income countries environment promotes sedentary lifestyle. Advances in environment and transportation, as well as time pressure in work makes us dash physical activity out of our lives. This is illustrated by studies for individuals who move from agricultural communities to urban environments (Hill & Peters 1998, Hill et al. 2003). Lanningham-Foster et al. (2003) studied the decline in daily energy requirements due to domestic mechanization. The decline equaled 111

kcal/d and authors suggested that it has contributed substantially to the obesity epidemic. (Lanningham-Foster et al. 2003.)

TABLE 1. Lifestyle-based physical activity levels (PAL) (Black et al. 1996).

Occupation type	PAL
Chair-bound or bed-bound	1,2
Seated work with no option of moving around and little or no strenuous leisure activity	1,4–1,5
Seated work with discretion and requirement to move around but little or no strenuous leisure activity	1,6–1,7
Standing work (eg. Housewife, shop assistant)	1,8–1,9
Strenuous work or highly active leisure	2,0–2,4

Socioeconomic status and educational level are related to higher likelihood of being physically active (Adler et al. 1994, Trost et al. 2002, Sjöström et al. 2006). Women having higher socioeconomic status spent significantly more time in leisure time, job-related and household physical activity compared to their lower socioeconomic status counterparts. Lower socioeconomic status men spent significantly more time in household activities and walking, whereas higher socioeconomic status men spent more time engaged in leisure time physical activities. (Adler et al. 1994.)

Seasonal effects on physical activity. People are more likely to be physically active during summer than during winter (Matthews et al. 2001, Pivarnik et al. 2003, Buchowski et al. 2009). Buchowski et al. (2009) stated that people spent less time in sedentary activities during summer than during winter (Buchowski et al 2009). Matthews et al. (2001) found out that total daily energy expenditure increased 1.4 METs in men and 1.0 METs in women during the summer time compared to winter time. Vigorous level leisure time activity did not differ between the seasons, but the difference was due to light to moderate intensity activities. There was also variation in physical activities during the week, such that people spent more time in household and leisure time activities during weekends than weekdays. (Matthews et al. 2001.)

2.3.3   Complementary nature of activity thermogenesis components

Despite the advice of physical activity guidelines to include moderate- and high-intensity activities to daily schedule, it still remains unknown whether the engagement

in high-intensity physical activity contributes to the physical activity level (PAL). In young people the total daily energy expenditure seems to increase due to training, even twice as much as estimated for the energy cost of the training session because of the excess postexercise energy expenditure (Van Etten et al. 1997, Westerterp et al. 1998). However, the impact of high-intensity physical activities on PAL may be compensated by a reduction of energy spent outside the training session (Westerterp 2001) particularly in obese (Ballor & Poehlman 1995) and elderly people (Meijer et al 1999).

Bonomi et al. (2010) showed, that sedentary time and the activities related to transportation, such as walking and bicycling, mainly determined the physical activity level in twenty normal weigh adult subjects (figure 5). Household tasks and other similar activities that required generic standing were significantly associated with PAL, suggesting a complementary nature between sedentary time and low intensity activities (Bonomi et al. 2010.) Healy et al. (2008a) made similar findings in 169 subjects (mean age: 53.4 years, mean BMI: 27.2 kg/m^2) indicating that the majority of waking hours (>90%) were spent in sedentary or in light-intensity activities, and these two variables were highly negatively correlated. In addition, they found that sedentary time was associated with waist circumference independent of moderate-to-vigorous-intensity physical activity, but moderate-to-vigorous-intensity activity did not have the same association independent of sedentary time. (Healy et al. 2008a.)
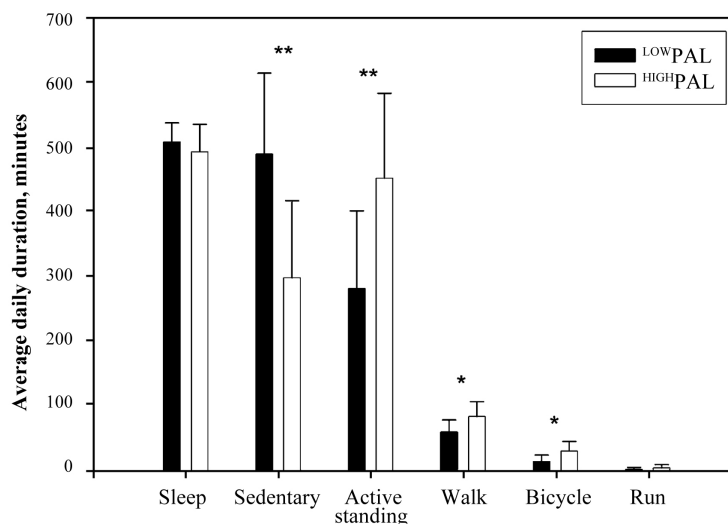
FIGURE 5. Differences in the activity types characterizing the behavior of subjects belonging to the ^{LOW}PAL group (PAL<1.75) compared with that of the ^{HIGH}PAL group (PAL>1.75) (Age: 26–60 years, body mass index: 24.5 ± 2.7 kg/m^2) (Adapted from Bonomi et al. 2010).

3 PHYSICAL ACTIVITY, INACTIVITY AND HEALTH: EP-IDEMIOLOGICAL STUDIES

Regular physical activity is widely accepted to produce a number of major health benefits. These benefits include a reduction in all-cause mortality, fatal and nonfatal cardiovascular disease and coronary heart disease, reduction in the incidence of obesity and type 2 diabetes mellitus, and an improvement in the metabolic control of individuals with established type 2 diabetes. Additionally, physical activity is connected to a reduction in the incidence of colon cancer and osteoporosis. In the elderly, regular physical activity is associated with an improved physical function and an independent living. Physically active individuals are less likely to develop depressive illnesses compared to those with lower level of physical activity, and in those with mild-to-moderate depression and anxiety, prescribed physical activity is associated with an improvement in symptoms. (Kesäniemi et al. 2001.) There are also favorable impacts with physical activity on several cardiovascular risk factors, as reduced blood pressure, improvement in the plasma lipid profile, enhanced insulin sensitivity and glycemic control, and benefits in coagulation, hemostatic factors and inflammatory defense systems. (Kesäniemi et al. 2001, Bassuk & Manson 2010).

Many epidemiological studies have shown, that sedentary time predicts all-cause mortality (Katzmardyk et al. 2009), obesity (Hu et al. 2003, Jakes et al. 2003), type 2 diabetes (Hu et al. 2001; Hu et al. 2003), abnormal glucose metabolism (Dunstan et al. 2004, Dunstan et al. 2007), the metabolic syndrome (Bertrais et al. 2005, Ford et al. 2005, Dunstan et al. 2005), high blood pressure (Jakes et al. 2003), and cardiovascular disease (Kronenberg et al. 2000) independent from exercise. Television watching time is frequently used as a measure of inactivity because it is a major form of inactivity and easy for subjects to report. Men and women who spend more time watching TV are more likely to smoke and drink alcohol and less likely to exercise, so adjustment is needed to find out the independent effect of inactivity on risk factors (Hu et al. 2001, Hu et al. 2003, Dunstan et al. 2004).

