

Department of General Practice and Primary Health Care
Institute of Clinical Medicine
Faculty of Medicine
University of Helsinki
Finland

INFLUENCE OF EXERCISE TRAINING ON DAILY PHYSICAL ACTIVITY AND RISK FACTORS FOR TYPE 2 DIABETES

Niko Wasenius

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Supervisors:

Professor Johan Eriksson
Department of General Practice and Primary Health Care
Institute of Clinical Medicine,
University of Helsinki
Helsinki, Finland

Emeritus Professor Esko Mälkiä
Department of Health Sciences
University of Jyväskylä
Jyväskylä, Finland

Reviewers

Professor Norman Morris
School of Allied Health Sciences
Griffith University
Brisbane, Australia

Docent Arto Hautala
Department of Exercise and Medical Physiology
VerveResearch
Oulu, Finland

Opponent

Docent Katriina Kukkonen-Harjula,
UKK Institute
Tampere, Finland

and

South Karelia Health Social and Health Care District (Eksote)
Lappeenranta, Finland

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CONTENTS

CONTENTS	1
LIST OF ORIGINAL PUBLICATIONS	3
ABBREVIATIONS	4
ABSTRACT	7
TIIVISTELMÄ	8
1 INTRODUCTION	9
2 REVIEW OF THE LITERATURE	11
2.1 Physical activity.....	11
2.1.1 Definition and categorization	11
2.1.2 Determinants of physical activity	12
2.1.3 Measurement methods	15
2.1.4 Physical activity related guidelines for health.....	25
2.2 Modulation of Physical activity	29
2.2.1 Physical activity transition.....	29
2.2.2 Regulation of physical activity	32
2.2.3 Exercise and total physical activity.....	35
2.3 Physical activity and prevention of type 2 diabetes	40
2.3.1 Type 2 diabetes, IFG, and IGT	40
2.3.2 Risk factors for type 2 diabetes.....	41
2.3.3 The independent effects of exercise on risk factors of type 2 diabetes	46
2.4 Summary of previous research	54
3 AIMS OF THE STUDY	55
4 MATERIALS AND METHODS	56
4.1 Study design and subjects in study I	56
4.2 Study design and subjects in studies II–IV	56
4.3 Physical activity interventions (I–IV)	57
4.3.1 Rehabilitation intervention (I)	57
4.3.2 Nordic walking intervention (II–IV)	58
4.3.3 Power type resistance training intervention (II–IV).....	59
4.3.4 Non-exercise control intervention (II–IV)	61
4.4 Measurements.....	61
4.4.1 Physical activity (I–IV)	61
4.4.2 Analysis of physical activity data (I–IV).....	63
4.4.3 Physical capacity (I–IV)	64
4.4.4 Dietary intake (II–IV)	64
4.4.5 Anthropometrics and body composition (I–IV)	65
4.4.6 Blood pressure (II–IV).....	65
4.4.7 Blood samples and clinical analysis (II–IV).....	65
4.5 Statistical analysis (I–IV)	66
5 RESULTS	68
5.1 The effect of rehabilitation intervention on daily physical activity (I)	68

5.2	The effect of structure exercise intervention on daily physical activity (II–III).....	70
5.2.1	Adherence to training and physical dose of structured exercise interventions (III)	70
5.2.2	The effect of structured exercise intervention on total physical activity (II).....	70
5.2.3	The correlates of change in physical activity during structured exercise intervention (II)	71
5.2.4	Between the group comparison of leisure-time physical activity during exercise intervention (III)	73
5.3	Effect of exercise intervention on risk factors for type 2 diabetes (IV)	75
5.3.1	Baseline data (IV).....	75
5.3.2	Between the group comparison (IV).....	75
5.4	Independent predictors of body composition and physical capacity responses to exercise intervention (unpublished)	77
6	DISCUSSION	80
6.1	Main findings	80
6.2	Interpretation of the results.....	80
6.2.1	The effect of rehabilitation interventions on higher intensity physical activity (I).....	80
6.2.2	The effect of exercise interventions on higher intensity physical activity (I).....	81
6.2.3	The effect of physical activity interventions on total physical activity (I–II).....	82
6.2.4	The effect of structured exercise on risk factors of type 2 diabetes (IV)	85
6.2.5	Leisure-time physical activity and response to exercise (Unpublished)	87
6.3	Methodological considerations.....	89
6.4	Strengths and weaknesses of the study	92
6.5	Implications of the findings.....	93
6.6	Implications for further studies.....	94
7	CONCLUSIONS AND FUTURE DIRECTIONS.....	95
	ACKNOWLEDGEMENTS	96
	REFERENCES	98
	ORIGINAL PUBLICATIONS.....	127

LIST OF ORIGINAL PUBLICATIONS

- I. Wasenius N, Karapalo T, Sjögren T, Pekkonen M, Mälkiä E. Physical dose of therapeutic exercises in institutional neck rehabilitation. *J Rehabil Med*, 2013;54 (3):300–307.
- II. Wasenius N, Venojärvi M, Manderoos S, Surakka J, Lindholm H, Heinonen OJ, Aunola S, Eriksson JG, Mälkiä E. The effect of structured exercise intervention on intensity and volume of total physical activity. *J Sports Sci Med*, 2014;13:829–835.
- III. Wasenius N, Venojärvi M, Manderoos S, Surakka J, Lindholm H, Heinonen OJ, Eriksson JG, Mälkiä E, Aunola S. Unfavourable influence of structured exercise program on total leisure-time physical activity. *Scand J Med Sci Sports*, 2014;24 (2):404–413.
- IV. Venojärvi M, Wasenius N, Manderoos S, Heinonen OJ, Hernelahti M, Lindholm H, Surakka J, Lindström J, Aunola S, Atalay M, Eriksson JG. Nordic walking decreased circulating chemerin and leptin concentrations in prediabetic middle-aged men. *Annals of Medicine*, 2013;45 (2):162–170.

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In addition, some unpublished data are presented.

ABBREVIATIONS

%HRR	Percentage of heart rate reserve
%Peak-MET	Relative peak intensity (percentage of METc)
%TWA-MET	Relative time-weighted average intensity (percentage of METc)
%VO_{2max}	Percentage of maximum oxygen uptake
%VO_{2maxR}	Percentage of maximum oxygen consumption reserve
²H	Deuterium (stable isotope of hydrogen)
¹⁷O	Stable isotope of oxygen
¹⁸O	Stable isotope of oxygen
95% CI	95% confidence intervals
ACC	Accelerometer
ACSM	American College of Sports Medicine
AD	Anno Domini
AMI	Activity metabolic index
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AT	Aerobic training
ATPA	Activity time physical activity (OPA+CPA+LTPA)
BC	Before Christ
BMI	Body mass index
BMR	Basal metabolic rate
BPM	Beats per minute
C	Control
CaO₂	Arterial oxygen content
CDC	Center of Disease Control and Prevention
CMJ	Countermovement jump
CO₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPA	Commuting physical activity
CSEP	Canadian Society of Exercise Physiology
C_vO₂	Venous oxygen content
DAN	Diabetic autonomic neuropathy
DRD₁	Dopamine receptor D ₁
DRD₂	Dopamine receptor D ₂
DRD₄	Dopamine receptor D ₄
DRI	Dietary reference intakes
E	Energy
EX	Exercise
F	Force
FAO	Food and Agriculture Organization
FDPS	Finnish diabetes prevention study

FLEX-HR	Flex heart rate
γ-GT	Gamma-glutamyl transpeptidase
GLUT4	Glucose transporter 4
GWAS	Genome-wide association study
HbA_{1c}	Glycated haemoglobin
hc-CRP	High-sensitive C-reactive protein
HDI	Human developmental index
HDL	High-density lipoprotein
HIT	High-intensity training
HOMA-IR	Homeostasis model assessment for insulin resistance
HR	Heart rate
IDEEA®	Intelligent device for energy expenditure and activity
IFG	Impaired fasting glucose
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
IL-6	Interleukin 6
IL-1b	Interleukin 1 beta
IPAQ	International physical activity questionnaire
IQR	Interquartile range
ISO	International Organization for Standardization
J	Joule
kcal	Kilocalorie
kJ	Kilojoule
KELA	Social Insurance Institution of Finland
LDL	Low-density lipoprotein
LSD	Least significant difference
LTPA	Leisure-time physical activity
MC4R	Melanocortin 4 receptor
MET	Metabolic equivalent of task
MET_c	Maximum oxygen consumption in MET
METH	MET-hours
MET_{min}	MET-minutes
MHPA	Miscellaneous physical activity
NCD	Non-communicable diseases
NAFLD	Non-alcoholic fatty liver disease
NEAT	Non-exercise activity thermogenesis
NEPA	Non-exercise physical activity
NHLH2	Nescient helix-loop-helix 2
NLTPA	Non-leisure-time physical activity
NOWASTEP	Nordic walking and strength exercise program
NW	Nordic walking
O₂	Oxygen
OPA	Occupational physical activity
P	Power
PAI	Physical activity index

PAL	Physical activity level
PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2
PAR	Physical activity rate
Peak-MET	The peak intensity within an activity cycle
Q	Quartile
r	Correlation
RAS	Relative physical activity strain
RBP4	Retinol binding protein 4
RCT	Randomized controlled trial
RER	Respiratory exchange ratio
RIPA	Rehabilitation intervention physical activity
RM	Repetition maximum
RPE	Rating of perceived exertion
RQ	Respiratory quotient
RR	Relative risk
RT	Resistance training
s	Distance
s	Second
SACN	Scientific Advisory Committee on Nutrition
SD	Standard deviation
SE	Standard error
SJ	Squat jump
SLC2A4	Solute carrier family 2 facilitated glucose transporter, member 4
SNPs	Single nucleotide polymorphisms
SPEA	Structured physical exercise activity
SPSS	Statistical package for social sciences
STF	Standard timeframe
SWA	SenseWear Armband
TNF-a	Tumor necrosis factor alpha
Total LTPA	LTPA + SPEA
TWA-MET	Time-weighted average intensity of an activity cycle
UNU	United Nations University
USD	The United States dollar
VAS	Visual analog scale
VCO₂	Carbon dioxide production
VO₂	Oxygen consumption
VO_{2max}	Maximum oxygen uptake
VO_{2peak}	Peak oxygen uptake
V_s	Stroke volume
W	Work
W	Watt
WHO	World Health Organization

ABSTRACT

The prevalence and incidence of non-communicable diseases, which have been associated with physical inactivity, are increasing worldwide. Thus, there is a great need for understanding possibilities to increase health enhancing physical activity. The main aims of this study were to investigate 1) the effects of a 13-day in-patient rehabilitation intervention and a 12-week exercise intervention on the intensity and volume of daily total physical activity and on its subcategories 2) the effect of exercise intervention on risk factors for type 2 diabetes, and 3) the effect of non-structured leisure-time physical activity (LTPA) on response to exercise training.

The study consists of two separate study cohorts. The first data set included subjects ($n = 19$, 16 women and 3 men) with chronic neck or shoulder pain and who participated in active rehabilitation interventions. The second data set included 144 overweight or obese middle aged men with impaired glucose regulation who were randomly allocated into a non-exercise control (C) group, a Nordic walking (NW) group, and a power type resistance training (RT) group. During the 12-week intervention, the exercise groups performed structured supervised exercises three times a week for 60 minutes. In both datasets intensity and volume of physical activity was measured in metabolic equivalents of tasks (MET) and MET-hours before and during the interventions with combinations of objective measurement, diaries, and questionnaires. In the second dataset changes in glucose, lipid, and liver enzymes metabolism, adipocytokines, body composition, blood pressure, physical capacity, and dietary intake were measured with standard methods. The measurements were performed before and after the intervention.

No increase in the volume of total physical activity was observed with either intervention. Both the rehabilitation and NW intervention increased the volume of leisure-time physical activity (LTPA). The weekly increase in the volume of total LTPA (structured exercises + non-structured LTPA) was associated with a decrease in the volume of non-LTPA (other than structured exercise or non-structured exercise). Compared to the control group, especially NW had beneficial effects on the body adiposity tissue and the adipocytokines (leptin and chemerin) associated with the regulation of lipid and glucose metabolism. The intensity of non-structured LTPA during the exercise intervention was found to independently explain 10%, 9%, and 7% of the variation of change in walking speed, body weight, and BMI, respectively. This effect was observed especially after the intensity threshold of 6.3 MET (77% of maximal physical capacity).

Thus, interventions aimed to increase physical activity do not automatically increase the volume of total physical activity due to the compensation. They can, however, increase the volume of LTPA, which can subsequently have beneficial health effect on risk factors of type 2 diabetes. Better understanding of the physical activity regulation in response to training can also increase the specificity of the physical activity dosage.

TIIVISTELMÄ

Fyysiseen inaktiivisuuteen yhdistettyjen elämäntapasairauksien esiintyvyys lisääntyy maailmanlaajuisesti. Tällä hetkellä onkin tarve löytää keinoja, joilla voidaan tehokkaasti lisätä terveyttä edistävää fyysistä aktiivisuutta. Tutkimuksen päätarkoituksena oli selvittää 1) 13 vuorokauden laitoskuntoutusintervention ja 12 viikon ohjatun harjoitteluintervention vaikutusta fyysiseen kokonaisaktiivisuuteen ja sen alakategorioihin, 2) harjoitteluintervention vaikutusta tyypin 2 diabeteksen riskitekijöihin ja 3) ei-ohjatun vapaa-ajan liikunnan vaikutusta harjoitteluintervention vasteeseen.

Tutkimus koostuu kahdesta erillisestä aineistosta. Ensimmäinen aineisto koostuu kahden aktiivisen kuntoutusintervention osallistujista (n = 19, 16 naista ja 3 miestä), jotka kärsivät kroonisesta niska- tai hartiakivusta. Toisessa aineistossa 144 ylipainoista tai lihavaa keski-ikäistä miestä, joilla on häiriintynyt glukoosiaineenvaihdunnansäätely, satunnaistettiin kontrolliryhmään ja kahteen ohjattuun harjoitusryhmään (sauvakävely tai nopeusvoimatyyppinen kuntosaliharjoittelu). Harjoitusryhmät harjoittelivat 12 viikkoa 3 kertaa viikossa 60 minuuttia. Fyysisen aktiivisuuden intensiteetti ja volyyymi mitattiin lepoaineenvaihdunnan kerrannaisina (MET) ja MET-tunteina ennen interventiota ja intervention aikana objektiivisten mittausten, päiväkirjojen ja kyselyiden yhdistelmällä. Tyypin 2 diabeteksen riskitekijät, glukoosi- ja rasva-aineenvaihdunnan ja maksan entsyymien aineenvaihdunnan indikaattorit, adiposytokiinit, kehon koostumus, verenpaine, fyysinen suorituskyky ja ravitsemus mitattiin standardimenetelmillä ennen ja jälkeen intervention.

Fyysisen kokonaisaktiivisuuden (24 tuntia vuorokaudessa) volyyymi ei lisääntynyt kuntoutus- tai harjoitteluintervention seurauksena. Sekä kuntoutus- että sauvakävelyinterventio lisäsivät vapaa-ajan liikunnan volyymia. Mitä enemmän sauva- ja kuntosaliryhmien viikoittainen vapaa-ajan kokonaisliikunnan (ohjattu harjoittelu + ei-ohjattu vapaa-ajan liikunta) volyyymi lisääntyi, sitä enemmän ei-vapaa-ajan liikunnan volyyymi väheni. Verrattuna kontrolliryhmään etenkin sauvakävelyllä oli terveydelle edullisia vaikutuksia kehon rasvakudokseen sekä rasva- ja glukoosiaineenvaihdunnan säätelyyn vaikuttaviin adiposytokiineihin (chemeriini ja leptiini). Lisäksi ei-ohjatun vapaa-ajan liikunnan intensiteetti selitti itsenäisesti 10 % kävelynopeuden, 9 % kehon painon ja 7 % kehon painoindeksin muutoksen vaihtelusta. Tämä vaikutus oli nähtävissä erityisesti 6.3 MET (77% maksimaalisesta fyysisestä suorituskyvystä) raja-arvon jälkeen.

Fyysisen aktiivisuuden lisäämiseen tähtäävät interventiot eivät automaattisesti lisää fyysisen kokonaisaktiivisuuden volyymia kompensatiivisesti johtuen. Ne näyttäisivät kuitenkin lisäävän vapaa-ajan liikunnan volyymia, jolla saattaa olla tyypin 2 diabeteksen riskitekijöihin edullisia terveystuloksia. Nykyistä parempi tietoisuus fyysisen aktiivisuuden säätelymekanismeista interventioiden aikana voi mahdollistaa nykyistä tarkemman terveyttä edistävän fyysisen aktiivisuuden annostelun.

1 INTRODUCTION

Physical activity has played a crucial part in the survival of human beings since the emergence of our ancient ancestors. The ability to move bipedally enabled an energy efficient way to hunt and gather food from large areas to satisfy the energy demands of our exceptional brains (Cordain et al., 1998; Leonard, 2010). Development of brains and liberation of hands due to bipedal gait enabled manufacturing and handling of tools for more efficient food scavenging (Bellisari, 2008). The human endeavors to reduce physical work requirements in order to retrieve food from the environment together with the mechanization and automatization of physical tasks have most likely resulted in a decreased demand of physical effort for subsistence (Katzmarzyk and Mason, 2009).