3.1 Physical activity, inactivity and all-cause mortality

Several studies strongly support an inverse relationship between physical activity and all-cause mortality rates. Physical Activity Advisory Committee (2008) reviewed 73 studies reporting associations with physical activity and all-cause mortality. According to this review, active individuals have approximately a 30% lower risk of dying during follow-up, compared with inactive individuals. The youngest subjects were 16 years old, but most studies included middle-aged subjects aged 40 years and older. Reasonable evidence was found in studies using subjects aged 65 years and older. Most of the studies employed healthy subjects. However, several studies included patients with coronary artery disease or at high risk, and patients with diabetes. These studies have assessed different domains of physical activity including leisure-time activity, occupational activity, household activity, and commuting activity, from which the leisure-time physical activity and especially walking are mostly used. (Physical Activity Guidelines Advisory Committee 2008.)

In addition to the convincing evidence about health benefits of moderate-to-vigorous intensity physical activity, there is increasing interest in identifying the health risks associated with sedentary behaviors. Morris et al. (1953), as a pioneers in modern exercise science, found that people with jobs that involve much sitting (bus drivers and mail sorters) have about twice the rate of cardiovascular disease than those with jobs requiring more standing and ambulatory activities (bus conductors and mail carriers)(Morris et al. 1953). Weller & Corey (1998) related daily sitting time to CVD mortality. After adjusting for age, they found that CVD mortality was 2.7-fold greater in women sitting more than a half of their waking hours compared to women sitting less than a half of their waking hours. Further adjustment to other confounding factors did not alter the estimates of the odds ratios. (Weller & Corey 1998.) Manson et al. (2002) assessed the relation between hours spent sitting, lying down or sleeping, and the risk of cardiovascular events in 73 743 women. After accounting for age and recreational energy expenditure, the relative risk of cardiovascular disease was 1.38 among women who spent 12 to 15 hours per day lying down or sleeping and 1.68 among women who spent at least 16 hours per day sitting, as compared with those who spent less than 4 hours per day sitting (Manson et al. 2002.) The dose-response relationship between daily sitting time and

mortality rates has been found to be similar among those who are physically inactive and active, among nonsmokers, former smokers and current smokers, and across BMI categories (figure 6) (Katzmardyk et al. 2009).
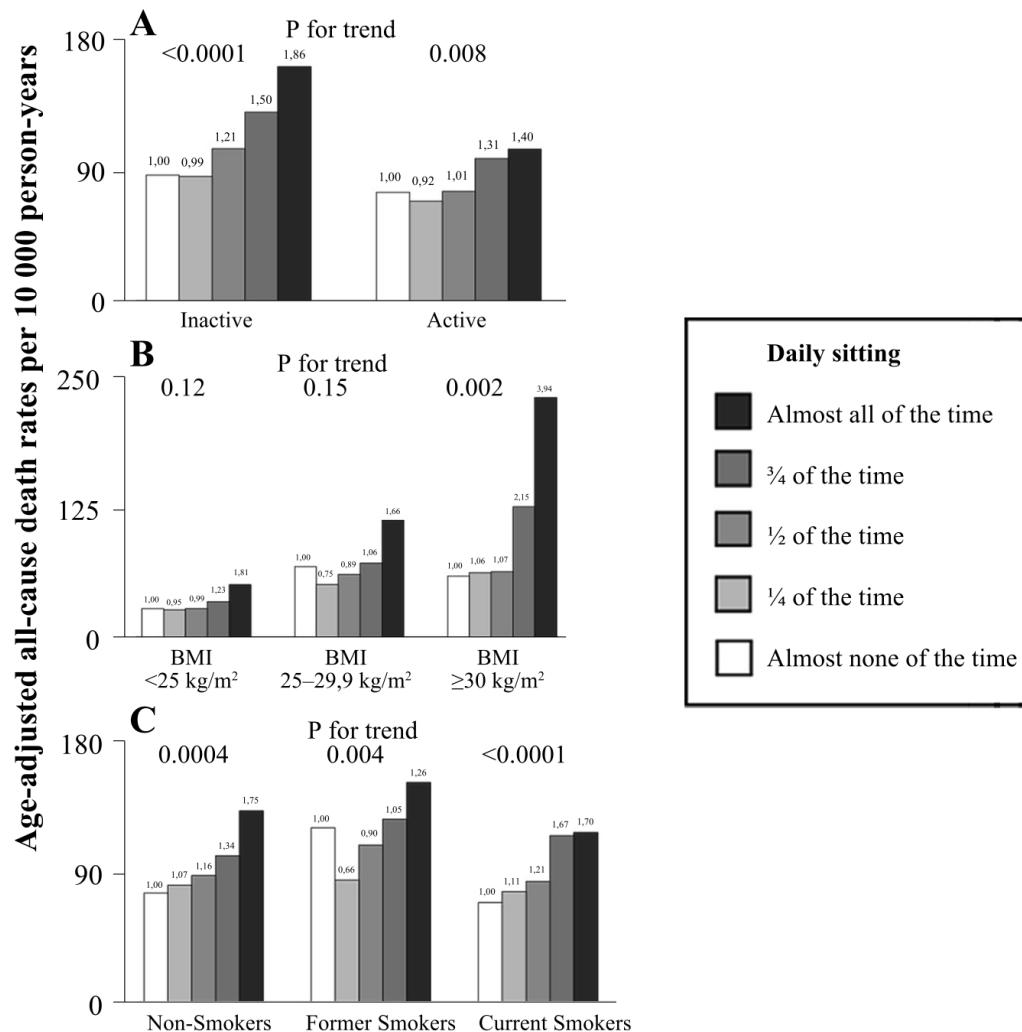
FIGURE 6. Age-adjusted all-cause death rates across categories of daily sitting time in subgroups defined by **(A)** leisure time physical activity (defined as ≥7.5 METh/wk), **(B)** body mass index, and **(C)** smoking status in 17 013 men and women from the Canada Fitness Survey, 1981–1993. The height of the bars indicates the mortality rates, and the numbers atop the bars are the hazard ratios from the proportional hazards regression. (Adapted from Katzmardyk et al. 2009.)

3.2 Dose-response relationship

The dose-response relation can be assessed with different dimensions of physical activity, such as the total volume of energy expended, the intensity of the physical activity

carried out, the duration of physical activity, or the frequency of physical activity. Most of the evidence is related to the effect, or benefits, of regular physical activity rather than addressing the relationship between dose and response. (Kesäniemi et al. 2001, Physical Activity Guidelines Advisory Committee 2008.) Different studies assess one or more domains of physical activity, including leisure-time, household, occupation, and commuting activity. In analyses subjects are classified using different classification schemes, such as by energy expended, duration of activity, and frequency of activity, or grouped by general physical activity descriptions, such as "sedentary", "light", "moderate" and "heavy". Thus, the accurate equation of actual energy expenditure or amount of activity between different studies is challenging. (Physical Activity Guidelines Advisory Committee 2008.)

3.2.1   Total amount of physical activity

Most of the studies that show an inverse relationship between physical activity and all-cause mortality primarily have assessed leisure-time physical activity, including walking. However, there is some evidence, that it may be the overall volume of energy expended, regardless of which activities produce this energy expenditure, which lowers the risk of mortality. Specifically, it seems clear, that the equivalent of at least 2 to 2.5 hours per week of moderate-intensity physical activity, walking 2 or more hours per week, or consuming 1000 kilocalories or 10 to 20 MET-hours per week in physical activities is sufficient to significantly decrease all-cause mortality rates. Additionally, more intensive activity, or faster pace of walking, compared with lower intensity or pace, is associated with lower risk. Thus, the message "some is good; more is better", is adequate to represent the evidence. (Physical Activity Guidelines Advisory Committee 2008.)

In the Shanghai Women's Health Study as amounts of energy expended on nonexercise activities (activities other than leisure-time activity, including household chores, walking and cycling as part of commuting, and climbing stairs) increased, rates of all-cause mortality declined (figure 7). Women who reported no regular exercise but 10 or more metabolic equivalent –hours/day of non-exercise activity were at 25–50% reduced risk relative to less active women (0–9.9 METh/day). Women who reported the least non-exercise activity but regular exercise participation, were also found to be at lower risk,

but there were only minimal differences in the mortality between women reporting and not reporting exercise at the highest levels of non-exercise activity. (Matthews et al. 2007.)
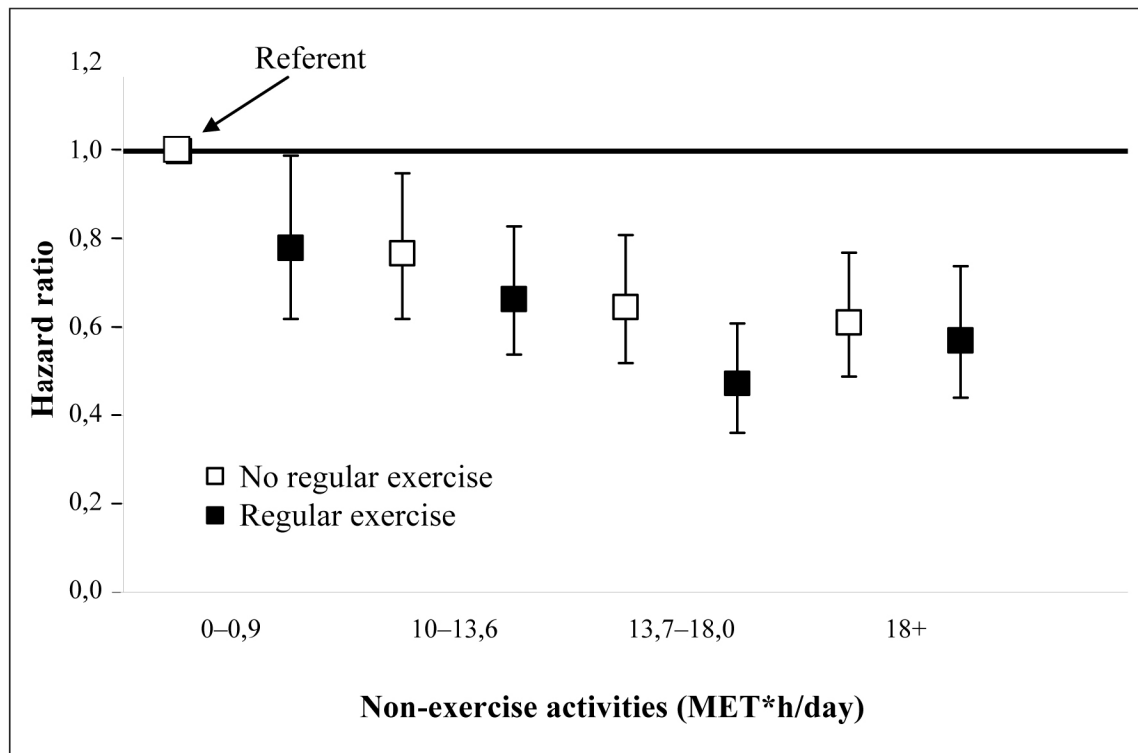
FIGURE 7. Risk for all-cause mortality by exercise and non-exercise physical activity, the Shanghai Women's Health Study, 1997–2004. Adjusted for age, marital status, education, household income, smoking, alcohol drinking, number of pregnancies, oral contraceptive use, menopausal status, and several chronic medical conditions, such as diabetes, hypertension, respiratory disease, and chronic hepatitis. (Adapted from Matthews et al. 2007.)

Manini et al. (2006) used double-labeled water to determine associations between free-living activity energy expenditure and all-cause mortality in 302 healthy older adults (aged 70–82 years). They divided subjects in tertiles according to their free-living activity energy expenditure (low <521kcal/d, middle 521–770kcal/d, high >770kcal/d) and found out that absolute risk of death was 12.1% in the highest tertile vs. 24.7% in the lowest tertile. As a continuous risk factor, an SD increase in free-living energy expenditure (287kcal/d) was associated with a 32% lower risk of mortality. Since self-reported high-intensity exercise and walking for exercise did not differ significantly across the tertiles, the difference in mortality risk was associated with nonexercise physical activity. (Manini et al. 2006.)

Although at least 2 to 2.5 hours per week of moderate intensity physical activity is needed to significantly decrease all-cause mortality rates, the Physical Activity Advisory Committee (2008) stated that it does not represent a minimum threshold level for risk reduction. (Physical Activity Guidelines Advisory Committee 2008.) Some data indicate, that already a much smaller amount of physical activity lowers the risk of mortality among populations where physical activity levels are low. In middle-aged women, a significant risk reduction (20–30%) was observed already with 1 to 1.9 hours per week of moderate-to-vigorous intensity leisure-time physical activity, and each level above the reference level had approximately the same risk reduction (Rockhill et al. 2001). In older women, the risk for all-cause mortality was found to be 3.22 higher in women with low physical activity (≤35METh/day) compared with the most active women (>50METh/day), but again no increased risk was found in women with moderate compared with high physical activity (Carlsson et al. 2006). Also the risk factors for chronic diseases were improved as effectively in adults participating in structured exercise as in lifestyle physical activity intervention (Dunn et al. 1999).

3.2.2 Intensity and frequency of physical activity

The effect of intensity and frequency for all-cause mortality is not straightforward, because the more intensive and frequent the exercise is, the bigger is the total volume of energy expended. The importance of the total amount of physical activity, rather than its constituents, is underlined in many review and original articles (Haskell 1994, Lee & Paffenbarger 1996, Pate 1995, Lee et. al. 2001), while in others there is some indication that vigorous-intensity activities may be more preventing (Lee & Paffenbarger 2000), even independent of their contribution to energy expenditure (Slattery et al. 1989, Swain & Franklin 2006, Tanasescu et al. 2002.)

Lee et al. (2004) studied the effect of physical activity frequency on all-cause mortality by following up "weekend warriors", people who carried out 1 to 2 exercises per week during which they consumed energy the recommended ≥1000 kcal/week. Overall, the relative risk for mortality among weekend warriors compared with sedentary men was 0.85. However, after further analysis, among men without major cardiovascular risk factors, weekend warriors had a significantly lower risk of dying, compared with seden-

tary men, but this was not seen among men with at least one major risk factor. (Lee et al. 2004.)

A major reason for limited data about time spent in activities of different intensities is the difficulty to measure sitting time and patterns of spontaneous non-exercise movements (Hamilton et al. 2007). Limitations in determining physical activity guidelines include wide variety of questionnaires used to assess physical activity and numerous different approaches to data analysis and presentation. Physical Activity Guidelines Advisory Committee recommended uniform data collection with respect to the type and characteristics of physical activity, and the use of motion sensors and physiological monitoring to improve the accuracy and reliability of health benefits and dose response. (Physical Activity Guidelines Advisory Committee 2008.)

3.2.3 Physical activity or physical fitness?

Physical activity and physical fitness are closely related to each other. Genetics contribute to fitness considerably, but probably not as much as environmental factors, principally physical activity (Bouchard & Pérusse 1994, 106–118). Blair et al. (2001) included in their review articles that were related to physical activity, physical fitness and health. They found out that both physical activity and fitness were inversely related to fatal and nonfatal health outcomes, and the dose-response gradient for various health outcomes was steeper for cardiorespiratory fitness than for physical activity groups. Authors discussed that the explanation for stronger dose-response –curve for fitness might be that fitness is measured objectively but physical activity is assessed mainly by self-report, which leads to misclassification. (Blair et al. 2001.)