A possible downside of mechanization has been an increased amount of sedentary behavior and physical inactivity, which have been linked to the epidemical increase in obesity and non-communicable diseases (NCDs). World Health Organization (WHO) (2009) has stated that physical inactivity is the fourth largest risk factor for mortality in the world. At least in some populations, decreased physical demands of occupational and household tasks due to the technological advances have increased the importance of recreational activity for maintenance of health, physical capacity, and functioning ability. Meanwhile, some continue to experience high physical demands during work (Karlqvist et al., 2003). The differences in daily physical activity profiles, in respect to intensity and volume, could modulate the individuals' responsiveness to exercise programs that are aimed for health effects.

Current estimates indicate that approximately one half of Finnish working age population is sufficiently active during their leisure-time, and that the participation to recreational exercise has steadily increased in the past 30 years (Helakorpi et al., 2012; Borodulin and Jousilahti, 2012). In spite of increase in leisure-time physical activities, occupational and commuting physical activity has steadily decreased (Borodulin and Jousilahti, 2012). Unfortunately, these estimates have not taken into account the intensity or volume of physical activity. However, simultaneously with these changes in physical activity behavior (participation) the proportion of overweight, obese, or type 2 diabetic individuals has increased (Koski, 2011; Männistö et al., 2012; Helakorpi et al., 2012).

In Finland, 66% of men and 46% of women are at least overweight and 20% of men and 19% of women are obese (Männistö et al., 2012). In addition, approximately 500 000 Finns suffer from diagnosed or undiagnosed type 2 diabetes (Reunanen, 2006; Koski, 2011) and 42% of Finnish men and 33% of Finnish women have some type of impairment in their glucose regulation (Peltonen et al., 2006). Globally, the incidence of diabetes has doubled in the past 30 years and the number of people with diabetes is expected to increase by 50% in the next 20 years (Danaei et al., 2011; Whiting et al., 2011). Due to the increasing prevalence of type 2 diabetes and its costly co-morbidities, the prevention of type

2 diabetes has become one of the leading health challenges of the 21st century. Lifestyle interventions, aimed at weight loss, increased physical activity, and improved diet, still remain the first line of defense against the development of type 2 diabetes (Eriksson, 1991; Pan et al., 1997; Tuomilehto et al., 2001; Knowler et al., 2002).

A substantial body of evidence supports the beneficial effects of physical exercise on health and prevention of diseases. The common finding in different types of exercise intervention studies is, however, a large inter-individual variation in response to training. There are a myriad of factors that can modulate individual responsiveness to exercise, of which alterations in non-exercise physical activity could have the most direct effect (King et al., 2007). Although the importance of exercise for health has been highly emphasized, only a few studies have investigated the effects of exercise on intensity and volume of daily physical activity. Typically, exercises account for only 3–5% of total weekly hours and sleep approximately 30%. Thus, 65% of our time would be available for other non-exercise physical activities. Compared to exercise, the remaining 65% of time embodies a substantially larger pool of physical activity that can affect the individual response to exercise. Recently, the importance of lower intensity non-exercise physical activity for health has been emphasized (Hamilton et al., 2007; Katzmarzyk, 2010). Thus, compensatory decrease or additional activation in intensity and volume of lower intensity physical activity during an exercise intervention can have substantial effects on individual responsiveness to training (Hautala et al., 2012). For proper promotion of health enhancing physical activity, it would be necessary to understand thoroughly how exercise intervention modifies the dose of daily total physical activity and its subcategories. Previous studies, which have focused on this question, have studied solely the volume of total physical activity (Goran and Poehlman, 1992; Hollowell et al., 2009; Colley et al., 2010; Turner et al., 2010), while the effect of exercise on intensity of total physical activity in different subcategories has remained undetermined.

Physical inactivity being the fourth largest risk factor for mortality in the world, and its association with several NCDs, means that there is a global urgency to find ways to activate people and increase their physical activity level (World Health Organization, 2009). Thus, the primary aims of this study were to investigate how different types of interventions modulate the intensity and volume of daily total physical activity and its subcategories and the response to risk factors of type 2 diabetes.

2 REVIEW OF THE LITERATURE

2.1 PHYSICAL ACTIVITY

2.1.1 DEFINITION AND CATEGORIZATION

Physical activity has been defined as any bodily movement induced by the contraction of the skeletal muscle that increases energy expenditure (Malkia, 1983; Caspersen et al., 1985; Howley, 2001). Of the total daily energy expenditure 15–50% is accounted for by the energy cost of physical activities (Horton and Danforth, 1982; Ravussin et al., 1986; Dauncey, 1990; Livingstone et al., 1991; Lamonte and Ainsworth, 2001) or movement (Pettee Gabriel et al., 2012). The remaining 50–85% is accounted for by resting metabolic rate (60–75%) and thermic effect of food also called the diet induced thermogenesis (10%) (Horton and Danforth, 1982). Resting metabolic rate corresponds to cellular functions that maintain body homeostasis. Thermic effect of food indicates the energy expenditure that exceeds resting metabolic rate after feeding as the result of digestion, absorption, transport, metabolism, and storage of ingested food (Horton and Danforth, 1982).

Human movements can be volitional, non-volitional, or spontaneous and they are accumulated throughout the day (Tremblay et al., 2007). Daily movements can be categorized into different subcategories according to the purpose of the movement or the location or surroundings in which the movements are executed (Caspersen et al., 1985). Roughly, physical activity related energy expenditure can be divided into an exercise-related thermogenesis and a non-exercise activity thermogenesis (NEAT) (Levine et al., 1999; Levine, 2003). NEAT includes all waking hour daily physical activities that are not exercise, e.g. occupational, leisure-time, and fidgeting. Thus, NEAT can be calculated by subtracting the basal metabolic rate, thermic effect of food, and exercise energy expenditure from total energy expenditure. NEAT includes the majority of physical activity energy expenditure. Currently, the major subcategories of physical activity include occupational physical activity (OPA), commuting physical activity (CPA), leisure-time physical activity (LTPA), miscellaneous home physical activities (MHPA), and sleep (Caspersen et al., 1985; Howley, 2001; Pettee Gabriel et al., 2012). The subcategories of physical activity can also be combined into larger categories for specific purpose (Figure 1).

OPA includes activities that are executed during the performance of a job (Caspersen et al., 1985; Howley, 2001). Alternatively, OPA subcategory can be defined as activities that have to be performed to ensure the economic survival of the individual and the community (FAO/WHO/UNU, 1985). For individuals that are not part of the working force, OPA subcategory can be broadened to include physical activities performed during the day-time, e.g. activities that are executed during school hours among students (Pettee Gabriel et al., 2012). Even today, OPA

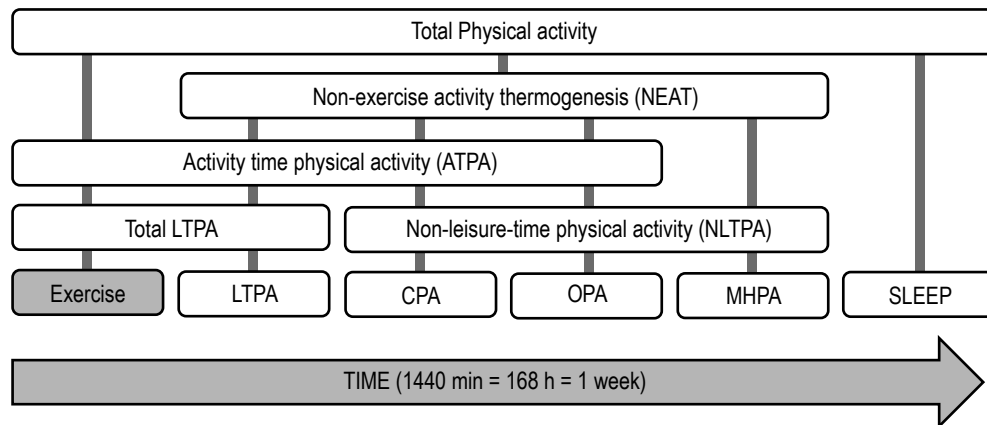


Figure 1. The different subcategories of physical activity. LTPA, leisure-time physical activity; CPA, commuting physical activity; OPA, occupational physical activity; MHPA, miscellaneous home physical activity.

embodies a major portion of daily human energy expenditure due to the long duration (Tremblay et al., 2007). In addition, the possibilities to regulate OPA according to the individual needs and desires are often limited.

According to Howley (2001), LTPA includes activities that substantially increase energy expenditure, such as gardening or physical exercise. Exercise is a subcategory of LTPA, and it can be defined as purposeful bodily movements that are aimed to improve or maintain muscular fitness, flexibility, balance, or body composition (Caspersen et al., 1985; Pettee Gabriel et al., 2012). LTPA can also include the MHPA subcategory (Caspersen et al., 1985), although according to the current framework of physical activity MHPA is separated as an individual subcategory of physical activity (Pettee Gabriel et al., 2012). Movements that are categorized in MHPA are domestic, household, and self-care types of activities (Pettee Gabriel et al., 2012). Movements related to transfer from one place to another are included in CPA subcategory (Caspersen et al., 1985; Pettee Gabriel et al., 2012). Finally, sleep, although it includes relatively minimal movements, is an important regulator of time available for physical activity (Tremblay et al., 2007). In addition, sleep deprivation or disturbance may induce fatigue, which can decrease daytime physical activity (Gupta et al., 2002; Taheri, 2006; Tremblay et al., 2007; Zimberg et al., 2012).

2.1.2 DETERMINANTS OF PHYSICAL ACTIVITY

The physiological responses to physical activity are dependent on the dose determinants of physical activity (type or mode, frequency, duration, intensity) (Howley, 2001). Type of physical activity, such as walking, cycling, and lifting, characterizes the functional entities of single movements of individual body segments. These single movements alter the function of different bodily systems, including muscle, cardiovascular, respiratory, and nervous system. The activated

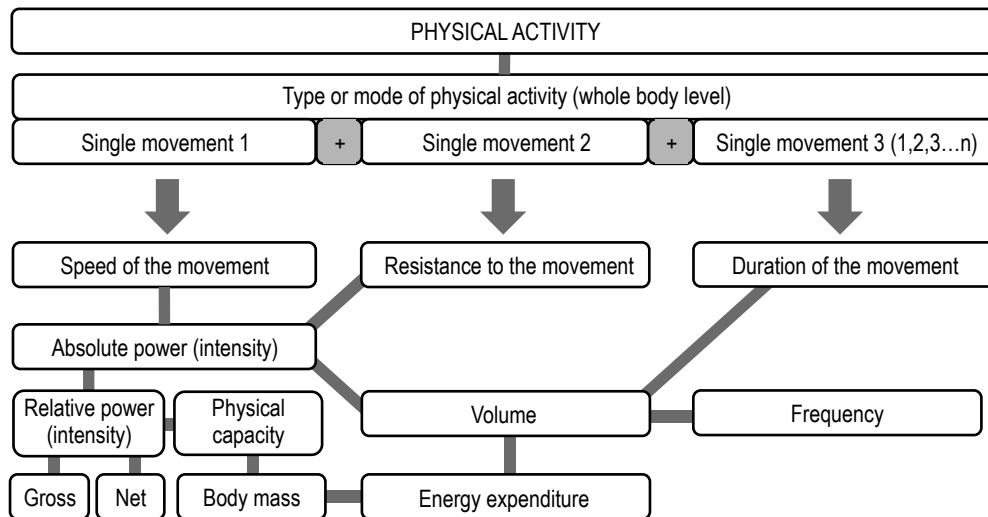


Figure 2. Physiological determinants of physical activity.

bodily systems and the ways they are functioning depend on the movements' characteristics (speed, duration and resistance). These characteristics, in relation to the individual's physical capacity, ultimately define the physiological or molecular effects of that specific movement (Figure 2) (Edington and Edgerton, 1976; Knuttgen, 2007; Hawley, 2009). Thus, the type of activity is a surrogate measure of the sum of individual movements and their effect on the body.

The number of times an activity, with certain type or intensity, is performed within a timeframe indicates the frequency of the physical activity, whereas duration of the physical activity indicates the number of minutes or hours that an activity is continuously performed (Howley, 2001). The determination of physical activity level based on the measures of type, frequency, and duration has been widely used, although it may be less accurate than methods based on the human energetics (Mudd et al., 2008).

In physics, energy [E] refers to the capacity to do work [W]. This energy capacity is consumed in proportion to the work performed, which is the product of force [F] and travelled distance or displacement [s] ($[W] = [F] \cdot [s]$). Both the energy and work can be expressed in the unit of joule [J] (Bureau international des poids et mesures, 2006). In human beings, energy is equivalent to the carbohydrate, protein and fat reserves of the body, which can be oxidized by cellular pathways to endorse bodily functions (Nelson and Cox, 2008). The oxidation produces approximately 9 kcal/g for fat, 4 kcal/g for carbohydrates and proteins, and 7 kcal/g for alcohol (Rubner, 1885; Atwater and Woods, 1896). Thus, in a man weighing 70 kg the energy capacity of these reserves would be equal to approximately 165 000 kcal, although the inter-individual variations are large (Horton and Danforth, 1982; Nelson and Cox, 2008). These bodily stores of potential or free chemical energy dictate the human capacity to perform work. By oxidizing macronutrients human cells liberate kinetic energy, of which

approximately 0–25% can be harnessed into mechanical work by the contractile element of the cells, mainly actin and myosin filaments of muscle fibers, and other cellular processes (e.g. the function of calcium pump). Remaining kinetic energy is dissipated as unusable heat (International Organization For Standardization, 2004; McArdle et al., 2007).

The rate of conversion of chemical potential energy into kinetic mechanical and thermal energy is equivalent to power [P], which is a quantity that dictates the work performed in a unit of time [t]. The unit of power is watt (W), which is defined by joules (J) generated per second (s) ($W = J/s^{-1}$) (Bureau international des poids et mesures, 2006). In physical activity research, the power is often replaced with the term metabolic rate or intensity (Howley, 2001; International Organization For Standardization, 2004), whereas in work physiology studies, physical stress or workload has been used. Absolute intensity of physical activity can be expressed with heat loss from body surface ($W \cdot m^{-2}$) (Rubner, 1883), oxygen consumption (VO_2 , $l \cdot min^{-1}$ or $ml \cdot kg^{-1} \cdot min^{-1}$) (Lavoisier and Laplace, 1780; Rubner, 1894; Atwater and Rosa, 1899a; Atwater and Rosa, 1899b; Atwater and Benedict, 1905; Benedict and Carpenter, 1910), kilojoules ($kJ \cdot min^{-1}$ or $kJ \cdot kg^{-1} \cdot h^{-1}$), kilocalories ($kcal \cdot min^{-1}$ or $kcal \cdot kg^{-1} \cdot h^{-1}$), heart rate (beats per minute, BPM) (Benedict and Carpenter, 1910; Boothby, 1915; Lindhard, 1915), or as a ratio between the energy expenditure and basal or resting metabolic rate (Smith, 1861).

Several different ratio figures have been applied to express the intensity of physical activity in the past 150 years (Smith, 1861; Lagrange, 1890; Dill, 1936). One of these ratios is the physical activity level (PAL), also referred to as physical activity index (PAI), which is determined by dividing total daily 24-hour energy expenditure with basal metabolic rate (FAO/WHO/UNU, 1985; Shetty et al., 1996; FAO/WHO/UNU, 2001; Dietary reference intakes, 2005). The other ratio, and more often used in physical activity research, is the metabolic equivalent of task (MET), also referred to as physical activity rate (PAR) (FAO/WHO/UNU, 1985; FAO/WHO/UNU, 2001), which is the ratio between the energy expenditure of a task and basal or resting metabolic rate (Gagge et al., 1941; Balke, 1960). One MET corresponds to the sitting metabolic rate of a 40 year old man with a body weight of 70 kg and a surface area of 1.8 m^2 , thus 1 MET equals approximately 50 $kcal \cdot h^{-1} \cdot m^{-2}$ (Gagge et al., 1941), 58.2 $W \cdot m^{-2}$ (American society of heating, refrigerating and air-conditioning engineers (ASHRAE), 2010), 3.5 $ml O_2 \cdot kg^{-1} \cdot min^{-1}$, 1 $kcal \cdot kg^{-1} \cdot h^{-1}$, or 4.184 $kJ \cdot kg^{-1} \cdot min^{-1}$ (Balke, 1960; Jette et al., 1990; Ainsworth et al., 1993; Ainsworth et al., 2000b; Howley, 2001). For example, walking on level surface 4 km/h consumes approximately 10.2 $ml O_2 \cdot kg^{-1} \cdot min^{-1}$ giving a MET-value of 2.9 MET ($10.2 \text{ ml } O_2 \cdot kg^{-1} \cdot min^{-1} / 3.5 \text{ ml } O_2 \cdot kg^{-1} \cdot min^{-1} = 2.9 \text{ MET}$). Studies have reported that the conventional definition of 1 MET as 3.5 $ml O_2 \cdot kg^{-1} \cdot min^{-1}$ may overestimate the individual energy expenditure (kcal) especially among obese and elderly subjects (Kwan et al., 2004; Byrne et al., 2005; Kozey et al., 2010). To increase the accuracy of MET based estimates of individual energy expenditure, the conventional 3.5 $ml O_2 \cdot kg^{-1} \cdot min^{-1}$ can be corrected with measured or estimated resting metabolic rate (Byrne et al., 2005; Kozey et al., 2010). It has, however, been suggested that standard MET-values should be used instead of corrected

MET-values when describing the physical activity of the population or comparing groups of subjects (Ainsworth et al., 2011). In addition, Howley (2011) has argued that the term MET should be only used when the fixed $3.5 \text{ ml of O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ is used as denominator; otherwise, the calculated ratio figure is not a MET-value.

Currently, MET has been widely applied in physical activity research, guidelines (Haskell et al., 2007; U.S. Departments of Health and Human Services, 2008; Garber et al., 2011), and in the standard of metabolic rate measurement (American society of heating, refrigerating and air-conditioning engineers (ASHRAE), 2010). By employing MET-values, the volume or energy expenditure of physical activity is determined with MET-minutes (METmin) or MET-hours (METh), which are products of MET x duration (minutes or hours) x frequency of the activity (Howley, 2001). The calculation of METh was introduced by Buskirk et al. (1971), although they used the term activity metabolic index (AMI) instead of METh. Daily METh has also been referred to as physical activity index (PAI) in previous research (Kannel and Sorlie, 1979).

Intensity of physical activity can also be expressed relative to the maximal physical capacity of an individual as relative intensity (Lange Andersen et al., 1978; Howley, 2001). In work physiological studies, the term physical strain or relative aerobic strain (RAS) has been used (Åstrand, 1967; Ilmarinen, 1992). Maximal physical capacity indicates the upper limit of aerobic power and it can be determined with maximal oxygen uptake ($\text{VO}_{2\text{max}}$). The relative intensity can be expressed either in gross or net values. Gross values include the resting metabolic rate and it can be calculated with the equation $((\text{absolute intensity of physical activity} / \text{VO}_{2\text{max}}) \cdot 100)$. Net relative intensity can be calculated with the same equation after the subtraction of the resting metabolic rate $((\text{absolute intensity of physical activity} - \text{resting metabolic rate}) / (\text{VO}_{2\text{max}} - \text{resting metabolic rate})) \cdot 100$ (Howley, 2001). The $\text{VO}_{2\text{max}}$ that is applied for calculation of relative intensity should be based on the $\text{VO}_{2\text{max}}$ of the musculature that is active during the particular movement. It has been shown that higher active muscle mass will result in higher $\text{VO}_{2\text{max}}$ (Shephard et al., 1988). Consistently, previous studies have reported higher $\text{VO}_{2\text{max}}$ values with cycling ergometer compared to the arm-crank ergometer (Åstrand and Saltin, 1961; Owens et al., 1988; Shephard et al., 1988; Louhevaara et al., 1990).

Intensity of physical activity can also be expressed as a rating of perceived exertion (RPE), in which an individual subjectively evaluate the intensity of the activity based on a given scale (Borg, 1982; Borg, 1998). Borg (1982) has suggested that RPE indicates a subjective intensity as a summary figure, which is integrated from the signals received from different bodily function, systems, and organs. Thus, RPE has specific psychophysical properties that can complement the more objective methods, such as heart rate measurement (Borg, 1982).

2.1.3 MEASUREMENT METHODS

The discovery of the vital role of atmospheric air for combustion and life (Mayow, 1907, original 1674), carbon dioxide (Ramsay, 1918), oxygen (Priestley, 1775;

Priestley, 1776; Priestley, 1977), and latent heat (Ramsay, 1918) enabled and initiated the modern measurement of human metabolism and energy expenditure. By definition, energy expenditure, both the rate and the amount, are a vital part of quantifying physical activity (Christensen, 1953; Christensen, 1955; Spitzer and Hettinger, 1964; Spitzer et al., 1982; Caspersen et al., 1985; Lamonte and Ainsworth, 2001; Howley, 2001; Pettee Gabriel et al., 2012). Currently there are multiple different methods to measure physical activity and/or energy expenditure, which all have their advantages and limitations. Currently, no single method is generally accepted as the “gold standard” method to measure physical activity. Although direct calorimeter, indirect calorimeter, and doubly labelled water are considered “gold standard” methods for measuring energy expenditure, they may not be that for the measurement of physical activity, since they are not suitable to measure behavioral aspects of physical activity (Warms, 2006).

Direct calorimetry, indirect calorimetry, and double labelled water

Direct calorimetry, which measures the heat loss or heat emitted from the body surface, is the most accurate way to measure energy transfer in living organisms (Murgatroyd et al., 1993; Kaiyala and Ramsay, 2011). The first direct animal calorimeters were developed in the late 1800s (Lavoisier and Laplace, 1780; Crawford, 1787; Ramsay, 1918; Lusk, 1922; Fenby, 1987; Frankenfield, 2010). The most famous of these early calorimeters was that constructed by Lavoisier and Laplace. Their ice-calorimeter applied the law of latent heat transformation discovered by Joseph Black (Ramsay, 1918) to measure the heat loss of the animal from the mass of melted ice (Frankenfield, 2010). The ice-calorimeter was never applied to human beings, and it took over 100 years until the first successful direct calorimeter measurements on human beings were performed (Atwater and Rosa, 1899a; Atwater and Rosa, 1899b; Atwater and Benedict, 1903; Atwater and Benedict, 1905) (Figure 3). Since the early days, several different types of calorimeters have been developed and described, including isothermal or heat sink (room or suit) (Webb et al., 1972; Dauncey et al., 1978; Jacobsen et al., 1985; Webster et al., 1986), gradient-layer (Murlin and Burton, 1935; Benzinger and Kitzinger, 1949; Spinnler et al., 1973; Walsberg and Hoffman, 2005; Zhang, 2010), convection or air (Palmes and Park, 1947; Carlson et al., 1964; Snellen et al., 1983; Reardon et al., 2006), partitional (Winslow et al., 1936), and differential calorimeters (Deighton, 1939). The function of these direct calorimeters has been reviewed previously in detail (Murlin, 1922; Mclean and Tobin, 1987; Jequier et al., 1987; Murgatroyd et al., 1993; Levine, 2005; Lighton, 2008; Kaiyala and Ramsay, 2011).

The direct calorimeter is based on heat balance equations, which is an alternative expression of the principle of conservation of energy as stated in the first law of thermodynamics (Mclean and Tobin, 1987). If no external work is performed and the heat storage of the body is zero, then metabolic rate, heat production, and total heat loss from the body are equal (Webb, 1980; Kaiyala and Ramsay, 2011). During exercise, it is possible that some of the kinetic energy derived from the energy stores of the body is transferred into mechanical energy

rather than heat (Simonson and DeFronzo, 1990). In addition, from the onset of exercise it takes approximately 30 to 50 minutes for heat loss to reach a new steady state or plateau that matches the heat production or the metabolic rate of the body (Webb et al., 1970; Chappuis et al., 1976; Crucza, 1983; Nagle et al., 1990; Webb, 1993; Webb, 1995). With sufficient cooling and collection of sweat, however, direct suit calorimeter has achieved over 97% agreement between the heat loss and heat production during a 24-hour measurement, which included three cycling exercise sessions (Hambraeus et al., 1994). In general, the measurement error associated with direct calorimeters varies from <1% to 3% (Levine, 2005). In spite of the accuracy, room size direct calorimeters are expensive (approximately 1 million USD), complex to operate, and impractical in free-living conditions or large populations, and they restrict daily human movement (LaPorte et al., 1985; Murgatroyd et al., 1993; Levine, 2005; Warms, 2006). Thus, they are applied mainly for the validation of other energy expenditure measurements and for basic thermodynamic research.

Indirect calorimeter, which measures heat production with O₂ consumption and CO₂ production, was the first method that was used to measure human metabolism (Frankenfield, 2010). The early indirect calorimeters were based on closed circuit spirometers (Regnault and Reiset, 1849; Murlin, 1922). In the closed systems, air (100% of O₂) is inspired from the prefilled container, expired O₂ is re-circulated to the container after removal of CO₂, and finally the depletion of O₂ from the container is measured (Figure 3). Currently, the open-circuit systems that allow more movement and less resistant breathing circuits are more suitable for the measurement of the exercise energy expenditure (Branson and Johannigman, 2004). Since the introduction of the first open-circuit system (Pettenkofer, 1962) several modifications have been developed, including bag (Douglas, 1911), portable (Zuntz et al., 1906; Müller and Franz, 1952), and automated systems (Wilmore et al., 1976; Salminen et al., 1982; Bassett et al., 2001; Pinnington et al., 2001; Macfarlane, 2001). In open-circuit systems the ambient air with constant composition is inspired through a breathing valve and the gas composition of expired air is analyzed with gas meter.

The measured VO₂ can be converted into calories based on the caloric or energetic equivalent of oxygen, which reportedly has varied from 4.16 kcal·l of O₂ to 5.05 kcal·l of O₂ depending on the stoichiometry of the oxidized substrate and associated respiratory quotient (RQ) (Weir, 1949; Consolazio and Johnson, 1971; Simonson and DeFronzo, 1990; Murgatroyd et al., 1993; Jeukendrup and Wallis, 2005). RQ indicates the ratio of VO₂ and VCO₂ at the cellular level (Zuntz and Schumburg, 1901; Williams et al., 1912; Lusk, 1924; Du Bois, 1924; Michaelis, 1924). In indirect calorimeters the RQ is estimated from the respiratory exchange ratio (RER), which indicates the net ratio of VO₂ and VCO₂ in the whole body level. The basic assumption in indirect calorimeter is the equality between the RQ and RER (Simonson and DeFronzo, 1990; Jeukendrup and Wallis, 2005). The equality assumption is violated when there is a net inter-conversion of substrates (e.g. lipogenesis, gluconeogenesis, ketogenesis) (Frayn, 1983), the CO₂ pool changes, the oxidation of protein is high or non-constant, or the proportion of the

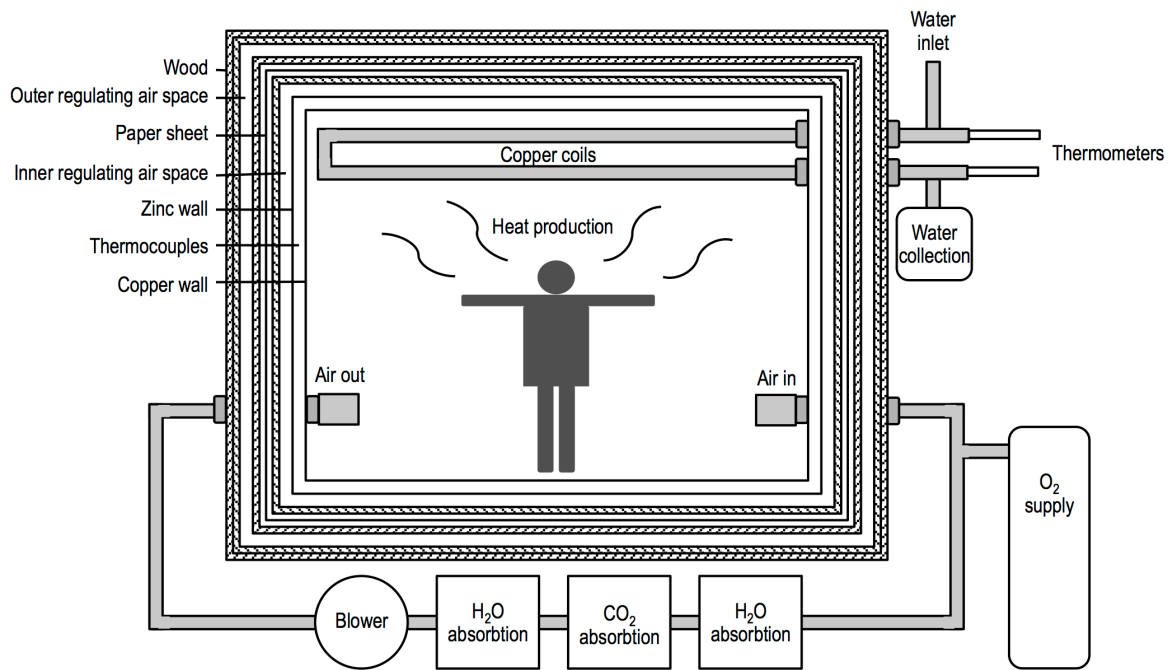


Figure 3. Basic structure of a room respiratory calorimeter for the measurement of metabolic rate of the body. Based on the report by Atwater and Rosa (1899a).

anaerobic energy production increases (Jeukendrup and Wallis, 2005). These types of alterations can be induced by several clinical, nutritional, or physical conditions, including ketosis, hyperventilation, hypoventilation, overfeeding, underfeeding, acidosis (high intensity exercise, $>75\%VO_{2max}$), or prolonged exercise (Mclean and Tobin, 1987; Simonson and DeFronzo, 1990; Jeukendrup and Wallis, 2005). In defined conditions and with robust calibration, however, the heat production equals heat loss (Lavoisier and Laplace, 1780; Rubner, 1894; Atwater and Benedict, 1903). In addition, the errors associated with violation of the aforementioned assumptions are relatively minor. For example, 100% decrease or increase in protein oxidation or by totally discounting the effect of protein on energy production allegedly yields an error of less than 2% (Simonson and DeFronzo, 1990). Compared to the direct calorimeters, indirect systems are less expensive (2 000–35 000 USD) (Holdy, 2004), easier to operate, and able to provide minute-by-minute data on intensity and volume of physical activity. They are, however, unpractical for long-term measurements in free-living conditions, and are best suited for short-term (10–30 min) validation studies of other energy expenditure measurements.

One application of the indirect calorimeter is the doubly labeled water method that was developed in the 1950's (Lifson et al., 1955), and first human experiments were done in the early 1980's (Schoeller and van Santen, 1982). The method is based on the direct estimation of CO₂ production by measuring the difference in the rate of elimination of the two, usually orally taken, stable isotopes of hydrogen (deuterium, ²H) and oxygen (¹⁸O or ¹⁷O) from the body (Lifson and McClintock,

1966). Deuterium is eliminated from the body as water whereas the isotope of oxygen is eliminated as water and CO₂. The CO₂ production can be measured, since the isotope of oxygen is in equilibrium with the oxygen of body water and the oxygen of respiratory CO₂ due to the decarboxylation and bicarbonate buffer system catalyzed by carbonic anhydrase (Lifson et al., 1949). The method is based on the assumption that the body water pool and flow rate of water and CO₂ are constant, concentration of the isotopes in water and CO₂ that exit the body equals that of the body water pool, there is no re-entry of the isotopes, only water and CO₂ are labeled, isotopes exit the body only in the form of water and CO₂, and the quantity of natural isotopes remain constant throughout the measurement period (Lifson and McClintock, 1966; Nagy, 1980; International Dietary Energy Consultancy Group, 1990; Butler et al., 2004; International Atomic Energy Agency, 2009). Although these assumptions are invalid in free-living human beings, the risk of error can be reduced with mathematical correction factors or methodological design (International Dietary Energy Consultancy Group, 1990; Racette et al., 1994). The estimates of produced CO₂ can be transformed into energy expenditure by estimating the mean RQ, for example from diary intake reports, after which standard equations of the indirect calorimeter can be applied (International Dietary Energy Consultancy Group, 1990).

On a group level, the accuracy of doubly labeled water is approximately 5% in strictly controlled conditions and 10% in free-living conditions (Jequier and Schutz, 1988; Goran et al., 1995; Speakman, 1998). On an individual level, the deviation can exceed 20%, which limits the suitability of the method for individual analysis (Speakman, 1998; Butler et al., 2004). The length of the measurement period is approximately 0.5–3 biological half lives of the isotopes or 3–25 days in human beings (Schoeller, 1988). In adult human beings it has been suggested that the minimum measurement period should be at least 2 biological half-lives of the isotopes or 12–14 days for sufficient accuracy (Murgatroyd et al., 1993; Shephard and Aoyagi, 2012). Regarding the measurement of physical activity, doubly labeled water provides only estimates of total amount and the average rate (PAL) of energy expenditure for the whole measurement period (LaPorte et al., 1985). Energy expenditure of physical activity can be estimated by subtracting the basal or resting energy expenditure and thermic effect of food from the total energy expenditure. Doubly labeled water is currently the most accurate tool to estimate long-term free-living energy expenditure. The cost of a single measurement, questionable validity in exceptional circumstances, technical demands, laborious analysis, and absence of detailed data, has, however, limited its applicability for large samples (Murgatroyd et al., 1993; Dishman et al., 2001). Therefore, the technique is mainly used for validation of other field methods and measurement of energy expenditure in specific populations (Dishman et al., 2001).

Heart rate method and other portable devices

The heart rate (HR) method is based on the relationship between the oxygen consumption (VO₂) and HR, as defined by the Fick's convection equation $VO_2 = HR \cdot V_s(C_aO_2 - C_vO_2)$, where V_s is the stroke volume of the heart and $C_aO_2 - C_vO_2$

is the arteriovenous oxygen difference (Butler et al., 2004; Green, 2011). Experimental evidence has also confirmed a close linear relationship with the rate of VO_2 and HR in humans (Boothby, 1915; Krogh and Lindhard, 1917; Berggren and Hohwü Christensen, 1950; Åstrand and Ryhming, 1954). The relationship is, however, non-linear at lower HR ($<50\% \text{VO}_{2\text{max}}$ or 120 bpm) and near maximal HR (20 beats below the maximum heart rate) (Henderson and Prince, 1914; Åstrand and Ryhming, 1954; International Organization For Standardization, 2004). The relationship can be distorted by multiple factors, including the fitness level, training status (Henderson et al., 1927; Bock et al., 1928), psychological stress (Carroll et al., 1986), surrounding temperature (Adolph and Molnar, 1946), dietary intake, body position (Asmussen et al., 1939; Asmussen and Hohwü Christensen, 1939), dehydration (Saltin, 1964), altitude (Vogel et al., 1967), dynamic or static muscle contraction (Maas et al., 1989), and leg or arm activity (Bevegård et al., 1966; Vokac et al., 1975; Louhevaara et al., 1990). In addition, medical conditions, including diabetic autonomic neuropathy (DAN), has been shown to impair the heart rate response to exercise (Hilsted et al., 1982), increase the resting HR, decrease maximum HR, decrease the slope between the HR and $\% \text{VO}_{2\text{max}}$, and impair the heart rate recovery after exercise (Bottini et al., 1995). Colberg et al. (2003), however, have reported no difference in percentage of HR reserve (maximum heart rate – resting heart rate) and $\% \text{VO}_{2\text{max}}$ R relationship between the subjects with DAN or without DAN. Several drugs, including beta-blockers, also modify the HR response to exercise (Powles, 1981; Peel and Mossberg, 1995).