3.3 Metabolic risk factors for chronic diseases

Cardiovascular diseases (CVD) account for the majority of premature morbidity and mortality in the developed world. Most of the risk factors for cardiovascular disease are metabolic in nature and thus modifiable by changes in physical activity. These metabolic risk factors include hypertension, atherogenic dyslipidemia, the axis of insulin resis-

tance to metabolic syndrome to frank type 2 diabetes, and obesity. (Physical Activity Guidelines Advisory Committee 2008.) The precise mechanisms underlying inverse relationship between physical activity and CVD is unclear, but differences in several cardiovascular risk factors may mediate this effect (Mora et al. 2007.)

3.3.1 Chronic physical activity and risk reduction

Paffenbarger et al. (1993) found that men who increased their physical activity index to 2000kcal or more per week during the 11–15 year follow up period had a 17% lower risk of death from coronary heart disease than those who remained more sedentary, but men who beginned moderately vigorous activity (4.5 or more METs) had a 41% lower risk compared to those who did not engage in such activity. Men with consistently normal blood pressure had a 49% lower risk of death from coronary heart disease than those with long-term hypertension. Also, maintenance of lean body mass was found to be associated with a 41% lower risk than those whose body-mass index increased to at least 26. (Paffenbarger et al. 1993.) Tanasescu et al. (2002) concluded from their cohort study, that every 50MET-h/week increase of cumulatively updated physical activity was associated with a 26% reduction in a risk of coronary heart disease (Tanasescu et al. 2002).

Mora et al. (2007) investigated the contribution of individual risk factors to physical activity-related reduction in CVD or CHD events. A large proportion (59%) of the risk reduction was explained by changes in risk factors, such that inflammatory/hemostatic biomarkers (32.6%) and blood pressure (27.1%) were the largest contributors. Traditional lipids (19.1%) had a larger contribution to risk reduction compared to novel lipids (15.5%). Body mass index (10.1%) and hemoglobin A1c (8.9%) had also some contribution. (Mora et al. 2007.)

Thompson et al. (2003) collected a meta-analysis from exercise training trials lasting longer than 12 weeks. They concluded that HDL-C levels increase 4.6% and triglycerides and LDL-C reduce by 3.7% and 5.0%, respectively. Resting blood pressure is reduced 3.4 mmHg (systolic) and 2.4 mmHg (diastolic). Also insulin resistance, glucose intolerance, postprandial hyperglycemia, and possibly hepatic glucose output are re-

duced. All reductions are greater in subjects with greater risk at baseline. (Thompson et al. 2003.)

Carroll & Dudfield (2004) concluded in their review article, that supervised, long-term, moderate to vigorous intensity exercise training improves dyslipidaemic profile in overweight and obese adults with characteristic of the metabolic syndrome, even in the absence of weight loss. When weight loss is achieved, also insulin resistance and glucose tolerance are enhanced and type 2 diabetes is effectively prevented or delayed. Exercise training also decreases blood pressure in overweight and obese individuals. (Carroll & Dudfield 2004.)

Petrella et al. (2005) concluded that participating in a 10 year regular exercise program at later life (68 year old individuals at the beginning) increased fitness by 3.5% and HDL cholesterol by 9% and reduced BMI, triglycerides and insulin by 0.37%, 0.18% and 3%, respectively. The results were significantly different compared to the reference group. In contrast systolic blood pressure, total and LDL cholesterol and waist circumference increased, but significantly less in the exercisers compared to the sedentary individuals. (Petrella et al. 2005.) Frank et al. (2005) found out that 12-month exercise intervention based on physical activity recommendations decreased insulin concentrations by 4% and leptin concentrations by 7%, but there were no changes in glucose or triglyceride concentrations in overweight postmenopausal women (Frank et al. 2005).

3.3.2 Chronic inactivity and risk increment

The effects of extended periods of sedentary behaviors seem to be characterized by metabolic alterations commonly seen in diabetogenic and atherogenic profiles (Katzmarzyk et al. 2009). Television watching time is associated with many adverse biomarkers, such as abnormal glucose, cholesterol, triglyceride and leptin metabolism, and high blood pressure. After adjustment for age, television watching time and fasting and 2-h plasma glucose were positively associated in both men and women. After further adjustment for other risk factors, such as waist circumference, smoking and, physical activity etc., television watching time had a significant positive association with 2-h plasma glucose in women, such that the mean value was 0.5mmol/l higher in those watching >3h of television per day compared with those watching <1h. The relationship was

not seen in fasting plasma glucose. In men the associations were positive, but not statistically significant. (Dunstan et al. 2007.) The number of hours of television watching is inversely associated with HDL cholesterol and Apolipoprotein A1 and positively associated with low density lipoprotein cholesterol and leptin independent of vigorous activity and BMI (Fung et al. 2000.) Inverse association has been also found with television watching time and systolic and diastolic blood pressure, such that in men watching television >4 h/d the values were 2.1mmHg and 1.5mmHg higher compared to men watching <2h/d. Results were adjusted for confounding factors, including age, BMI and vigorous and total physical activity. (Jakes et al. 2003.) Even in a sample of adults who met the physical activity guidelines (≥2.5h/wk of moderate-to-vigorous intensity physical activity), a significant, adverse dose-response relationship of television-watching time were observed with waist circumference, systolic blood pressure, and 2-h plasma glucose in men and women, and with fasting plasma glucose, triglycerides, and HDL-C in women. The results were clinically significant, such that compared with women who watched television less than 0.7 h per day, those who watched more than 2.16h/d had, on average, a 4.2-cm-higher waist circumference. (Healy et al. 2008c.)

Men who watched television for more than 40 h/week had a 2.87 times higher risk for diabetes compared to men watching television <1h/week, when adjusted for smoking, alcohol use, physical activity and other covariates. Even after adjustment for BMI (RR 2.31) and fat and fiber intake did not appreciably change the results. (Hu et al. 2001.) Every additional 2h/d watching television was associated with a 20% increase in risk for diabetes in men and 14% in women, and 23% increase in risk for obesity in women. An increment of 18MET-hours per week (for example very brisk walking for 40 minutes per day) was associated with a 19% reduction in risk for diabetes in men. In women each 1h/d increment of brisk walking reduced the risk for diabetes for 34% and importantly, every 2h/d increment in standing or walking around at home was associated with 12% risk reduction. These findings suggest the importance of reducing sedentary behavior alongside of promoting physical activity in preventing diabetes. (Hu et al. 2001, Hu et al. 2003.)

Likelihood to have metabolic syndrome is increased with increasing inactivity time. Television watching or computer use during leisure time is strongly associated with metabolic syndrome especially in women after adjustment for several confounding fac-

tors, such as leisure time physical activity level, age and smoking (Bertrais et al. 2005). Compared with participants who spend time in front of screen <1h/d in leisure time, the risks for having metabolic syndrome were 1.41 for 1h/d, 1.37 for 2h/d, 1.7 for 3h/d and 2.1 for ≥4h/d. Risk ratios were adjusted for several confounding factors and importantly additional adjustment for physical activity or sedentary behavior minimally affected the risk. (Ford et al. 2005.) Similarly, the adjusted odds ratio of having metabolic syndrome was 2.07 in women and 1.48 in men who watched television for >14h/week compared with those who watched ≤7h/week (Dunstan et al. 2005).