Due to multiple factors that can influence HR, individual calibration curve of HR response to the increase in work rate have to be determined with a traditional step incremental ergometer test or by FLEX-heart rate (FLEX-HR) method (Booyens and Hervey, 1960; Spurr et al., 1988). In the FLEX-HR method, VO_2 and HR are measured in three resting positions (lying down, sitting, and standing) and while performing exercises with different intensities. The FLEX-HR is the mean between the highest HR during a resting condition and lowest HR monitored during the exercise. If the measured HR is lower than the FLEX-HR, then resting energy expenditure is used to estimate energy expenditure. When HR exceeds the FLEX-HR, then a calibration curve determined during the exercise test is applied for estimation. According to the review by Leonard (2003), in 70% of subjects the energy expenditure estimates are within $\pm 10\%$ of the values retrieved from the direct calorimeter or doubly labeled water. It should be emphasized that the accuracy of the HR method is decreased if aforementioned individual, environmental, or pharmacological factors differ during the determination of the calibration curve and the actual period of energy expenditure measurement. If individual calibration cannot be performed, then the accuracy of the HR method to estimate energy expenditure can be improved by regression equations based on the subjects characteristic and/or HR variability (Strath et al., 2000; Rennie et al., 2001; Smolander et al., 2011). The advantages of the method are that HR is easy to measure beat-by-beat, equipment are affordable, and the method is relatively convenient and unrestrictive. The data analysis, however, can be laborious and in

clinical populations it requires a stable sinus rhythm. The HR method enables the measurement of absolute and relative intensity and volume of physical activity and simultaneous logs can be applied to retrieve data about the behavioral aspects physical activity.

Motion sensors are mechanical or electronic devices that detect or count human movement. Such sensors include pedometers and accelerometers, which are widely available. The pedometers are mounted on the waist or ankle to measure the number of steps and/or distance. The first pedometer was developed over 500 years ago by Leonardo da Vinci (Gibbs-Smith and Rees, 1978). The early modern mechanical gear driven pedometers were inaccurate largely because of fluctuation of the spring tension, which determined the sensitivity of the device to detect movement (Montoye et al., 1996). Some contemporary electronic pedometers have been shown to be reasonably accurate in measuring steps and distance, to overestimate walking energy expenditure, and to underestimate the energy expenditure of other types of activities (Bassett et al., 1996). Bassett et al (2000) have reported that the pedometer underestimates the actual energy cost in 28 daily activities on average by 1.12 MET (95% confidence interval [CI] 0.96–1.28). They also found a low correlation between the estimated and actual energy expenditure ($r = 0.49$). When energy expenditure estimates of eight electronic pedometers were compared to indirect calorimetry in different walking speeds, a large variation in gross and net energy expenditure was found, especially at low walking speeds (Crouter et al., 2003). At low walking speed, estimates of number of steps and walked distance have also been highest (Bassett et al., 1996; Crouter et al., 2003). In a study by Schneider et al. (2003) comparing the accuracy of 10 pedometers to the actual number of steps measured during a 400-meter walk, the authors found that some pedometers were relatively accurate ($\pm 3\%$ of actual steps), whereas in other pedometers had a substantially lower accuracy ($\pm 37\%$ of actual steps). The pedometers are affordable and small; however, they measure only ambulatory activities within a certain speed range. In addition, they are unable to measure the type, frequency, duration, or intensity of specific activities.

Accelerometers detect acceleration of the human body around one, two, or three axis. The development of accelerometers for measuring human movement started during the 1960's (Cavagna et al., 1961). Since then, several types of acceleration transducers have been used in accelerometers, including piezoelectric cantilevered beam, piezoelectric or piezoresistive compressive integrated chip, or differential capacitance (Chen et al., 2012). In modern accelerometers, the sinusoidal acceleration signal provided by the transducer is converted from analog to digital, filtered, rectified (full or half wave), and then summarized for specific period or epochs (Bassett et al., 2012; Butte et al., 2012). Recent advances also allow the non-filtered raw gravitational forces to be analyzed, as was recommended by a general consensus meeting (John and Freedson, 2012; Butte et al., 2012). Despite these advances, the accelerometer data is still commonly expressed in activity counts (counts per unit of time), which is an arbitrary unit dependent on the analog voltage, amplification factors, analog-to-digital conversion factor, and sensors (Chen and Bassett, 2005). In addition, there are at

least three different analytical approaches to express counts. The count can express the number of times the signal crosses the predefined threshold, a maximum value for specific epoch or an area under the curve for specific epoch (Chen and Bassett, 2005). Depending on the variation in the aforementioned factors, the counts between the different accelerometer manufacturers are incomparable (Chen and Bassett, 2005; Welk et al., 2012). The counts, however, can be converted into estimates of energy expenditure by applying single regression equations (Crouter et al., 2006a), two regression equations (Crouter et al., 2006b), or pattern recognition approaches (Bassett et al., 2012; Liu et al., 2012). The accuracy of the methods that apply pattern recognition has been shown to be greater than that of the basic regression based methods (Rothney et al., 2007; Staudenmayer et al., 2009; Trost et al., 2012). In a review of 28 validation studies from 8 different accelerometers, the correlation between the free-living data of motion sensors and doubly labeled water varied from -0.09 to 0.96 (Plasqui and Westerterp, 2007). In more constraint environments, accelerometers have been shown to underestimate the actual total energy expenditure approximately by 10% compared to the 24-hour room calorimetry measurement (Corder et al., 2007). The accelerometers can provide information about the intensity, duration, and frequency of physical activity, the prediction of energy expenditure, and distinguish a few types of activities (e.g., lying, sitting, standing, walking, jogging, running) (Butte et al., 2012). They are also relatively inexpensive, non-constrictive, and easy to operate. It has been suggested that accelerometers should be developed from the usage of counts and regression calibrations to an analysis of raw acceleration signals. (Troiano et al., 2014). The major shortcomings of the accelerometers are that they are unable to detect a wide range of specific activities, they provide no information about the context or surrounding of the activity, counts are arbitrary and non-standardized, and algorithms are proprietary (Butte et al., 2012).

Several wearable monitors have been developed to combine the information from multiple sensors to improve the energy expenditure estimates. According to a recent systematic review, these devices have been more accurate than uniaxial accelerometers and at least as good as triaxial accelerometers at estimating total and activity energy expenditure (Van Remoortel et al., 2012). Intelligent device for energy expenditure and activity (IDEAA®, MiniSun, CA, USA) combines information from 5 motion sensors placed on chest, anterior portion of thighs, and each foot (Zhang et al., 2003). The accuracy of the estimation of energy expenditure has been on average 99% (range: 90–111%) compared to the indirect calorimeter during a 50 min treadmill test (Zhang et al., 2004). Slightly smaller average values, although with narrower range, were observed between the energy expenditure of the IDEAA and a 23-hour room calorimeter measurement (mean: 95%, range: 92–99%) (Zhang et al., 2004). The IDEAA has also been shown to accurately differentiate at least 32 types of activities and their duration, frequency, and intensity (Zhang et al., 2003).

SenseWear Armband (SWA, Bodymedia, Pittsburgh, USA) is another kind of multi-sensor device that measures accelerations (around two or three axis), heat

flux, skin temperature, and galvanic skin response and applies specific algorithms that are based on the supervised machine learning or pattern recognition (Jakicic et al., 2004). The correlation between the SWA estimates of energy expenditure compared to that of the indirect calorimetry has varied from 0.23 to 0.76 when first generation generalized algorithms were employed (Jakicic et al., 2004). With exercise specific algorithms, the correlations increased and varied between 0.51 and 0.89 (Jakicic et al., 2004). In addition, the SWA has been shown to predict the measured energy expenditure more accurately than other accelerometers (CSA, BioTrainer, TricTrac, RT3) in most speeds of walking or running, ($r = 0.50-0.85$) (King et al., 2004). The energy expenditure estimates of the SWA have also been highly correlated ($r = 0.81$) with the doubly labeled water method during 10-day free-living conditions (St-Onge et al., 2007). Correlation between the energy expenditure estimates of IDEEA and SWA has also been high ($r = 0.82$, range: 0.68–0.92) when second generation algorithms have been applied (Welk et al., 2007). More recently, Hill et al. (2010) reported that the mean difference between SWA energy expenditure measurements and indirect calorimeter was insignificant -0.2 MET (limits of agreement was 1.3 MET) in five movements (supine lying, sitting, standing and self paced slow and fast walking) in patients with chronic obstructive pulmonary disease. In their study SWA was also highly repeatable.

There have also been some attempts to combine accelerometers with simultaneous HR monitoring to provide verification that the increased acceleration actually signifies increased physical activity (increased HR) (Rennie et al., 2000). The 12-hour energy expenditure estimates of combined HR and accelerometer (HR+ACC) deviated on average 0% (range: $-22-+19$) from the room calorimeter based on findings in 8 healthy subjects (Rennie et al., 2000). In another study by Brage et al. (2005), HR+ACC method predicted well ($R^2 > 0.84$, standard error of estimates $\sim 1.2-1.5$ MET) the intensity of walking and running. Butte et al. (2010) have reported an acceptable agreement between the HR+ACC method and doubly labeled water in children and adolescents. In 48 adult participants, the mean bias between the HR+ACC method and indirect calorimeter was 0.8 MET (95% prediction interval: -2.0 MET– $+3.5$ MET) in 18 different types of daily activities (Crouter et al., 2008).

Interviews, diaries and questionnaires

Interviews and self-report methods, including surveys, questionnaires, diaries, and logs, provide an inexpensive way to measure physical activity. There is a myriad of different types of questionnaires, which differ in the duration of recall, included physical activity subcategories, number of items measured, difficulty in scoring, and population tested (Washburn and Montoye, 1986; Pereira et al., 1997; Neilson et al., 2008). The review by Powell et al. (1987) suggested that the transition from questionnaires that measured only OPA to ones that incorporated also LTPA took place in the 1970's. They have shown that the number of physical activity coronary heart disease studies in which only OPA was measured, was

substantially greater among studies that were published before 1970 (20 out of 24) compared to the studies published later (3 out of 19) (Powell et al., 1987).

Some questionnaires have been applied to dichotomize individuals as sedentary or active for example based on the reported participation in vigorous (7.5 kcal/min or 6.4 MET for 70 kg man) physical activity (Morris et al., 1973) or whether their OPA or LTPA were mainly sedentary or not (Salonen et al., 1982). In other types of questionnaires, the participation in moderate or vigorous physical activity has been measured (Sallis et al., 1985), whereas in some questionnaires different types of scales and indexes have been used. For example, daily energy expenditure has been calculated and expressed in kilocalories (Johnson et al., 1956; Reiff et al., 1967; Sallis et al., 1985) or in MET-hours (Kannel and Sorlie, 1979). Other types of questionnaires have measured only the energy expenditure of LTPA (Taylor et al., 1978) or specific types of activities (Paffenbarger et al., 1978). Shapiro et al. (1965) applied a questionnaire, in which multiple choice questions about the type, duration, frequency, or travelled distance related to job or off-job time were asked, weighted, summed, and classified into four categories. Overall, physical activity level was then expressed as a sum of job and off-job time and categorized into light, intermediary, or heavy groups. Similar type of approach has later been applied by Baecke et al. (1982) to calculate work, leisure-time, and sports index (sports also included estimates of energy expenditure) from 16 multiple-choice questions. In International Physical Activity Questionnaire (IPAQ) the categorisation of the individual's physical activity level as low, moderate, or vigorous is based on the frequency, duration, or MET-hours of moderate or vigorous walking activity performed continuously at least for 10 minutes (International physical activity questionnaire, 2005).

Several factors influence the accuracy of the self-reports. In recall questionnaires, the demanding cognitive process of recalling has been recognized as a possible source of error (Baranowski, 1988). With diaries, the recalling error is minimal, but it increases the burden on both the subject and the researchers and it can alter the daily physical activity (Ainslie et al., 2005). It has also been suggested that high intensity activities are reported more accurately than low intensity activities (Taylor et al., 1978; Bouchard et al., 1983). In addition, individuals with higher fat percentage tend to over report the high intensity activities (≥ 4.5 MET) and underreport low to moderate intensity activities (2.5–4.4 MET) (Buchowski et al., 1999). Social desirability and approval has also been shown to affect the reporting of physical activity (Adams et al., 2005). With diaries, however, it is possible that the conscious or unconscious manipulation of data may be more difficult than with questionnaires, since the subjects are asked to report what they actually do, rather than self-evaluate their physical activity level. Thus, as expected, the diaries are considered a more accurate measure of physical activity than recalls (Ainslie et al., 2005).

The two comprehensive reviews of studies evaluating the accuracy of the self-reports against more objective measures (accelerometers, doubly labeled water, HR method) have reported a low to moderate mean correlation ($r = 0.37$, range = $-0.71-0.98$) (Prince et al., 2008) and low to acceptable median validity

correlation ($r = 0.24-0.41$) (Helmerhorst et al., 2012) between the methods. In a review by Prince et al. (2008) the mean correlation was somewhat higher in men ($r = 0.47$, range = $-0.17-0.93$) than in women ($r = 0.36$, range = $-0.17-0.95$). The mean difference between the doubly labeled water and questionnaires has been shown to vary from -62% to $+113\%$ for active energy expenditure and from -31% to $+62\%$ for total energy expenditure (Neilson et al., 2008). Schulz et al. (1989) compared the energy expenditure measured with doubly labeled water and estimated from the 24-hour diary record. The mean difference between the methods varied from -4% (± 14) to -7% (± 13) and the correlation from 0.57 to 0.72 depending on the employed calculations. The relatively low associations between the self-reports and objective methods, however, do not automatically signify inaccuracy of the subjective measures. Haskell (2012) has proposed that subjective measures and objective measures can measure different aspects of physical activity, which complement each other's weaknesses. The advantage of the self-reports, especially diaries, is that they can provide reasonably accurate estimates about the surroundings, environment, subcategory, type, frequency, duration, and intensity of the physical activity (Shephard, 2003), which is currently impossible with individual objective methods.

2.1.4 PHYSICAL ACTIVITY RELATED GUIDELINES FOR HEALTH

Physical activity recommendations have been given separately for occupation and leisure-time. In work physiology the goal has been to determine the upper tolerance limits for daily energy expenditure during the working hours (8 hours/day). Meanwhile, in exercise physiology the recommendations have been given for a minimum amount of physical activity that is needed to sustain or improve health (Rutenfranz, 1985).

In 1865, probably the first estimation on the amount of work man can perform on an yearly basis was reported (Playfair, 1865a; Playfair, 1865b). Playfair (Playfair, 1865a; Playfair, 1865b) suggested that man could walk 32 km without a load or 14 km while carrying 32 kg backpack per day six days a week throughout the year without physical break-down. The threshold was based on their experience on rural postmen and infantrymen. While in 1924, Pearl and his associates (Pearl, 1924) were probably the first that linked physical energy requirements of occupation and health. They classified 132 occupational groups into quintiles according to their estimated physical energy requirements. They reported that the overall mortality increased from less to more physically demanding occupations, and the strength of this association increased with age. Following these early publications, Dill et al. (1936) made a physical threshold recommendation for an 8-hour working day so that the full recovery would take place during the following 16-hours. They approximated that the maximum mean intensity that could be maintained for an 8-hour working period would be 8 MET. Since then, it has been suggested that the upper energy expenditure limit for 8-hour work would be $3.9-5.2 \text{ kcal} \cdot \text{min}^{-1}$ (4.3 MET) for gross energy expenditure (Lehmann et al., 1949; Lehmann, 1953; Passmore and Durnin, 1955;

Lehmann, 1962; Spitzer and Hettinger, 1964; Bonjer, 1968; Spitzer et al., 1982), 4 kcal·min⁻¹ (3.4 MET) for net energy expenditure (Müller, 1953), 21–35%VO_{2max} for work including manual handling and lifting (Petrofsky and Lind, 1978; Legg and Myles, 1981; Jorgensen, 1985), and 30–55%VO_{2max} for leg or total body work (Christensen, 1953; Christensen, 1955; Åstrand, 1960; Michael et al., 1961; Wyndham et al., 1962; Singleton, 1972; Lange Andersen et al., 1978). It has also been shown that individuals working in a construction site (Åstrand, 1967), doing housekeeping activities (Åstrand, 1971), fishing professionally (Rodahl and Vokac, 1979), walking while carrying a load (Evans et al., 1980), or doing heavy physical labor (Chaffin and Couto Hde, 1986; Kurumatani et al., 1992) adjust their work pace (intensity) so that they are utilizing approximately 40–45% of their VO_{2max}. Likewise, there is evidence that soldiers performing combat type activities or individuals walking while carrying different loads adapt their rate of energy expenditure within the limits of 400–450 kcal·h⁻¹ (or 5.7–6.4 MET) or 425 kcal·h⁻¹ ± 10% (or 6.1 MET) (Goldman, 1965; Hughes and Goldman, 1970). According to the current consensus, recommendation for the upper limit for daily energy expenditure during an 8-hour working day is 30–33%VO_{2max} for dynamic continuous work without specific breaks, and 50%VO_{2max} for intermittent dynamic or static work with specific breaks (Rutenfranz, 1985; Ilmarinen, 1992).

The development of recommendations for LTPA and exercise prescriptions were initiated by studies reporting an inverse association between vigorous LTPA and incidence of coronary heart disease (Morris et al., 1973). In 1975 American College of Sports Medicine (ACSM) published their first exercise recommendations for cardiorespiratory fitness in the first edition of Guidelines for Graded Exercise Testing and Exercise Prescription (Blair et al., 2004). Since the 1970's, a growing body of epidemiological evidence about the linkage between the daily physical activity and health, and the exercise physiological evidence about the effect of exercise dose on health, has provided the foundation for the development of physical activity recommendations. Since the early exercise recommendations, there has been little change in the recommended exercise dose. The early recommendations were, however, mainly aimed to induce improvement of cardiorespiratory fitness, whereas the more contemporary ones have aimed to improve general health. In addition, the different recommendations, promoted by different institution, countries, or organizations, are relatively similar (Table 1) (U.S. Departments of Health and Human Services, 2008; UKK Institute, 2010; World Health Organization, 2010; Garber et al., 2011; Government of United Kingdom, 2011; Current Clinical Guidelines, 2012; Australian Government, 2013; Canadian Society for Exercise Physiology, 2014) . According to the current physical activity recommendations, adults should perform in addition to the individual's daily physical activity a moderate to vigorous physical activity 3–5 times a week for 30–60 minutes, which can be accumulated throughout the day in ≥10 minute bouts.

The absolute intensity thresholds for light, moderate, vigorous, very vigorous, and extreme values reported for exercise and occupation are shown in Table 2. It seems from a historical perspective that the exercise thresholds are somewhat

Table 1. Current physical activity guidelines for health promotion

Guidelines	Aerobic						Strength training				
	Moderate			Vigorous			Total	Freq	Exerc	Sets	Reps
	Dur	Int	Freq	Dur	Int	Freq					
USA (2008)	≥150	3.0–5.9	ns	≥75	≥6.0	ns	COM	≥2	MMG	≥1	≥8–12
UKK (2009)	≥150	ns	≥3	≥75	ns	≥3	COM	≥2	8–10	ns	≥8–12
CCG (2012)	≥150	ns	≥3	≥75	ns	≥3	COM	≥2	ns	ns	ns
WHO (2010)	≥150	ns	MD	≥150	ns	ns	COM	≥2	MMG	ns	ns
ACSM (2011)	≥30 ^a	ns	≥5	≥20 ^a	ns	≥3	≥500 ^b	2–3	MMG	2–4	8–20
UK (2011)	≥150	ns	≥5	≥75	ns	≥5	COM	≥	MMG	ns	ns
Australia (2013)	≥30 ^a	ns	MD	≥20 ^a	ns	3–4	COM	ns	ns	ns	ns
CSEP (2014)	≥150	ns	ns	≥150	ns	ns	COM	≥2	MMG	ns	ns

Dur, duration (minutes per week); Int, intensity (metabolic equivalent of task (MET)); Freq, frequency (times per week); Exerc, number of exercises; Reps, number of repetitions ns, not specified; COM, combination of moderate and vigorous; MMG, major muscle groups; md, most days UKK, Urho Kekkonen Fitness Institute Foundation; CCG, Current Clinical Guidelines (Finland); ACSM, American College of Sports Medicine; CSEP, Canadian Society of Exercise Physiology, ^aminutes per day, ^b MET-minutes per week

derived from those given for occupation. The function of time, that is the volume, should however be acknowledged when the classifications are applied to the study of health risks and benefits. Current physical activity guidelines have evolved from exercise only recommendations to ones that include all types of higher intensity activities of daily living. In spite of this development, neither occupational nor current physical activity guidelines take into account total daily physical activity. Alternatively, total daily energy expenditure has been applied for characterizing physical activity level (Table 2) (Orr and Leitch, 1938; Taylor and MacLeod, 1949; FAO/WHO, 1973; FAO/WHO/UNU, 1985; FAO/WHO/UNU, 2001; Dietary reference intakes, 2005; Scientific Advisory Committee on Nutrition, 2012). It has been estimated that PAL of 1.27 indicates the minimum level of physical activity that is required for survival (FAO/WHO/UNU, 1985), while the PAL of ≥1.70 is required for health benefits (FAO/WHO/UNU, 2001). One major limitation of PAL based guidelines is that it does not include the possible effect of fluctuation in the intensity pattern of daily physical activity.

In addition, the existing evidence supports that physical activities that do not reach the intensity threshold of the current physical activity guidelines could still have beneficial health effects independently of the moderate/vigorous physical activity status (Hamilton et al., 2007; Katzmarzyk, 2010; Tremblay et al., 2011b). Thus, in addition to physical activity guidelines, recommendations for minimizing sedentary behavior or screen time have been made, unfortunately only for children and youth (American Academy of Pediatrics. Committee on Public Education, 2001; Jordan and Robinson, 2008; Tremblay et al., 2011a; Australian Government, 2013). Sedentary behavior has been defined to include all waking time spent in sitting in a reclining posture with an intensity of lower or equal to 1.5 MET (Sedentary Behaviour Research, 2012). The general conclusion from these guidelines is that the time used for sedentary behavior should be minimized or limited to 1–2 hours per day. Among Finnish children, 52% of boys and 56% of girls viewed television ≤2 hours per day (Tammelin et al., 2007). In spite of

Table 2. Physical activity intensity categories for work, leisure, and total 24 hours

Study	Target	Very Light or sedentary			Moderate	Heavy or vigorous	Very heavy	Extremely heavy
		Light						
Dill et al. (1936)	8 h of Work	-	-	1.0–3.0	3.0–8.0	-	-	
Christensen et al. (1953) ^a	8 h of Work	-	2.0–4.1	4.1–6.1	6.1–8.2	8.2–10.2	>10.2	
Brown (1963) ^b	8 h of Work	0.9–1.7	1.7–2.6	2.6–4.3	4.3–6.9	>6.9	-	
WHO (1978)	8 h of Work	-	<3.0	3.0–4.5	4.6–7.0	>7.0	-	
Åstrand (1988) ^a	8 h of Work	2.0–3.1	3.1–4.1	4.1–6.1	6.1–7.1	-	>7.1	
ISO 8996 (2004) ^c	8 h of Work	-	1.3–2.4	2.4–3.6	3.6–4.7	>4.7	-	
Durnin (1985) men	30–60 min of Leisure/EX	<2.3	2.3–4.6	4.6–6.9	>6.9	-	-	
Durnin (1985) women	30–60 min of Leisure/EX	<2.2	2.2–4.4	4.4–6.5	>6.5	-	-	
Howley (2001) ^d	30–60 min of Leisure/EX	<2.8	2.8–4.5	4.6–6.3	6.4–8.6	≥8.6	10	
Haskell et al (2007)	30–60 min of Leisure/EX	-	-	3.0–6.0	>6.0	-	-	
ACSM (2011)	30–60 min of Leisure/EX	<2.0	2.0–2.9	3.0–5.9	6.0–8.7	≥8.8	-	
Orr and Leitch (1938), men ^e	24 h of day (PAL)	1.43	1.62	1.82	-	2.99	-	
Orr and Leitch (1938), women ^e	24 h of day (PAL)	-	1.67	-	-	2.65	-	
Taylor & Macleod (1949), men ^e	24 h of day (PAL)	-	1.48–1.56	1.69–1.90	2.11–2.32	2.74	3.13	
Taylor & Macleod (1949), women ^e	24 h of day (PAL)	-	1.58–1.71	1.89–2.03	2.48	-	-	
FAO/WHO (1973), men ^e	24 h of day (PAL)	-	1.49–2.01	1.69–2.21	2.01–2.53	2.34–2.85	-	
FAO/WHO (1973), women ^e	24 h of day (PAL)	-	1.36–1.67	1.52–1.82	1.82–2.05	2.12–2.42	-	
FAO/WHO/UNU (1985), men	24 h of day (PAL)	-	1.55	1.78	2.1	-	-	
FAO/WHO/UNU (1985), women	24 h of day (PAL)	-	1.56	1.64	1.82	-	-	
FAO/WHO/UNU (2004)	24 h of day (PAL)		1.40–1.69	1.70–1.99	2.00–2.40	-	-	
DRI (2005)	24 h of day (PAL)	1.0–1.4	1.4–1.6	1.6–1.9	1.9–2.5	-	-	
SACN (2012) ^f	24 h of day (PAL)	-	1.27–1.49	1.50–1.77	1.78–2.5	-	-	

Values are metabolic equivalents of task (MET) unless PAL. WHO, World health Organization; ISO, International Organization for Standardization; EX, exercise; ACSM, American College of Sports Medicine; PAL, Physical activity level; FAO, Food and Agriculture Organization; UNU, United Nations University; DRI, Dietary Reference Intakes; SACN, Scientific Advisory Committee on Nutrition. aMET-values are estimated for 70 kg man and 55 kg woman from reported aoxxygen consumption, bKcal/min values, cW/m² or etotal energy expenditure, fLight = minimum–1 quartile (Q), moderate = Q1–Q3, heavy = Q3–maximum.

combining sedentary behavior and physical activity guidelines, the intensity and volume patterns of total physical activity requirements for health remains to be determined.

Above, four different physical activity related guidelines have been presented; 1) for 8 hour continuous work (<30–33% of VO_{2max}), 2) for moderate to vigorous physical activity (30–60 min/day), 3) for sedentary behavior (<1–2 h/day, children and youth only), and 4) for total energy expenditure (PAL ≥1.7). If the generally recommended amount of sleep (7–9 hours per day) is included, it is possible to schematically present the physical activity profile for health that meets all these recommendations. For an individual who sleeps 8 h/day and works 8 h/day with an intensity of 2.2 MET (28% of VO_{2max}), watches TV 2 h/day, and performs 30 min of moderate exercise, the average intensity of remaining 5.5 hours would have to be at least 1.6 MET to meet the PAL of 1.7 (Figure 4). If the intensity of work decreases to sedentary levels (1.4 MET), then the intensity of the remaining 5.5 hours should be at least 2.7 MET to achieve PAL of 1.7. In this latter case, however, the sedentary behavior recommendations (if, applied for adults) cannot be met due to the obligatory low intensity levels of occupation. These two

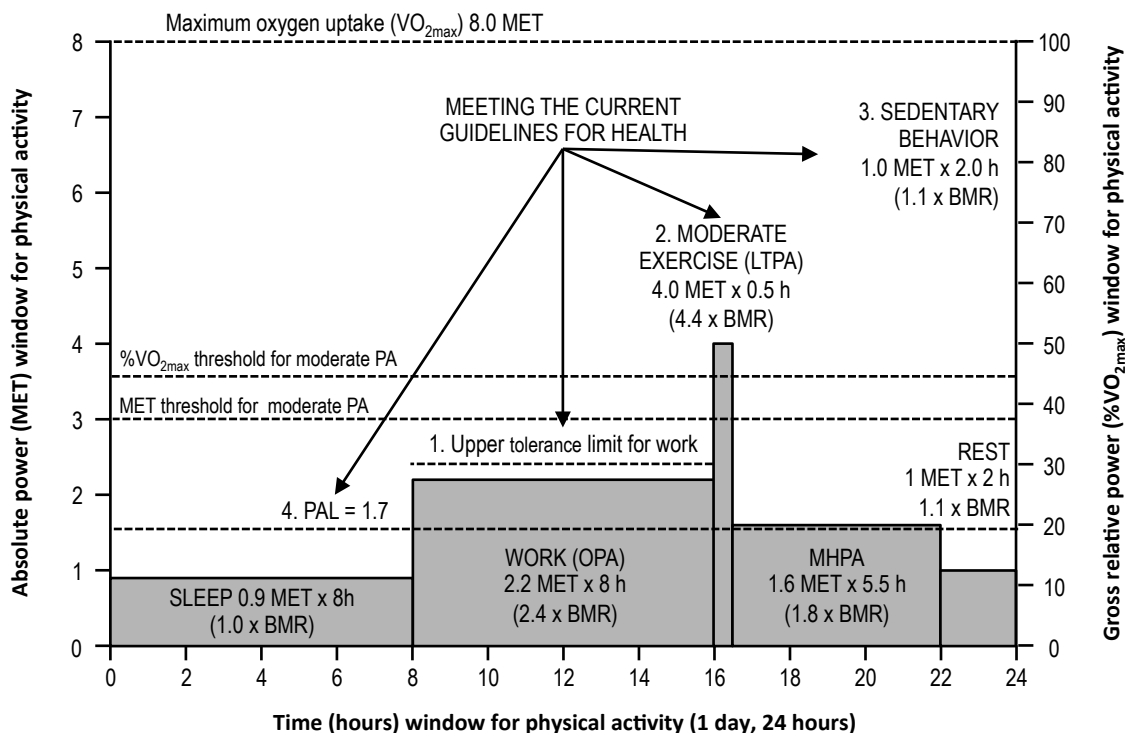


Figure 4. Schematic profile of 24-hour physical activity in an average adult that meets different physical activity related recommendations for health. MET, metabolic equivalent; BMR, basal metabolic rate (0.9 MET); PA, physical activity; OPA, occupational physical activity, MHPA, miscellaneous home physical activity.

simple examples clearly emphasize the importance of total physical activity intensity and volume pattern on health and the interrelationships of different recommendations. In any given occasion, it seems that people are more likely to meet the current moderate or vigorous guidelines than guidelines for sedentary behavior and PAL.

2.2 MODULATION OF PHYSICAL ACTIVITY

2.2.1 PHYSICAL ACTIVITY TRANSITION

Physical activity transition is a concept introduced by Katzmarzyk and Mason (2009) to describe the effect of changes in macro-level economic and demographic factors to physical activity levels and ultimately to human health. The driving force for movement of the early homo group hominids was to forage and hunt food, with good energetic and nutritional value, from large areas to satisfy the needs of their brains and bodies (Bellisari, 2008; Leonard, 2010). The hunter-gatherer or forage societies flourished until the agriculture established its place as the global leader of subsistence about 10 000–3 000 years ago (Bellisari, 2008). During the last centuries, the mechanization, automation, and emerging new technologies have

been aimed to increase the efficiency of extracting energy from environment per unit of physical labor (Bellisari, 2008; Leonard, 2010), and also to decrease the energy cost of occupations, transportation, and household tasks (Katzmarzyk and Mason, 2009; Archer et al., 2013). Thus, it has been postulated that the industrialization or westernization has induced an obesogenic environment with abundance of available high-energy foods and low physical activity (O'Dea, 1992; Misra and Khurana, 2009; Katzmarzyk and Mason, 2009).

The physically active Paleolithic era was probably the period in human history, when the genome of modern human evolved (Booth et al., 2002). The human genome has been reported to have remained relatively unchanged since the late Paleolithic era (Cavalli-Sforza et al., 1994), which implies that the human genes are inheritably programmed to function in an environment of high physical activity (Booth et al., 2002). In fact, Booth et al. (2002; 2009; 2010) have postulated that the regulation of human genes is programmed to function optimally in a certain ancestral physical activity and that the optimal gene function is a prerequisite for health. The average PAL of modern westerners (PAL = 1.37) has been estimated to be substantially lower than that of the human ancestors (PAL = 1.6–1.8) or foragers (PAL = 1.51–2.15) (Cordain et al., 1998). Cordain et al. (1998) have estimated that the daily total energy expenditure of modern westerners is only about 65% of that of the human ancestors. Even more strikingly PAL of modern human is only about 38% of that of the PAL during the Paleolithic years of foraging. To meet the level of energy expenditure of our ancestors Cordain et al. (1998) have approximated that an average American should increase his daily total energy expenditure by about $17 \text{ kcal}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, which corresponds to a 19 km walk for a 70 kg man. Even with brisk walking speed (6.5 km/h) it would take nearly 3 hours per day to complete this task, thus far exceeding the amount of physical activity required to meet the current physical activity guidelines (30–60 min).

Interestingly, the evidence concerning the decrease in physical activity with modernization has not been conclusive (Dugas et al., 2011). To support the decrease in physical activity, Esparza et al. (2000) have reported that daily energy expenditure was approximately $500\text{--}600 \text{ kcal}\cdot\text{d}^{-1}$ higher among Pima Indians living a traditional lifestyle in Mexico than among their age and sex matched westernized Pima Indians living in the USA. In addition, the PAL of modern humans has been estimated to be substantially lower compared to the free-ranging mammals (Hayes et al., 2005). In contrast, it has been reported that physical activity energy expenditure has not decreased from 1980 to 2005 among Europeans and North Americans compared to the wild mammals, which can be used as a proxy to study the effect of development on human physical activity (Westerterp and Speakman, 2008). Pontzer et al. (2012) have also reported no differences in daily energy expenditure between the Hadza hunter-gatherers living in Northern Tanzania and westerners when adjusted for sex, age and body mass. They however found that the PAL was higher in Hadza than in westerners, which would suggest that the Hadza in general spend less time resting. Furthermore, the physical activity level of the Yakut, a subsistence population living in Siberia, has

been shown to match that of the sedentary populations, however the energy expenditure was higher among those who were more involved with subsistence activities (Snodgrass et al., 2006).