When physical inactivity time is measured more accurately, the association between inactivity time and metabolic risk markers becomes even clearer. Healy et al. (2007) used accelerometers to quantify daily time spent in activities of different intensities. After adjustment for confounding factors including waist circumference, they found that sedentary time was positively and almost linearly associated with 2-h plasma glucose, and light-intensity activity time and moderate-to vigorous intensity activity time were negatively associated. Importantly, light-intensity activity time remained significantly associated with 2-h plasma glucose after further adjustment for moderate-to-vigorous intensity activity, suggesting that replacing inactivity time with light-intensity activities is an important preventive strategy to reduce the risk of type 2 diabetes and cardiovascular disease. (Healy et al. 2007.)

In addition to the effects of total sedentary time, the pattern in which it is accumulated may be also important. Healy et al. (2008b) found out, that total number of breaks in sedentary time was associated with significantly lower waist circumference, BMI, triglycerides, and 2-h plasma glucose, independent of total sedentary time (figure 8). The associations with metabolic risk markers were clinically significant, because those in the highest quartile of breaks in sedentary time had on average a 5.9cm lower waist circumference compared to those in the lowest quartile. The associations with triglycerides and 2-h plasma glucose were attenuated when waist circumference was included in the model. The breaks were on average on light-intensity range, and lasted on average less than 5min. Authors suggested, that breaking prolonged periods of sitting might be a valuable addition to the public health recommendations, but the possible causal nature and biological and behavioral mechanisms require further investigation. (Healy et al. 2008b.)
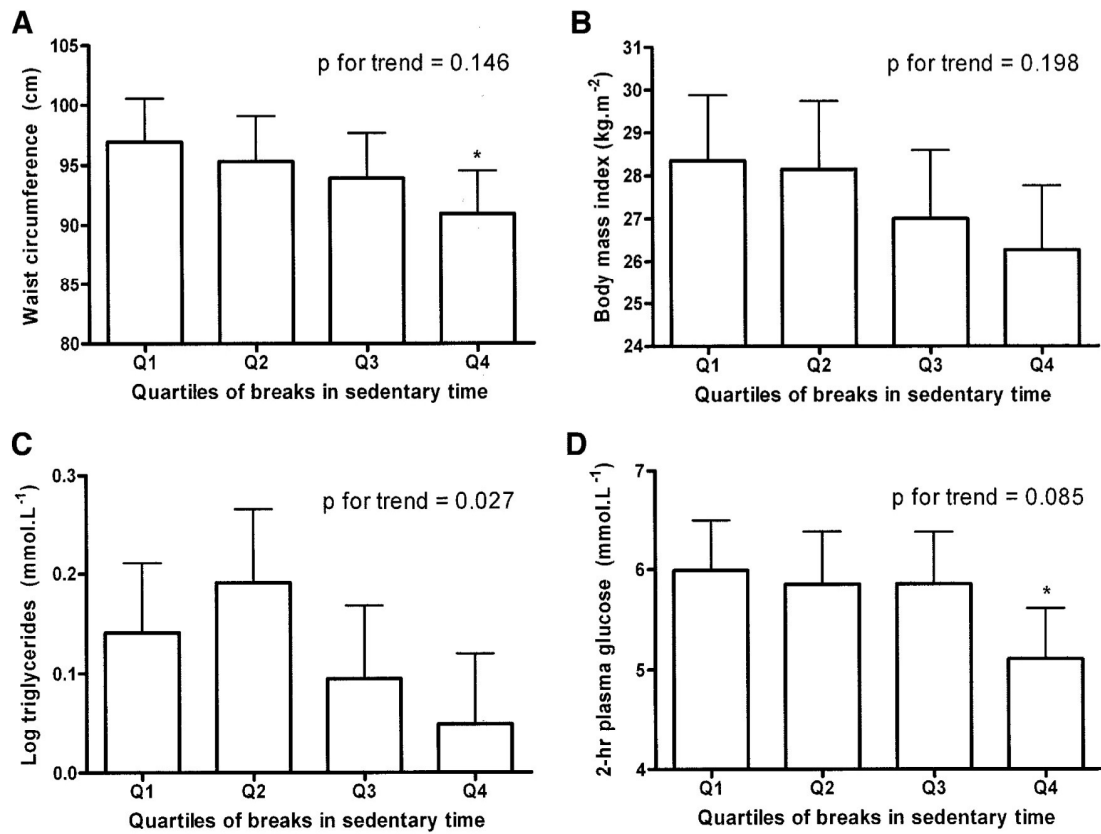
FIGURE 8. Quartiles of breaks in sedentary time with metabolic risk variables: waist circumfe-rence (**A**), BMI (**B**), triglycerides (**C**), and 2-h plasma glucose (**D**). Adjusted for age, sex, em-ployment, alcohol intake, income, education, smoking, family history of diabetes, diet quality, moderate- to vigorous-intensity time, mean intensity of breaks, and total sedentary time. (Healy et al. 2008b.)

4 CELLULAR MECHANISMS OF PHYSICAL ACTIVITY AND INACTIVITY

4.1 Paradigm of inactivity physiology

Recent epidemiologic evidence suggests that sitting time has deleterious metabolic and cardiovascular effects that are independent of whether adults meet physical activity guidelines. There is growing evidence from "inactivity physiology" laboratory studies, that physical inactivity is not only lack of physical activity, but may have separate, unique molecular and physiologic effects that are detrimental for health. In part, this may be because non-exercise 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. (Hamilton et al. 2007, Tremblay et al. 2007.) Thompson et al. (2001) stated that the minimal amount of exercise required to produce an important, acute exercise effect cannot be defined with certainty from the available literature, and even one day of activity, well before traditional standards of physical fitness, can produce significant enhancements in risk factors for metabolic diseases (Thompson et al. 2001).

Hamilton et al. (2007) proposed four tenets, on which inactivity physiology is based:
1. Sitting and limited non-exercise activity may independently increase the risk of chronic diseases.
2. Various times that people spend in sedentary behaviors or participating in exercise training are distinct classes of behavior, with independent effects on risk for disease.
3. The specific cellular and molecular processes during inactivity and exercise are qualitatively different from each other.
4. In people, who do not exercise, further increases in age adjusted rates for diseases cannot be caused by additional exercise deficiency. (Hamilton et al. 2007.)

4.2   Acute effects of exercise on metabolic health markers

Acute effects of physical activity are health-related changes that occur during and in the hours after physical activity, and may disappear rapidly with no influence on the response to subsequent exercise. When repeated, this acute physical activity could also have a cumulative effect, which produce permanent adaptations. The effect of repeated, low-intensity physical activities may also result in small changes that may not be detectable in clinical studies, but when adopted by large populations, still may have a huge effect on public health. (Kesäniemi et al. 2001.)

Physical activity has favorable effects on traditional risk factors, namely blood pressure (Dunn et al. 1999), traditional lipids (total, LDL, HDL cholesterol) (Kraus et al. 2002), insulin resistance and glucose intolerance (Thompson et al. 2001), and obesity (Jakicic et al. 2003). Most individuals experience modest short-term changes of about 5% for blood lipids and 3–5 mmHg for blood pressure (Fagard 2001, Thompson et al. 2001, Mora et al. 2007), but some individuals may achieve much larger changes (Thompson et al. 2003). Oral fat tolerance and the ability to clear intravenously administered triglycerides may be enhanced by 50%. The activity of enzymes involved with lipid metabolism is also altered with increases in lipoprotein lipase activity (LPLA) of approximately 13% and decreases in hepatic triglyceride lipase activity (HTGLA). (Thompson et al. 2001.) Novel lipids (lipoprotein(a), apolipoprotein A1 and B-100) are also associated with risk reduction (Mora et al 2007).

Exercise affects positively also on more recently recognized inflammatory factors. Acute bouts of exercise result in short-term increase in acute-phase reactants and cytokines, which are proportional to the amount of exercise and muscle injury. In contrast, regular exercise is associated with a chronic anti-inflammatory effect. (Kasapis & Thompson 2005.) The mechanism behind this effect is partially related to body weight (Mora et al. 2006), but includes also effects on proatherogenic adipokines, insulin-sensitizing pathways, or the hemostatic and antioxidant functions of the coronary endothelium (Hambrecht et al. 2000, Kasapis & Thompson 2005).

Endurance athletes have 40–50% higher serum high-density lipoprotein (HDL), 20% lower triglyceride (TG) and 5–10% lower low-density lipoprotein (LDL) cholesterol concentrations than their sedentary counterparts (Thompson et al. 1991, Thompson et al. 2001). Acute effects of exercise can explain at least some of the differences in lipids and lipoproteins between trained and untrained individuals. In an exercise expending 350–400kcal in moderately fit and 1000kcal in well-trained subjects an acute and significant increase in HDL-C has been reported. The acute changes in HDL-C are probably due to enhanced cholesterol delivery to the HDL particle, and it generally parallels the decrease in TGs. The LDL-C generally decreases in trained men after prolonged exercise about 8%, and acute decrease of 5–8% can be seen in hypercholesterolemic men with exercise. (Thompson et al. 2001.)

The reduction in resting systolic and diastolic blood pressure immediately after a bout of aerobic exercise has been termed "postexercise hypotension". This effect can be expected after moderate-intensity dynamic exercise in normotensive and hypertensive middle-aged and older people, with the largest absolute and relative blood pressure reductions seen in hypertensive subjects. Maximal decreases of 18–20mmHG in systolic and 7–9mmHG in diastolic blood pressure has been reported. It has been found that postexercise hypotension may persist for up to 16h after exercise. (Thompson et al. 2001.)

Even a single session of exercise can improve glucose control in type 2 diabetics and decrease insulin resistance in other subjects. Unfortunately, this acute improvement in insulin sensitivity is short-lived and lasts only for several days. A single exercise session increases the skeletal muscle's insulin sensitivity and ability to resynthesize glycogen probably by increasing the muscle's number and activity of the GLUT 4 glucose transporters and the content and activity of hexokinase. The acute effects of exercise on insulin sensitivity may relate to depletion of muscle glycogen or triglycerides. Depletion of muscle glycogen leads to enhanced glucose uptake, and muscle triglyceride content is inversely related to insulin sensitivity and insulin stimulated glucose uptake. Vigorous intensity exercise is required to deplete muscle glycogen stores, but already low level energy expenditure may be enough to produce the acute effect mediated by triglycerides. (Thompson et al. 2001.)

4.3 Acute effects of inactivity on metabolic health markers

Several studies have reported potentially harmful consequences of reduced standing and nonexercise ambulation on metabolic processes. Krogh-Madsen et al. (2010) studied the effects of reducing daily steps from about 10 500 to about 1350 for two weeks in ten healthy nonexercising men. As a consequence glucose infusion rate was reduced by 17% during hyperinsulinemic-euglycemic clamp due to a decline in peripheral insulin sensitivity. In addition VO_2max and lean mass of legs were decreased. (Krogh-Madsen et al. 2010.) Stephens et al. (2010) studied acute effects of 1 day of sitting on insulin action on 14 healthy recreationally active men and women (age 19-32 years). The whole-body insulin action was 39% lower (P<.001) after one day of sitting compared to a day with minimal sitting condition. There were no significant changes in fasting glucose rate of appearance, hepatic insulin action, or fatty acid oxidation, suggesting that most of the effects of inactivity are mediated in skeletal muscle. After reducing energy intake to balance the reduced energy intake due to prolonged sitting the declined insulin action attenuated, but was not completely prevented. This study suggests the contribution of also other factors than energy surplus that are involved in the detrimental effects of sitting of only one day. (Stephens et al. 2010.)

During bed rest, which is an extreme form of inactivity, attenuation of metabolic processes gets worse. The shortest period used in bed rest studies is three days, which is enough to reduce insulin action (Smoravinski et al. 2000). When a group of previously healthy individuals (n=20) engaged in a 5-day bed rest, there were significant increases in insulin resistance, vascular dysfunction, systolic blood pressure, total cholesterol and triglyceride levels, and there was a trend toward higher LDL cholesterol and diastolic blood pressure. The increase in net response to an oral glucose load was 6% (*P*<.05) for glucose and 67% (*P*<.001) for insulin. The changes in risk markers due to bed rest occurred without changes in systemic inflammatory markers or adiponectin levels. In control subjects continuing normal activity, there was no changes in any of the risk markers. (Hamburg et al. 2007.) Although the progression of systemic proinflammatory state was not seen during 5 days bed rest, sedentary lifestyle and states of insulin resistance are associated with altered levels of circulating cytokines and adipocytokines (Mora et al. 2006, Goldstein & Scalia 2004).

Vascular dysfunction was found to develop after less than 48 hours of bed rest, even though subjects were allowed to get out of bed for up to 30 minutes per day. The concurrent development of vascular dysfunction and a rise in risk markers suggests their common mechanism (Hamburg et al. 2007). Reduced resting blood flow during inactivity and the resulting reduction in local shear stress decrease the expression of endothelial nitric oxide synthase and induce production of reactive oxygen species and endogenous vasoconstrictors, that alter vascular function (Suvorava et al. 2004, Laufs et al. 2005). These again may contribute to the development of insulin resistance and cardiovascular diseases (Wheatcroft et al. 2003, Kim et al. 2006). Also diminished basal sympathetic activity, which attenuates sympathoadrenal response to feeding, may mediate the adverse effects of acute inactivity (Smoravinski et al. 2000).

Smoraviski et al. (2000) found out that even though a three days bed rest was enough to increase the plasma insulin response to an oral glucose tolerance test, the blood glucose response after bed rest was significantly higher only in sedentary men, whereas in athletes the decrement in peripheral insulin sensitivity was compensated by enhancement of the insulin secretion. (Smoravinski et al. 2000.) In addition, Stettler et al. (2005) showed that 60h bed rest associated with high-saturated fat intake was enough to impair insulin sensitivity in healthy humans, but if moderate physical activity was performed after the treatment there were no signs of insulin resistance. (Stettler et al. 2005).

4.4 Effects of energy surplus on insulin resistance

Obesity epidemic has arisen from gradual weight gain in the population produced by very small difference between energy intake and energy expenditure (Brown et al. 2005). The mechanisms behind adverse effects during acute inactivity could be related to energy surplus. Nutrient excess leading to increased availability of free fatty acids and amino acids induce directly insulin resistance because they interfere with insulin signaling and thus inhibit glucose transport and the insulin dependent rise of glucose-6-phosphate. (Krebs & Roden 2004.)