In agriculture societies, it has been shown that total daily energy expenditure and PAL is similar between rural and urban dwelling Nigerians and African-American adults living in the USA (Luke et al., 2002). Likewise, the active energy expenditure of Nigerian women, of who 21% were engaged in subsistence farming, corresponded with that of the African-American women living in suburban areas of Chicago (Ebersole et al., 2008). In an agropastoral community, living in the Andes (Bolivia), the total energy expenditure of men corresponds to that of physically active men in Northern Ireland and young men in the USA, whereas the energy expenditure of women was substantially higher than previously reported values of urban-dwelling women (Kashiwazaki et al., 1995). As expected, the energy expenditure of rural Gambian women during the most physically demanding season of agriculture has been shown to be substantially higher than among the affluent women living in Cambridge (Singh et al., 1989). In addition, total acceleration and standing time was higher and sitting time lower among rural dwelling Jamaicans compared to urbanized Jamaicans or North Americans (Levine et al., 2011).

According to a meta-analysis of 98 doubly labeled water studies, the daily energy expenditure was similar between countries with low or middle human developmental index (HDI) and countries with high HDI (Dugas et al., 2011). This analysis however did not account for the occupation or living environments (urban or rural), which may have affected the results. In fact, Sobgnwi et al. (2002) have previously reported a substantial difference in energy expenditure between urban and rural-dwelling people living in Cameroon, which has a middle level HDI (Malik, 2013). Another review, including 26 studies, suggested that the PAL of the farmers in developing countries is mostly located in the upper end of the moderate physical activity range (Dufour and Piperata, 2008). The body of evidence seems to favor the general conception that the immigration from traditional to western culture is associated with decrease in health due to the acculturation, including a more sedentary lifestyle (Caperchione et al., 2009). Based on the current evidence, it seems, however, that at a population level people living in industrialized societies are somewhat more active than expected, whereas people living in subsistence societies are less active than intuitively reasoned (Snodgrass, 2012).

Albeit the changes in total physical activity with industrialization tend to be less than expected, it is obvious that technological advances have decreased occupational workload. Sukhatme (1969) has estimated that the average occupational energy expenditure among American citizens declined approximately 200–300 kcal·day⁻¹ between the years 1940 and 1964. Since 1960 to 2008, it has been estimated based on the annual United States employment records that the average intensity of OPA has decreased about 0.25 MET, and that work related energy expenditure has decreased approximately 140 kcal·day⁻¹ in men and 124·kcal·day⁻¹ in women (Church et al., 2011). Thus, it seems that the decrease in

the occupational physical activity energy expenditure has slowed down during the last half of the 20th century.

The major shift in the focus of health research, from OPA to LTPA, occurred in the 1970's. The early works of Morris in London largely influenced this change in focus. Morris and co-workers (Morris and Heady, 1953; Morris et al., 1953) demonstrated a greater prevalence of chronic diseases among those in physically light occupations compared to those in physically demanding occupations. They also demonstrated that the incidence of coronary heart disease was lower among those British Civil Servants in physical low occupations who participated in vigorous LTPA (Morris et al., 1973). As described in the previous chapter, this change in scientific climate is also evident in the development of physical activity recommendations (Table 1 and 2) and physical activity questionnaires applied in research (Powell et al., 1987).

From 1978 to 2011, an annual survey on Finnish adult population has shown that the participation rate in LTPA at least twice a week has increased steadily from approximately 40% to over 60% (Helakorpi et al., 2012). The participation in LTPA at least four times has remained relatively stable between the years 1995 and 2011 (30%) (Helakorpi et al., 2012). In another Finnish survey based on a random population sample, participation in LTPA at least four hours per week has been shown to increase between 1972 and 2012, especially among Finnish men (Borodulin et al., 2008; Borodulin and Jousilahti, 2012). Similarly, the LTPA trends in the USA, have suggested an increased prevalence of regular LTPA while the prevalence of no participation at all in LTPA or exercise has decreased (Centers for Disease Control and Prevention (CDC), 2004; Centers for Disease Control and Prevention (CDC), 2007). Simultaneously with increased LTPA, the occupational and commuting physical activity has decreased (Borodulin et al., 2008; Borodulin and Jousilahti, 2012; Helakorpi et al., 2012). Archer et al. (2013) have also suggested that between the years 1965 and 2010, the energy expenditure of household activities has decreased 30–42% among US women, mainly due to the technological advances and changes in women's employment. During these years researchers also found an 8.3 h·wk⁻¹ increase in screen based media time and 1.2 h·wk⁻¹ increase in time used for LTPA (Archer et al., 2013). Interestingly, researchers reported that a stepwise increase in LTPA took place in the 1970's and has remained in that level since (Archer et al., 2013). These types of cultural changes in daily physical activity have possibly resulted in an increased importance of LTPA and exercise for health (Katzmarzyk and Mason, 2009).

2.2.2 REGULATION OF PHYSICAL ACTIVITY

An in-depth review of factors and mechanisms that regulate daily physical activity is beyond the scope of this literature review, due to the number of possible factors and their inter-relatedness. Regulation of physical activity can be divided simply into biological/genetic factors, environmental factors, or their interactions. This approach is common in genetic studies (Knab and Lightfoot, 2010). From a more behavioral perspective, Dishman et al. (1985) divided factors that affect physical

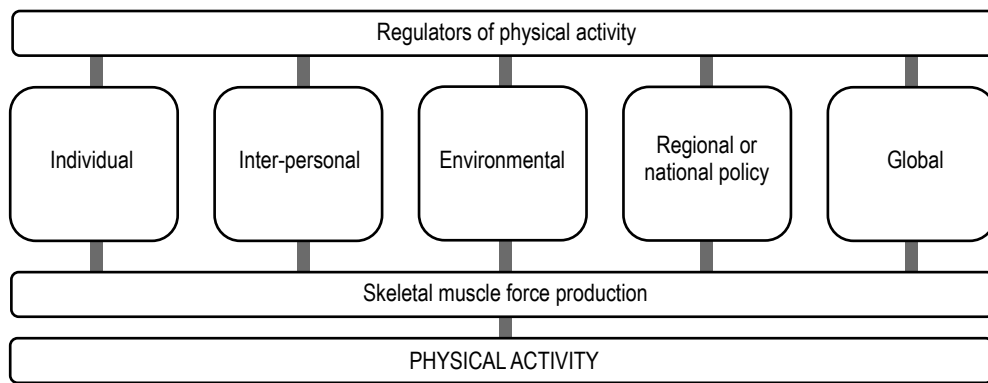


Figure 5. Regulation of physical activity via skeletal muscle contraction. Classification of the regulation factors according to Bauman et al. (2012).

activity in to three categories; 1) personal characteristics, 2) environmental charactersitics, and 3) activity characteristics. This model can be further refined into an ecological model, in which factors that can contribute to physical activity have been divided into five categories; 1) individual, 2) interpersonal, 3) environmental, 4) regional or national policy, and 5) global factors (Bauman et al., 2012). Furthermore, the individual category can be divided into interplay of psychological and biological factors, which include evolutionary physiology and genetic factors (Figure 5).

Twin and family studies have reported that heritability explains 0–85% of physical activity (de Vilhena e Santos et al., 2012). This large variability between the studies is most likely explained by the difference in the physical activity measurement methods, design of the study, population investigated, and the phenotype studied (determinant of physical activity). Among 13–16 year old children, it has been shown that mostly environmental factors contribute to the participation in sports (Stubbe et al., 2005). The influence of genetic factors however increases with age, explaining 35% of the variance in sports participation among 17–18 year olds and 85% among 19–20 year old subjects (Stubbe et al., 2005). From 18–29 year olds to 50–59 year olds, the effect of heritability seems to steadily decrease from 64% to 32%, respectively, until it curves back to 62% among subjects who were at least 60 years old (Kaprio et al., 1981). These findings together with findings from a 26-week follow-up study on mice (Turner et al., 2005) suggest a possible gene x age interaction effect on physical activity.

Several possible candidate genes and quantitative trait loci for physical activity have been identified and previously reviewed (Dishman, 2008; Lightfoot, 2011a; Lightfoot, 2011b; de Vilhena e Santos et al., 2012; Bauman et al., 2012). The current evidence about the candidate genes is inconsistent, possibly due to the variability in the studied phenotype. In addition, the specific mechanism by which physical activity genes mediate their regulative effect is unknown. In the only genome-wide association study (GWAs) on regular leisure-time exercise (≥ 4 METh per week) 37 novel single nucleotide polymorphisms (SNPs) from 3 different DNA regions were found, including 3'-phosphoadenosine 5'-

phosphosulfate synthase 2 (*PAPSS2*) gene (De Moor et al., 2009). *PAPSS2* has loosely been associated with the ability to exercise, which could influence physical activity (Ikeda et al., 2001; Rico-Sanz et al., 2004). Regulation of exercise ability has also been associated with the nescient helix-loop-helix 2 (*NHLH2*) gene and solute carrier family 2 facilitated glucose transporter, member 4 (*SLC2A4*) gene (Tsao et al., 2001; Good et al., 2008). *SLC2A4*, which codes primary glucose transporter (GLUT4) of skeletal muscles, could increase the tolerance for exercise-induced fatigue. Meanwhile Good et al. (2008) have suggested that *NHLH2* could affect peripherally by regulating skeletal or heart muscle function. It has also been proposed that the hypothalamic expression of *NHLH2* transcription factor could decrease energy expenditure by decreasing the level of functional hypothalamic neuropeptides (Jing et al., 2004). In addition, inhibition of *NHLH2* activity in brain could inhibit β -endorphin response to exercise, thus reducing the motivation to exercise (Good et al., 2008). *NHLH2* has also been associated with the regulation of melanocortin 4 receptor (*MC4R*) gene and melanocortin pathway (Wankhade and Good, 2011). *MC4R* is another candidate gene for physical activity and it has been shown to regulate the physical activity response to altered diet (Butler et al., 2001; Loos et al., 2005; Cole et al., 2010). Furthermore, dopamine receptor genes (*DRD1*, *DRD2*, *DRD4*) may also regulate physical activity through the dopamine system, which is involved in the regulation of motor movement, reward, and motivation (Knab and Lightfoot, 2010). In fact, it has been postulated that the dopamine system could increase the inner drive for voluntary physical activity (Knab and Lightfoot, 2010; Lightfoot, 2011a). In contrast, Jozkow et al. (2013) have reported no association between the *DRD2* or *DRD4* single nucleotide polymorphisms (SNPs) and physical activity in healthy men. To support the role of the dopamine system in the regulation of self-reported physical activity, Teske et al. (2008) have reported that dopaminergic pathways interact reciprocally with several different neuropeptides that have been linked to physical activity, including orexin. The multifactorial role of neuropeptides, especially orexin, in the regulation of physical activity has previously been extensively reviewed (Teske et al., 2008; Kotz et al., 2012; Butterick et al., 2013).

Early development, prenatal environment, epigenetic inheritance, early-life nutrition or physical activity status, and behavioral development can also influence physical activity later in life. In rodents, fetal growth restriction (Baker et al., 2010), maternal undernourishment (Vickers et al., 2003), and protein intake restriction (Bellinger et al., 2006) during pregnancy have been associated with physical inactivity. In humans, both low and high birth weight has been associated with decreased odds of participation to LTPA (Andersen et al., 2009). In contrast, birth weight has not been linked to reported sedentary lifestyle in 10–12 year old children (Hallal et al., 2006; Mattocks et al., 2008). Objectively measured physical activity (accelerometer) has however been greater among 11–12-year old children whose mothers did not smoke and were physically more active during pregnancy (Mattocks et al., 2008). The molecular mechanisms underlying the possible association between the prenatal environment and

physical activity are not understood, albeit epigenetics including DNA methylation or histone acetylation are likely to have an affect.

In addition to genes, there are multiple individual, interpersonal, and environmental factors that can modify physical activity (Dishman et al., 1985). The leading environmental barrier for exercise is the concern about the safety of the neighborhood (Mier et al., 2007; Kamphuis et al., 2008; Caperchione et al., 2009) but also lack of facilities (Brownson et al., 2001; Mier et al., 2007; Skowron et al., 2008), and poor weather (Hays and Clark, 1999; Mier et al., 2007), have been reported. Barriers related to the household are the lack of childcare, insufficient space at home (Piana et al., 2013), financial issues (Caperchione et al., 2009), and social deprivation (Kamphuis et al., 2008). As expected, the largest group of possible barriers are related to individual factors, including lack of time (Brownson et al., 2001; Mier et al., 2007), lack of motivation (Hays and Clark, 1999; Brownson et al., 2001), negative outcome expectancies, low self-efficacy (Kamphuis et al., 2008), health issues (Hays and Clark, 1999; Mier et al., 2007; Caperchione et al., 2009), daytime sleepiness (Chasens et al., 2009), obtaining enough occupational activity (Brownson et al., 2001), religious activities (Caperchione et al., 2009), and fatigue (Brownson et al., 2001; Piana et al., 2013). It has also been suggested that the fear of losing the security of habitual behavior can feed the resistance to change among obese people (Piana et al., 2013). Interpersonal factors that may affect physical activity include limited social connections and support (Kamphuis et al., 2008; Caperchione et al., 2009), language (Caperchione et al., 2009), and cultural norms or codes (Caperchione et al., 2009). It is worth noting that the relevance of these modulators of physical activity or “barriers to exercise” tends to vary depending on the sex, race, socioeconomic position, and cultural background (Bauman et al., 2012). Based on the 574 double labeled water measurements, the physical activity related energy expenditure was 11% lower among women compared to the age and size matched men (Black et al., 1996). This difference could be intermediated by difference in the sex hormones, although the evidence is limited (Bowen et al., 2011).

2.2.3 EXERCISE AND TOTAL PHYSICAL ACTIVITY

The main purpose of physical exercise in health sciences is to induce physiological or psychological adaptation that enhances health, functioning ability, physical capacity, physical ability, or physical performance and longevity by preventing the development or progression of diseases or disabilities. These adaptations cannot occur if the existing state of affairs remains unchanged and the initial signal for adaptation procedures is lacking. Thus, the goal of exercise is to overload (overload principle) the bodily systems that are specifically (specificity principle) related to the targeted health factor (McArdle et al., 2007). To obtain wanted changes in the observed determinant of health, the overload and specificity should be sufficiently high or specific to overcome the load of the daily physical activity, and hence to provide the initial spark for adaptation. In humans, exercise should be regular and repetitive in nature to enable clinically significant health

adaptation to take place. Furthermore, the daily non-exercise physical activity, which could alter the true effects of exercise, should remain unchanged during the exercise intervention. Epstein and Wing were probably the first to report this type of compensatory behavior in health research (1980) in their review about the effect of aerobic exercise on body weight. In addition, increasing the daily physical activity during the exercise intervention is possible. Naturally, activation beyond the prescribed intervention is generally viewed as a positive result. In research it is also important to take into account that the excess activation during non-exercise time could result in overestimation of the effect of specific exercise intervention. Thus, it is important to understand how exercise interventions affect the non-exercise daily physical activity.

Previous studies that have investigated the effect of exercise on total physical activity by comparing baseline and intervention physical activity have been described in Table 3. In these 14 previous publications reviewed (Meijer et al., 1991; Goran and Poehlman, 1992; Blaak et al., 1992; Van Etten et al., 1997; Morio et al., 1998; Meijer et al., 1999; Hunter et al., 2000; Barwell et al., 2009; Hollowell et al., 2009; Colley et al., 2010; Manthou et al., 2010; Breyer et al., 2010; Turner et al., 2010; Rangan et al., 2011), the effect of aerobic exercise was investigated in 11 studies, the effect of resistance training in 3 studies, and the effect of combined aerobic and resistance training in 2 studies. The duration of the interventions varied from 4 weeks to 10 months. Based on the data provided by the authors, it was estimated that the physical activity measurements during the intervention accounted for only 15% (range: 2–50%) on average of the total duration of the whole intervention period (range: 4–40 weeks).

In five previous studies, it was reported that exercise induced a compensatory decrease in non-exercise energy expenditures and no change in total energy expenditure (Goran and Poehlman, 1992; Morio et al., 1998; Meijer et al., 1999; Colley et al., 2010; Manthou et al., 2010). The effect of aerobic exercise intervention alone was studied in four studies, whereas one study explored the effect of combined aerobic and resistance training (Meijer et al., 1999). Two studies on aerobic training (Meijer et al., 1991; Hollowell et al., 2009) and one study on resistance training (Rangan et al., 2011) have reported that exercise intervention induces no change in either total energy expenditure or non-exercise energy expenditure. In contrast, one aerobic study (Blaak et al., 1992) and one resistance training study (Hunter et al., 2000) have reported an increase in both total energy expenditure and non-exercise energy expenditure with exercise intervention. In addition, Breyer et al. (2010) have reported that a Nordic walking intervention increases non-exercise energy expenditure among subjects with chronic obstructive pulmonary disease (COPD). In 6 studies (7 analyses), exercise interventions have been reported to increase total energy expenditure without the compensatory or activatory change in non-exercise energy expenditure (Meijer et al., 1991; Van Etten et al., 1997; Barwell et al., 2009; Hollowell et al., 2009; Turner et al., 2010; Rangan et al., 2011). Of these studies, five investigated the effect of aerobic training, one the effect of resistance training, and one the effect of combined training. In a study by Hollowell et al. (2009), however, only the high-

Table 3. Description of studies reporting on the effect of exercise on total energy expenditure

Study	n (% men)	Age (years)	BMI (kg/m ²)	PA level (/wk)	Health	Type	Intensity	Freq	Intervention		PA method	%	nonEX EE	Total EE
									min/ session	Duration				
Aerobic training (AT)														
Banwell (2009)	55 (0)	35	28	< 1 h + SW	good	ns	65–80 %HR _{max}	3–5	30–60	7 wk	HR	14.3	↔	↑
Blaak (1992)	10 (100)	11	32*	nr	good	CE	55–67%VO _{2max}	5	60	4 wk	ICM + DLW	50	↑	↑
Breyer (2010)	60 (45)	62	26	nr	COPD	NW	75%HR _{max}	3	60	3 mo	ACC	5.3	↑	nr
Colley (2010)	13 (77)	41	34	< 1 h	good	W	HR _{ave} 129–137 bpm	3–4	~60	8 wk	HR + DLW	25	↔	↔
Goran (1992)	11 (55)	66	22*	nr	good	CE	60–85%VO _{2max}	3	150–300 kcal/ses	8 wk	HR + DLW	17.9	↓	↔
Hollowell (2009) ^a	14 (64)	51	30	< 2 x	PMP, DL	AT	65–80%VO _{2peak}	3–5	8372 kJ/wk	8–9 mo	HR + ACC	1.7	↔	↑
Hollowell (2009) ^b	20 (50)	54	30	< 2 x	PMP, DL	AT	65–80%VO _{2peak}	3–5	5023 kJ/wk	8–9 mo	HR + ACC		↔	↔
Hollowell (2009) ^c	8 (37)	57	29	< 2 x	PMP, DL	AT	40–50%VO _{2peak}	3–5	5023 kJ/wk	8–9 mo	HR + ACC		↔	↔
Hollowell (2009) ^d	8 (50)	51	31	< 2 x	PMP, DL	Control	na	na	na	8–9 mo	ACC		↔	↔
Manthou (2010)	34 (0)	27	30	< 1 h + SW	good	CE	90–95%LT	2 or 5	75 or 30	8 wk	PAD + HR	12.5	↓	↔
Meijer (1991) ^a	16 (0)	35	23	< 1 h	good	RUN	70–100%HR _{max}	3–4	60 or 15–40 km/wk	10 mo	ACC + DLW	2.5	↔	↔
Meijer (1991) ^b	16 (100)	37	23	< 1 h	good	RUN	70–100%HR _{max}	3–4	60 or 15–40 km/wk	10 mo	ACC + DLW		↔	↑
Morio (1998)	13 (38)	63	33*	no regular EP	PMP	CE	50%VO _{2max} – LT	3	40*	14 wk	DIA + DCM + ICM	14.3	↓	↔
Rangan (2011) ^a	28 (50)	52	31	< 1–2 times	DL	ns	65–80%VO _{2peak}	3	14 kcal/kg/wk	8 mo	ACC	<3.1	↔	↑
Turner (2010)	29 (100)	45–64	28	sedentary	good	W/RUN	50–70%VO _{2max}	3–4	30–60	24 wk	ACC + HR	12.5	↔	↑
Resistance training (RT)														
Hunter (2000)	15 (47)	67	25	< 1 h	good	10 x 2 x 10	65–80%RM	3	45	26 wk	EST + DLW	7.7	↑	↑
Rangan (2011) ^b	28 (29)	51	30	< 1–2 times	DL	8 x 3 x 8–12	8–12RM	3	nr	8 mo	ACC + IDC	<3.1	↔	↔
Van Etten (1997)	26 (0)	34	23*	no regular EP	good	10 x 3 x 15	nr	2	nr	18 wk	HR + DLW + ACC	22.2	↔	↑
Combined AT + RT														
Meijer (1999)	22 (45)	>55	25	nr	good	AT	nr	2 (total)	150 (total)	12 wk	ACC	21.8	↓	↔
Rangan (2011) ^c	26 (38)	48	31	< 1–2 times	DL	RT: 8 x 2 x 10	65–80%VO _{2peak}	3	14 kcal/kg/wk	8 mo	ACC + IDC	<3.1	↔	↑
						RT: 8 x 3 x 8–12	8–12RM	3	nr	8 mo	ACC + IDC		↔	↔

BMI, body mass index; PA, physical activity level; Freq, frequency; %, estimated percentage of total intervention time (24 hours and 7 days a week) measured; nonEX, non-exercise; EE, energy expenditure; AT, aerobic training; SW, sedentary work, ns, not specified; HR_{max}, maximum heart rate; HR, heart rate, nr, not reported; CE, cycle ergometer; VO_{2max}, maximum oxygen uptake, ICM, indirect calorimeter; DLW, double labeled water; COPD, chronic obstructive pulmonary disease; NW, Nordic walking; ACC, accelerometer; W, walking; VO_{2peak}, peak oxygen uptake; PMP, post-menopausal; DL, dyslipidemia; RUN, running; PRW, ^{a-d}indicate the individual analysis within a study.

intensity and high-volume aerobic training group was associated with increased total energy expenditure, while no change in total energy expenditure was found in the other two groups with lower intensity and/or volume compared to the non-exercise control group. In addition, in the study by Meijer et al. (1991) the effect of a running intervention was found to increase total energy expenditure only among men, whereas among women no change in total energy expenditure was found. It has also been shown that physical activity and/or total energy expenditure increases after resistance training interventions (Campbell et al., 1994; Ades et al., 2005).

It is difficult to compare these studies directly due to the differences in subjects' characteristics, applied measurements, prescribed exercise doses, and duration of the interventions. The duration of intervention, however, seems to be systematically shorter in 5 studies reporting compensatory behavior (mean 10.0 weeks, SD 2.8) than in 6 studies providing evidence for no compensation (mean 25.8 weeks, SD 12.0). This could suggest that longer interventions are required to balance out the extra load of the exercise intervention and the development of new daily energy expenditure level (Hollowell et al., 2009; Pedersen et al., 2012). Inconsistently, one 60 min session of walking on a treadmill with a speed of 6 km/hour with or without 5 min intervals with 10% grade has been found not to induce decrease in non-exercise energy expenditure in the following days (Alahmadi et al., 2011). It could also be that the proportion of time measured during the intervention may have affected the results. It can be argued that the higher the proportion measured from the total intervention duration, the more accurate are the estimates of change in physical activity energy expenditure. The average proportion of intervention measured among the studies that found compensatory decrease in non-exercise energy expenditure was almost twice as high (mean 18 %, SD 5) compared to the studies that demonstrated increase in total physical activity without related compensation (mean 9%, SD 8).

The aforementioned studies are limited to the measurement of total energy expenditure and energy balance aspects of physical activity, and no studies exist that have investigated the effect of exercise on both the physiological (intensity and volume) and behavioral aspects of physical activity. In addition, the energy expenditure measurements have included only a relatively small portion of the intervention. Thus, the assumption of consistency of physical activity of subjects throughout the intervention has to be made and taken into consideration when interpreting the results. It is also important to consider whether the predisposition to compensate is similar between those who have clinical condition and those who are healthy. In a previous review on subjects with COPD, the exercise had only a small effect on the physical activity (walking time increased approximately 5 min·day⁻¹) (Cindy Ng et al., 2012). It has been also suggested that biological control of body homeostasis could drive compensation behavior (Rowland, 1998). The evidence, largely those studies summarized in the Table 3, concerning this ActivityStat hypothesis, which suggests that physical activity level has a tendency to remain stable, is however inconsistent and future studies are required (Gomersall et al., 2013).

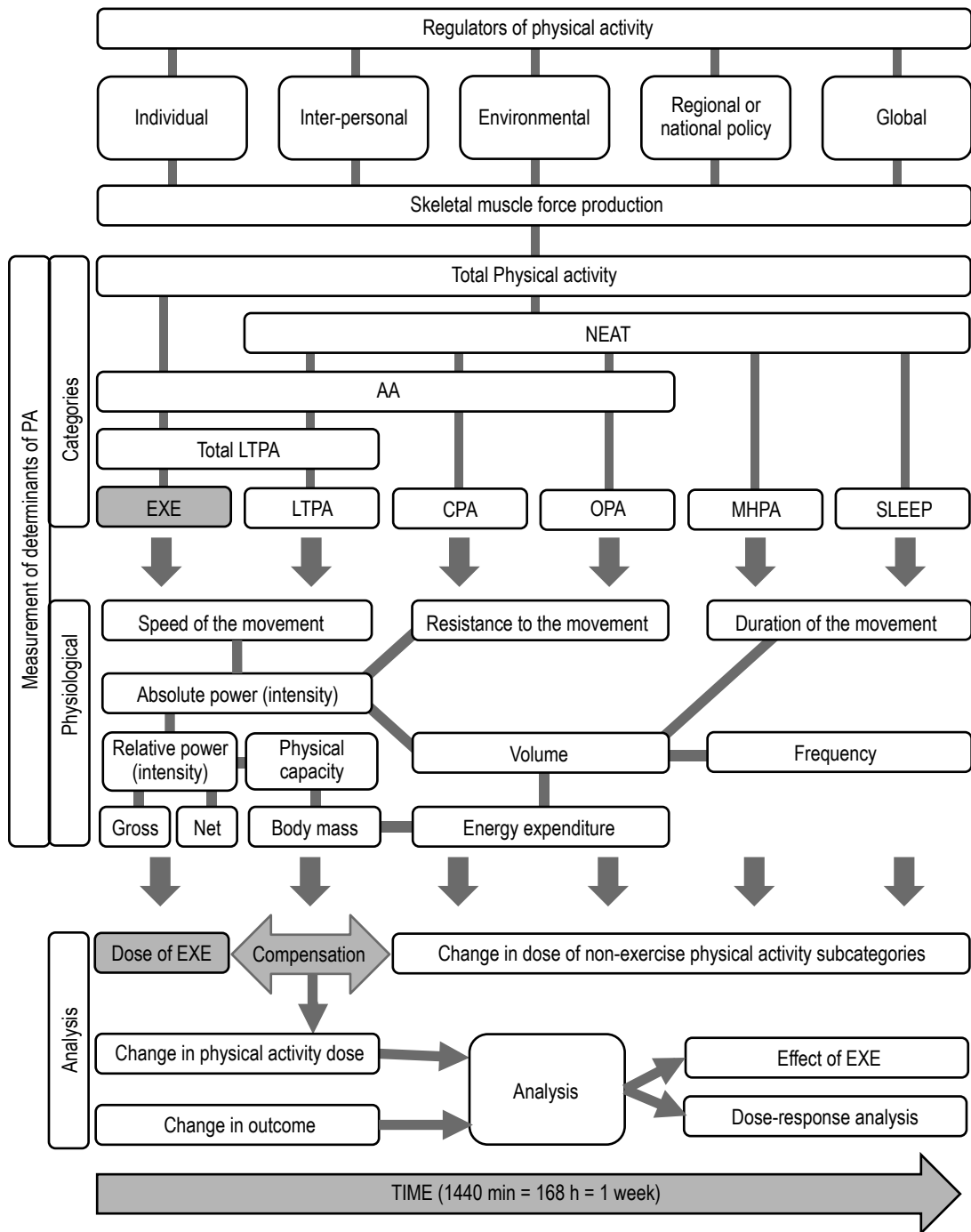


Figure 6. Theoretical model of physical activity measurements and analysis. NEAT, non-exercise activity thermogenesis, AA, activity time, EXE, exercise, LTPA, leisure-time physical activity; CPA, commuting physical activity; OPA, occupational physical activity; MHPA, miscellaneous home physical activity.

The theoretical model of physical activity measurement and analysis described in Figure 6 demonstrates the independency of the physiological determinants of physical activity from physical activity categories, and relative importance of exercise and non-exercise physical activity in determining the change in outcomes.

2.3 PHYSICAL ACTIVITY AND PREVENTION OF TYPE 2 DIABETES

2.3.1 TYPE 2 DIABETES, IFG, AND IGT

Type 2 diabetes is a metabolic disorder associated with chronically elevated blood glucose levels due to several metabolic factors, including insulin resistance and relative insulin deficiency. There are no specific diagnostic criteria for type 2 diabetes. According to the definitions by WHO, the diagnosis of diabetes can be based on elevated fasting plasma glucose ($\geq 7.0 \text{ mmol}\cdot\text{l}^{-1}$), plasma glucose after a 75-gram standard 2-hour glucose tolerance test ($\geq 11.1 \text{ mmol}\cdot\text{l}^{-1}$), or glycated haemoglobin ($\text{HbA}_{1c} \geq 6.5\%$). Plasma glucose levels below the diabetic threshold have been referred to as a non-diabetic fasting value, impaired fasting glucose (IFG, $6.1\text{--}6.9 \text{ mmol}\cdot\text{l}^{-1}$), or impaired glucose tolerance (IGT, 2-h value during an OGTT $7.8\text{--}11.0 \text{ mmol}\cdot\text{l}^{-1}$). IFG and IGT are considered prediabetic stages that increase the risk of developing type 2 diabetes. In general, impaired glucose regulation (IGR) has been used as a hypernym of type 2 diabetes, IGT, and IFG.

Elevated HbA_{1c} , IGT, and IFG all increase the risk of developing type 2 diabetes. The risk of type 2 diabetes has been shown to increase exponentially with HbA_{1c} among Asian and Caucasian populations (Droumaguet et al., 2006; Sato et al., 2009). In a prospective cohort study with a 3-year follow-up time, HbA_{1c} was a stronger predictor of the incidence of type 2 diabetes than BMI (Edelman et al., 2004). In the Hoorn study, the Caucasian subjects with IFG (odds ratio, OR, 10.0; 95% confidence interval, CI, 6.1–16.5), IGT (OR, 10.9; 95% CI, 6.0: 19.9), and especially those with both IFG and IGT (OR, 39.5; 95% CI, 17.0: 92.1) were at an increased risk of developing type 2 diabetes (de Vegt et al., 2001). In Middle Eastern populations the odds ratios for developing type 2 diabetes were 7.4 (95%CI, 3.6: 15.0) for subjects with IFG, 5.9 (95% CI, 4.2: 8.4) for IGT, and 42.2 (95% CI, 23.8: 74.9) for combined IFG and IGT (Harati et al., 2009). It has been estimated that even up to 70% of subjects with IGT or IFG develop type 2 diabetes during their lifetime (Nathan et al., 2007). In addition, elevated HbA_{1c} , IFG, and IGT all increase the risk of cardiovascular complications and mortality among non-diabetic subjects (Gabir et al., 2000; Saydah et al., 2001; DECODE Study Group, European Diabetes Epidemiology Group, 2003; Khaw et al., 2004).

Type 2 diabetes is caused by an interaction between genetic and environmental factors, although the specific mechanisms remain unclear. Pathophysiological consequences of type 2 diabetes include reduced insulin secretion from pancreatic beta-cells, insulin resistance in muscles, liver and fat tissue, increased glucagon secretion from pancreatic alpha cells, increased lipolysis, increased hepatic glucose production, increased renal reabsorption of glucose, impaired incretin effect, and dysfunction of neurotransmitters. The major adverse effects of type 2 diabetes, especially when untreated or poorly controlled, are increased mortality and increased risk for co-morbidities, including microvascular complications (e.g. retinopathy) and macrovascular complications (e.g. cardiovascular disease).

Lifestyle changes, together with the population growth and ageing, have more than doubled the worldwide incidence of diabetes in the past three decades (Danaei et al., 2011). Recently, it has been estimated that approximately 10% (350 million) of adults worldwide are suffering from diabetes (Danaei et al., 2011; Whiting et al., 2011) and the figure is estimated to increase by 51% by the year 2030 (Whiting et al., 2011). In Finland, the number of people with diabetes is approximately 500 000 (Reunanen, 2006; Koski, 2011), of which 85% suffer from type 2 diabetes (Sund and Koski, 2009). According to the latest estimates, the prevalence of type 2 diabetes is 8% in Finnish men and 7% in Finnish women (Peltonen et al., 2006).

2.3.2 RISK FACTORS FOR TYPE 2 DIABETES

The most important modifiable risk factors for type 2 diabetes are overweight or obesity and physical inactivity. In addition, there are several other modifiable risk factors, including smoking, dyslipidemia, hypertension (Gress et al., 2000), depression (Eaton et al., 1996; Kawakami et al., 1999), psychosocial factors (e.g. effort-reward imbalance) (Kumari et al., 2004), statin treatment, and environmental toxins. The risk factors of type 2 diabetes can be divided into modifiable and non-modifiable risk factors as listed in Table 4. In this chapter, the epidemiological evidence of closely associated modifiable lifestyle related risk factors, including obesity, inflammation, physical activity, cardiorespiratory fitness, dietary intake, and sleep has been reviewed.

The link between the excess adiposity and insulin resistance has been established in several studies (Joslin et al., 1936; Newburgh and Conn, 1939; Karam et al., 1963; Bogardus et al., 1985). Studies with large samples have reported a close relationship between the incidence of type 2 diabetes and body mass index (BMI) (Knowler et al., 1981; Must et al., 1999; Wannamethee and Shaper, 1999; Fox et al., 2006). In a study by Field et al. (2001), the 10-year risk of developing type 2 diabetes was approximately 10 times higher in obese people (BMI = 30.0–34.9 kg/m²) and 20 times higher in people with severe obesity (BMI ≥ 35.0 kg/m²) than in their lean counterparts. In addition, weight gain or weight fluctuations have been shown to increase the risk of type 2 diabetes (Holbrook et al., 1989; Colditz et al., 1990; Colditz et al., 1995; Ford et al., 1997; Wannamethee and Shaper, 1999). According to a study by Wannamethee and Shaper, a weight gain of ≥10% increased the risk of type 2 diabetes in initially lean (BMI < 25.0 kg/m²) or overweight (BMI 25–27.9 kg/m²) men, but not in initially obese (BMI ≥ 28.0 kg/m²) men. It has also been shown that risk of developing type 2 diabetes increases with the duration of overweight or obesity (Wannamethee and Shaper, 1999), thus weight gain in early adulthood may be especially hazardous (Schienkiewitz et al., 2006). In addition to overall adiposity, the distribution of fat may affect the risk of type 2 diabetes (Vague, 1947; Vague, 1956; Feldman et al., 1969; Kissebah et al., 1982). In large studies, indicators of abdominal obesity, including waist circumference, waist-to-hip ratio, or waist-to-height ratio have been shown to be independent predictors of type 2 diabetes

Table 4. List of modifiable and non-modifiable risk factors for type 2 diabetes.