High-fat diets induce insulin resistance in rats (Oakes et al. 1997, Hancock et al. 2008) and human (Lovejoy et al. 2001), although only in overweight subjects (Lovejoy et al. 2002). Short-term lipid infusion increases plasma concentrations of free fatty acids (FFA) and induces hyperglycemia (Roden et al. 2000). Roden et al. (1996) studied the mechanism by which lipids cause insulin resistance in humans by nuclear magnetic resonance spectroscopy. The authors found out, that instead of direct inhibition of pyruvate dehydrogenase by FFAs, elevation in plasma FFAs caused insulin resistance by inhibiting glucose transport and/or phosphorylation, which again resulted in reduction in rates of glucose oxidation and muscle glycogen synthesis (figure 9). (Roden et al. 1996.)

High protein intake is associated with insulin resistance and glucose intolerance in humans (Linn et al. 2000). Many amino acids are metabolized to acetyl-CoA and undergo mitochondrial oxidation, suggesting a similar hypothesis of direct competition between substrates as between glucose and FFAs (Krebs & Roden 2004). Again, nuclear magnetic resonance spectroscopy showed that a twofold rise in plasma amino acids was associated with a 25% decrease in insulin stimulated whole body glucose disposal. The effect was preceded by an impaired rise in intramuscular glucose-6-phosphate concentrations and followed by a 64% reduction in rates of glycogen synthesis, suggesting inhibiting effects of amino acids on glucose transport/phosphorylation (figure 9). (Krebs et al. 2002.)

The phenomenon that hyperglycemia per se explains a part of insulin resistance has been termed glucose toxicity. Lowering plasma glucose by insulin therapy enhances insulin resistance in type 1 diabetes patients, but only moderate effect is seen in type 2 diabetic patients. This suggests that the insulin resistance of type 2 diabetes patients is the cause rather than the consequence of hyperglycemia. (Krebs & Roden 2004.)
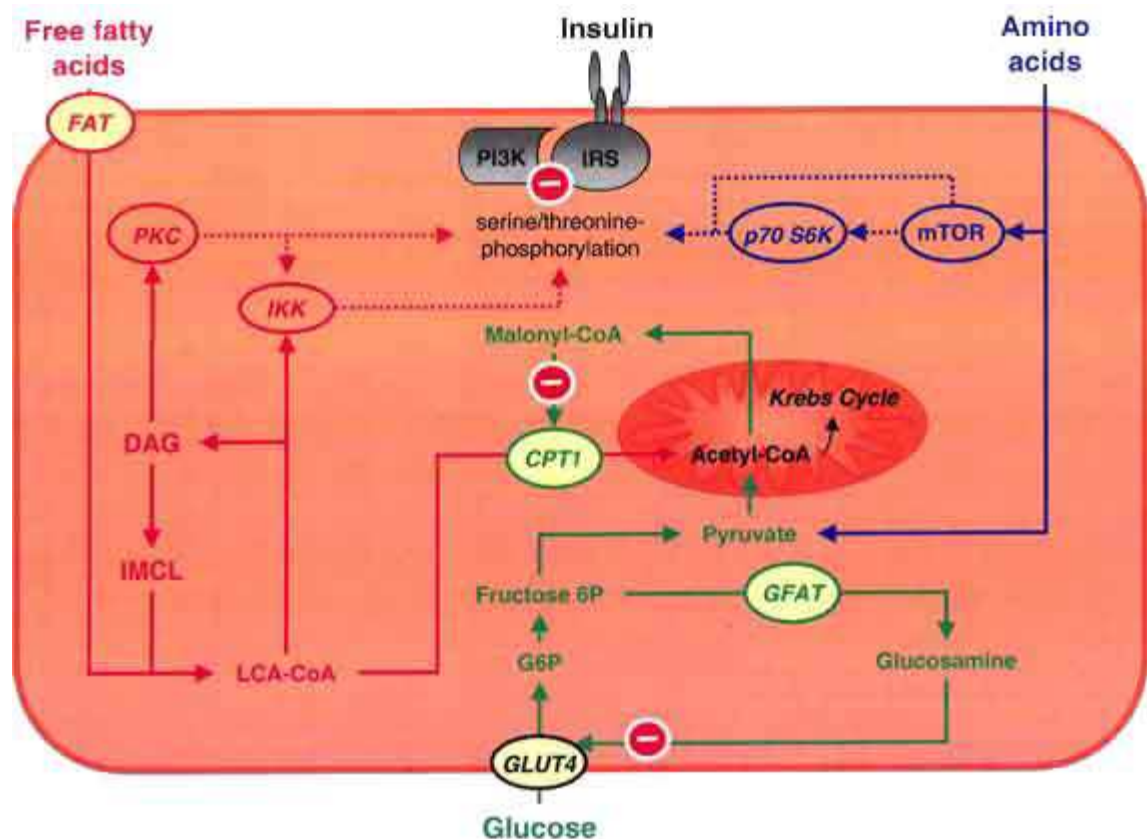
FIGURE 9. Potential mechanisms of nutrient induced skeletal muscle insulin resistance include inhibiting effect of free fatty acids on muscular glycogen synthesis, activating effect of amino acids on mTOR/p70 S6 kinase pathway which phosphorylates insulin receptor substrates, and formation of glucosamine and malonyl-CoA by hyperglycemia, which inhibit glucose uptake and augment cytoplasmic long-chain fatty acid CoA pool (Krebs & Roden 2004.)

4.5 Lipoprotein lipase activity

A consensus panel concluded that altered triglyceride metabolism reflects the strongest category of evidence for diseases related to inactivity (Kesäniemi et al. 2001, Bouchard 2001). Lipoprotein lipase (LPL) enzyme is present at the vascular endothelium and it has a central role in several aspects of lipid metabolism. LPL is capable of breaking down plasma triglycerides of triglyceride-rich lipoproteins, including chylomicrons and very low density lipoproteins (VLDL). (Tsutsumi 2003.) A decrease in LPL activity impairs optimal tissue-specific uptake of lipoprotein-derived fatty acids and is associated with an increase in plasma triglycerides (Bey & Hamilton 2003, Gotoda et al. 1991, Herd et al. 2001) and decrease in high density lipoprotein (HDL) cholesterol (Bey

& Hamilton 2003, Goldberg et al. 1988). These changes may contribute to the risks of metabolic diseases (Austin 1991). On the other hand, higher levels of plasma LPL activity are associated with decreased TG and increased HDL cholesterol, and protection against atherosclerosis (Tsutsumi et al. 1993).

LPL is synthesized in a number of tissues and is regulated in a tissue-specific manner by nutrients and hormones (table 2). Feeding increases LPL activity in adipose and muscle tissue. (Wang & Eckel 2009.) Kiens et al. (1989) concluded that physiological concentrations of insulin decrease muscle LPL activity in proportion to the effect of insulin on muscle glucose uptake. In contrast, muscle contractions cause a local transient increase in muscle LPL activity. (Kiens et al. 1989.) During body immobilization in rats adipose tissue LPL activity was decreased but skeletal muscle, heart and adrenal LPL activities were increased. The authors discussed that this could be related to high catecholamine levels in plasma during stress caused by immobilization (Ricart-Jané et al. 2005)

TABLE 2. Responses of adipose tissue and skeletal muscle LPL to nutritional and hormonal signals and to metabolic disease states (Wang & Eckel 2009).

| Condition	Subcutaneous Adipose Tissue LPL	Skeletal Muscle LPL
Fasting	↓	↑
Feeding		
High CHO	↑↑	↑
High fat	↑	±↑
Exercise	Variable	±↑
Insulin	↑↑	↓
Catecholamines	↓	No change
Thyroid hormone	↓ in rat, ↑ in human	↓
Estrogen	↓	↑
Testosterone	↓	↑
Obesity	↑↑ (/cell)	±↓
Diabetes	↓	↓

4.5.1 LPL regulation during exercise

In fit subjects acute extreme exercise increases fat tolerance and LPL activity (LPLA). In untrained individuals as little as 1h at 80% of maximal heart rate has been shown to increase LPLA, leading to hypothesis that exercise acutely depletes intramuscular triglycerides, which stimulates the synthesis of translocation of LPL, which hydrolyzes triglycerides from lower-density lipoproteins with transfer of the excess surface cholesterol to the HDL particle. (Thompson et al. 2001.) Acute exercise does not change the already high LPLA of most oxidative muscle fibers recruited for posture allocation, suggesting the different threshold and mechanism for LPLA in different muscle fiber types (Hamilton et al. 1998).

Skeletal muscle LPL activity increases following short-term exercise training in rats (Hamilton et al. 1998) and in humans (Seip et al. 1997). In rat hindlimb white skeletal muscles the LPL mRNA concentration and LPL immunoreactive mass was found to increase about threefold following short-term voluntary run training, increasing total LPL enzyme activity. LPL regulation was not enhanced in a white muscle that was not recruited, and not either on the oxidative muscle sections, indicating that local contractile activity is necessary for the exercise-induced increase in LPL expression. According to that, in all muscle types (especially oxidative muscles) of control rats LPL levels were already high because of postural activity. In rats with immobilized hindlimbs LPL expression was several times lesser than in rats with normal postural activity. (Hamilton et al. 1998.) The transient temporal pattern for LPL expression after stopping exercise proposes that regulation is pretranslational (Seip et al. 1997, Hamilton et al. 1998).

4.5.2 LPL regulation during inactivity and low-intensity activity

A comprehensive illustration of LPL activation during inactivity and low intensity activity is presented in the study of Bey & Hamilton (2003). Heparin-releasable (HR) LPL activity was significantly reduced after eleven days of inactivity, but there was no statistical difference between a single day of inactivity and 11 days of inactivity (figure 10A). After 4h lag period, unloading of the soleus and red quadriceps (RQ) muscles caused the mono-exponential decrease of both HR-LPL and intracellular LPL activities (figures

10B, C and D), such that the half-life for LPL in both muscles was 2 hours. 4h standing and slow walking was enough to return the LPL activity back to control levels after 12h hindlimb unloading (figures 10B and C) without increase in LPL mRNA concentration suggesting a posttranslational regulation. (Bey & Hamilton 2003.)
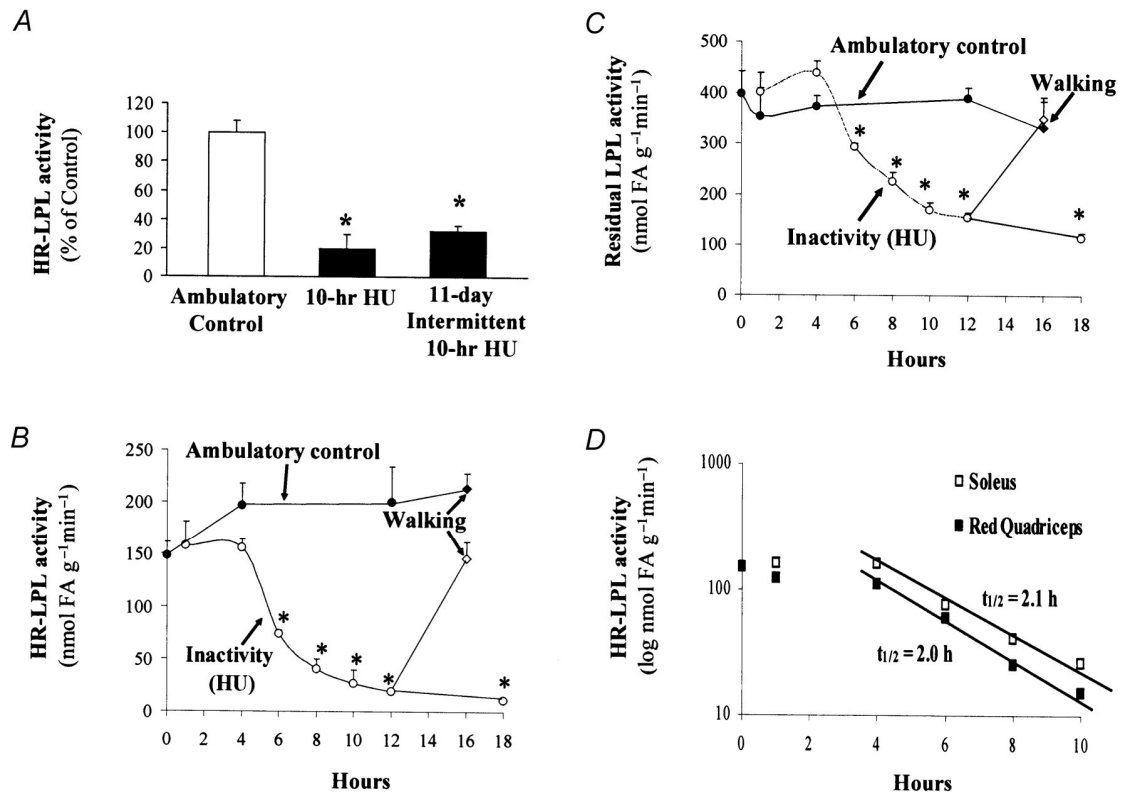
FIGURE 10. Time course for the decrease in muscle LPL activity after inactivity (HU, hindlimb unloading) compared with low-intensity ambulatory activity. (Bey & Hamilton 2003.)

Table 3 lists differences in LPL regulatory processes during physical inactivity and exercise. LPL mRNA did not change in any muscle type when comparing inactivity with lower intensity ambulatory activity, suggesting that there is a threshold for the process increasing LPL mRNA. However, there is not such a threshold for the process regulating capillary LPL activity, because even the normal ambulatory activity maintains LPL activity many fold more compared with the LPL activity in the inactive muscle. Compared to sedentary, during control ambulatory activity all muscle types in the rat had greater LPL activity, but running only increased LPL activity and protein in the fast white muscles and had no effect on any of the oxidative muscle sections (Hamilton et al. 1998.)

TABLE 3. Lipoprotein lipase regulatory processes at the two ends of the physical activity continuum. Results from Hamilton et al. 1998 and Bey & Hamilton 2003 (adapted from Hamilton et al. 2004).

	Referent Control	
	Effects of Physical Inactivity	Effects of Intense Exercise
LPL mRNA	No change in LPL mRNA in any red oxidative or white glycolytic muscles	↑ LPL mRNA in all white glycolytic leg muscles; no change in oxidative muscles of rats with already high levels of ambulatory activity and LPL mRNA
LPL protein	↓ LPL protein concentration without ↓ in LPL mRNA concentration	↑ LPL protein may be partly because ↑ LPL mRNA in glycolytic muscles
LPL activity	↓ 10–20 times in LPL activity in red oxidative muscle sections and 50% ↓ white glycolytic sections	2–3 times ↑ in LPL activity in white glycolytic fibers; no change in red oxidative muscles when compared with referent ambulatory control
Time course for LPL activity	In most oxidative red muscles, ↓ LPL activity begins 4–6 hours after initiating inactivity, reaches steady state after ~18 hrs; chronic (11 days) and acute (12–18 hours) have similar LPL effects	↑ LPL activity after exercise that does not even begin to return to ambulatory control levels 27 hours after last exercise bout

Methods, results and discussion will be published in scientific journals and are not presented here.

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