Modifiable risk factors	Non-modifiable risk factors
Overweight or obesity	Age
Distribution of body fat	Family history of diabetes
Waist circumference	Genetic factors
Waist-to-hip ratio	Race or ethnic background
Physical Inactivity	Gestational diabetes
Lack of exercise	Low birth size
Sedentary occupation	High birth size
Low cardiorespiratory fitness	Cardiovascular disease
Low musculoskeletal fitness	Depression
Sleep duration	
Dietary factors	
Refined carbohydrates	
High fat low fiber diet	
Alcohol consumption	
Prediabetic condition	
Elevated glycated haemoglobin	
Impaired glucose tolerance	
Impaired fasting glucose	
Chronic systemic low-grade inflammation	
Low adiponectin level	
Smoking	
Hypertension	
Dyslipidemia	
Statin medication	
Environmental toxins	

(Kaye et al., 1991; Chan et al., 1994; Carey et al., 1997; Wang et al., 2005; Meisinger et al., 2006; Huerta et al., 2013). The risk of type 2 diabetes is substantially increased when both high levels of overall and central adiposity are present (Kaye et al., 1991; Meisinger et al., 2006). According to recent meta-analyses of 15 studies by Kodama et al. (2012), the waist-to-height ratio and waist circumference were stronger predictors of type 2 diabetes than BMI or waist-to-hip ratio. The relative risk was, however, similar between the indicators (RR = 1.52–1.63) (Kodama et al., 2012). It has been suggested that chronic systemic low-grade inflammation could explain the pathogenesis of metabolic and cardiovascular complications in obesity. In obesity, the adipocyte enlargement has been associated with greater recruitment of macrophages in adipose tissue (Weisberg et al., 2003), proinflammatory changes in macrophages phenotype (Wentworth et al., 2010), and increased secretion of proinflammatory cytokines (Fried et al., 1998), especially in the visceral adipose tissue (Skurk et al., 2007). Proinflammatory cytokines, possible triggers of low-grade inflammation,

including tumor necrosis factor alpha (TNF- α) and interleukin 6 (IL-6), have been shown to impair the sensitivity of the cells to insulin. In a case-control study by Spranger et al. (2003) IL-6 was independently associated with an increased risk of type 2 diabetes, although the interaction term between IL-6 and interleukin 1 beta (IL-6 x IL-1 β) increased the risk of type 2 diabetes even further. TNF- α was also an independent predictor of type 2 diabetes but not after the model was further adjusted for BMI and waist to hip ratio. In addition to adipose derived cytokines, other inflammatory markers, e.g. high-sensitive C-reactive protein (hc-CRP), have been shown to be independent predictors of type 2 diabetes (Spranger et al., 2003; Rubio-Martin et al., 2013). In contrast, the adipose tissue of lean subjects has been shown to secrete anti-inflammatory cytokines, such as adiponectin, that has been shown to protect against the development of type 2 diabetes (Li et al., 2009). Interestingly, it has been postulated that the subcutaneous fat tissue secretes higher portion of anti-inflammatory cytokines, and thus it can have preventive properties against type 2 diabetes (Fontana et al., 2007).

The association of active lifestyle and exercise in the prevention of diabetes was observed by Indian physicians in the turn of the 20th century (Havelock C., 1907). In 1916, Elliot Joslin noticed that exercise could have a role in the treatment of diabetes, although his work concentrated almost exclusively on the effect of strict diet and prolonged fasting (Joslin, 1916). In 1953, Morris and Heady reported that all-cause mortality rates were inversely associated with physical demands of the work among people with diabetes (Morris and Heady, 1953). Subsequently, epidemiological evidence from Pacific populations has shown that the prevalence of diabetes is lower in traditional rural areas than among westernized urban populations (Zimmet, 1979). These early findings provided indirect evidence about the beneficial effects of physical activity and other lifestyle factors on the prevention of type 2 diabetes. This evidence was eventually supported by findings from cross-sectional comparisons between populations and migration studies. The early studies, however, did not clearly distinguish between type 1 and type 2 diabetes.

Migration of the Japanese to the Island of Hawaii has been shown to be associated with decreased physical activity, dietary changes, and increased prevalence of diabetes (Kawate et al., 1979). Zimmet et al. (1981) have found that the prevalence of diabetes was almost three times lower in the rural population of Western Samoa than among the urban population. In another study, it has been reported that independently of the rural or urban living environment, the prevalence of diabetes was higher among physically inactive compared to the physically active (Taylor et al., 1984). King et al. (1984) have reported a higher prevalence of type 2 diabetes among inactive and/or urban population compared to the more active and/or rural populations. The associations, however, were not consistent between different ethnic groups or sexes.

In the early 1990's, the first prospective evidence established the independent protective effect of physical activity on development of type 2 diabetes. Helmrich et al. (1991) followed male alumni of the University of Pennsylvania from 1962 to 1976, and they found that the incidence of type 2 diabetes was inversely associated

with baseline physical activity (mainly LTPA) energy expenditure. In the Nurses' Health study, the incidence rate of type 2 diabetes was lower among women who reported exercising at least once a week than among those who reported no such activity (Manson et al., 1991). Similar findings have been reported among US male physicians (Manson et al., 1992). Lynch et al. (1996) have reported that LTPA of at least 40 minutes with an intensity of at least 5.5 MET reduces the risk of developing type 2 diabetes in a population based sample of Eastern Finnish men.

Low cardiorespiratory fitness, as a surrogate measure of long-term daily aerobic physical activity, has been shown to increase the risk of type 2 diabetes (Wei et al., 1999; Sawada et al., 2003; Sawada et al., 2010a). In a prospective study of 23 444 men, the 18-year incidence of type 2 diabetes was inversely associated with cardiorespiratory fitness, even after the model was adjusted for other established well-known risk factors of type 2 diabetes and self-reported physical activity (Sieverdes et al., 2010). According to a study by Sui et al. (2008), higher fitness reduced the risk of type 2 diabetes only among overweight or obese women, whereas no protective effect was found among women with normal weight. Moreover, the decrease in cardiorespiratory fitness during the 20-year follow-up has been shown to increase the risk of type 2 diabetes, although the results were attenuated among black men and women and white women, but not among white men, after the model was adjusted for initial BMI (Carnethon et al., 2009). Regular physical activity can also affect other bodily functions than cardiorespiratory fitness, thus overall musculoskeletal fitness level could also have protective properties against diabetes. Katzmarzyk et al. (2007) found that a musculoskeletal fitness score that was based on the performance in sits-ups, push-ups, grip strength, and trunk flexibility tests was an independent predictor of type 2 diabetes during a 15.5-year follow-up. In this study, however the model was not adjusted for cardiorespiratory fitness or BMI. In the study by Sawada et al. (2010b) the 15.4-year incidence of type 2 diabetes was not associated with the musculoskeletal performance score after the model was adjusted for several risk factors, including cardiorespiratory fitness and BMI. In their study, however, the musculoskeletal fitness score was based on the performance in a vertical jump test, a sit-up test, a side-step test for agility, and a functional reach test, which differs substantially from that applied in the study by Katzmarzyk et al (2007).

High dietary intake of long-chain ω -3 fatty acids, trans fatty acids, cholesterol, processed meats, eggs, rapidly absorbed carbohydrates; or low intake of whole grain or cereal fiber has been associated with an increased risk of type 2 diabetes (Meyer et al., 2001; Montonen et al., 2003; Schulze et al., 2004; Ericson et al., 2013). The diabetes risk has been shown to reduce with the increased intake of carbohydrates in expense of protein or polyunsaturated fatty acid intake (Schulze et al., 2008). Likewise, replacing saturated fats with vegetable fats or polyunsaturated fatty acids have been shown to decrease the diabetes risk (Meyer et al., 2001). Moreover, the risk of type 2 diabetes is lower with dietary pattern that favors fruits and vegetables over butter, potatoes, and whole milk (Montonen et al., 2005). Schulze et al. (2005) have also proposed that dietary pattern that was strongly associated with biomarkers of chronic inflammation, elevated the risk of

type 2 diabetes. The diet pattern included high intake of sugar-sweetened soft drinks, diet softs drinks, refined grains, and processed meats; and low intake of wine, coffee, and vegetables. Regarding the intake, there seems to be also a U-shaped association between the alcohol consumption and the risk of type 2 diabetes (Carlsson et al., 2003). Like alcohol consumption, sleep duration has been reported to have a U-shaped relationship with type 2 diabetes risk (Yaggi et al., 2006). It has been also suggested that alcohol consumption worsens the U-shaped association between sleep duration and hyperglycemia (Kadono et al., 2007).

Several large clinical trials have shown that lifestyle interventions, which are planned to affect multiple modifiable risk factors at once, can reduce the prevalence of type 2 diabetes. In the Swedish Malmö feasibility study, a 5-year lifestyle intervention significantly decreased the risk of developing type 2 diabetes in subjects with IGT (odds ratio, OR: 0.37, 95% CI 0.20: 0.68) (Eriksson, 1991). In the Da Qing study (China), it was found that a 6-year exercise intervention with or without diet intervention decreased the prevalence of type 2 diabetes in people with IGT compared to a randomized control group (Pan et al., 1997). In the Finnish Diabetes Prevention Study (FDPS), a randomized controlled trial (RCT) with lifestyle intervention aimed to decrease body weight, decrease fat intake, increase fiber intake, and increase moderate exercise, the risk of developing type 2 diabetes was reduced by 58% in overweight middle-aged subjects with IGT (Tuomilehto et al., 2001). In addition, Laaksonen et al. (2005) have reported by employing the data from FDPS that the change in hours spend in total LTPA after adjusting for baseline LTPA, change in dietary intake, and change in body mass index (BMI) was inversely associated with the risk of developing type 2 diabetes. Similarly with FDPS, in the Diabetes Prevention Program (USA) a lifestyle intervention was associated with a 58% reduction in the incidence of type 2 diabetes in subjects with elevated risk of developing type 2 diabetes (Knowler et al., 2002). Interestingly, this reduction was higher than that found in the group that was medically treated with metformin (31%). Based on this evidence, current clinical guidelines state that the lifestyle changes aimed at increasing physical activity, healthier diet and weight loss form a corner stone in the prevention and treatment of type 2 diabetes. In the look action for health in diabetes (Look AHEAD) study, the intensive lifestyle intervention did not reduce the risk of cardiovascular mortality or morbidity in people with type 2 diabetes (hazard ratio 0.95, 95% CI, 0.83: 1.09) (Look AHEAD Research Group et al., 2013). This was found albeit there was a significant decrease in body weigh, waist circumference, and HbA_{1c}, and significant increase in physical fitness (Look AHEAD Research Group et al., 2013). These negative results could highlight the importance of the prevention of type 2 diabetes. In addition, this type of lifestyle intervention can have other health benefits as well that may be of importance for patients and for society, including decrease in depression (Faulconbridge et al., 2012), incidence of urinary incontinency (Phelan et al., 2012), and sleep apnea (Foster et al., 2009), and increase in the quality of life (Williamson et al., 2009), physical functioning (Foy et al., 2011), and mobility (Rejeski et al., 2012). The aforementioned lifestyle

intervention studies, however, were unable to determine the independent effects of exercise on the risk of type 2 diabetes, mortality, or morbidity.

2.3.3 THE INDEPENDENT EFFECTS OF EXERCISE ON RISK FACTORS OF TYPE 2 DIABETES

Exercise, games, and sports have been part of the ancient civilizations, but it has been thought that the major attribution to exercise physiology of the western civilization has come from early Greek physicians, including Herodotus (5th century BC), Hippocrates (460–377 BC) and especially Roman physician Galen (131–201 AD) (Green, 1951; McArdle et al., 2007). In the 19th century, physical exercises were applied systematically for rehabilitative purposes as a part of the rising profession of physical therapy, as the 17th and 18th century anatomists had laid the path for understanding the human function (Bakewell, 1997). In ancient India, however, an Indian physician Susruta (or Sushruta, approximately 600 BC) was probably the first to prescribe exercise, such as long walks, different sports, and riding on a horse or an elephant, as a treatment for diseases including diabetes (Tipton, 2008). Until the turn of the 19th century, some physicians supported exercise as a treatment for diabetes, whereas some recommended avoiding exercise at least in severe cases of diabetes (Allen et al., 1919). The real effort to promote exercise as part of diabetes treatment was made and re-started by a French pharmacist and hygienist Apollinaire Bouchardat in the mid 19th century (Bouchardat, 1865). Eventually, Chaveou and Kaufman (1887) experimentally proved the reduction of blood glucose levels with exercise, which initiated the acceptance of exercise as a common treatment for diabetes. In the early 20th century, before the insulin era, exercise was recommended as a supplementary treatment for diabetes (Allen, 1915; Joslin, 1916; Allen et al., 1919; Joslin, 1921). After the discovery of insulin, Lawrence (1926) found that exercise could enhance the hypoglycemic effects of insulin.

Currently, at least 36 RCTs and 31 randomized comparative trials, and over 70 non-randomized studies have been conducted to investigate the independent long-term (non-acute) effect of exercise on risk factors of type 2 diabetes among people with different levels of IGR. The details of 30 RCTs, with reasonably robust statistics and reporting, that have investigated the effect of aerobic training, resistance training, or combined aerobic and resistance training on common risk factors of type 2 diabetes have been described in Tables 5 and 6. Altogether 20 out of the 30 RCTs investigated the effect of aerobic only intervention, 8 of them studied the resistance training only interventions, and 11 of them focused on the combined aerobic and resistance training interventions. Thus, 30 RCTs equaled 39 comparisons between the exercise intervention group and control groups (Table 5). The average portion of the RCTs reporting an improvement in outcome per risk factor was 25%. This figure was higher among the 15 largest studies (31%) compared to the RCTs with smaller sample sizes (22%). Interestingly, an improvement in risk factors was more frequently reported after combined aerobic and resistance intervention (29%) than after aerobic only intervention (22%) or

Table 5. Description of randomized controlled trials on the effect of aerobic, resistance, or combined training on the risk factors of type 2 diabetes among people with impaired glucose regulation.

Study	Group	n (% men)	Age, years	BMI, kg/m ²	T2D, years	Intervention				
						Type	Intensity	Frequency	min / session	Duration
Araiza (2006)	AT	15 (nr)	49.0	30.0	>1	Walking	nr	≥5	10 000 s/d	6 wk
	C	15 (nr)	51.0	33.5	>1	Standard care	na	na	na	6 wk
Baker (2010) ^a	AT	19 (47)	71.0	30.6	na	Treadmill, cycle ergometer, elliptical trainer	75–85%HR _{max}	4	45–60	6 mo
	C	9 (11)	66.0	30.1	na	Stretching balance training	≤50%HR _{max}	4	45–60	6 mo
Boudou (2003)	AT	8 (100)	42.9	28.3	<10	nr	75–50+85%VO _{2peak}	3	45	8 wk
	C	8 (100)	47.9	30.9	<10	Cycle ergometer	30 Watts	1	20	8 wk
Castaneda (2002)	RT	29 (32)	66.0	30.9	8.0	5 exercises x 3 sets x 8 repetitions	60–80%RM	3	45	16 wk
Brooks (2007)	C	31 (39)	66.0	31.2	11.0	Standard care	na	na	na	16 wk
Cauza (2006)	AT+RT	10 (50)	57.1	32.4	9.1	AT: cycle ergometer RT: 6 exercises x 1 sets x 10–15 repetitions	60%VO _{2peak} 10–15RM	3	20	4 mo
	C	10 (50)	56.9	32.9	9.7	Standard care	na	na	na	4 mo
Cheung (2009)	RT	20 (35)	59.0	39.7	nr	7 exercises x 2 sets x 12 repetitions	12RM	5	40	4 mo
	C	17 (29)	62.0	37.7	nr	nr	na	na	na	4 mo
Church (2010)	AT	72 (38)	53.7	34.7	7.4	nr	50–80%VO _{2max}	nr	12 kcal/kg/wk	9 mo
Swift (2012)	RT	73 (41)	56.9	34.1	7.2	9 exercises x 2–3 sets x 10–12 repetitions	nr	3	nr	9 mo
	AT+RT	76 (36)	55.4	35.8	6.7	AT: nr RT: 9 exercises x 1 sets x 10–12 repetitions	50–80%VO _{2max} 12RM	nr	10 kcal/kg/wk	9 mo
	C	37 (32)	58.6	34.8	7.2	Standard care + stretching + relaxation	nr	1	nr	9 mo
Cuff (2003)	AT	9 (0)	59.4	32.5	3.2	Treadmill, cycle ergometer, stepper, elliptical trainer, rowing	60–75%HRR	3 (total)	75 (total)	16 wk
	AT+RT	10 (0)	63.4	33.3	3.7	Low-impact aerobic movements	0.1 kcal/kg/min	na	na	16 wk
	C	9 (0)	60.0	36.7	4.7	Treadmill, cycle ergometer, stepper, elliptical trainer, rowing	60–75%HRR	3 (total)	75 (total)	16 wk
Desch (2010) ^a	AT	14 (78)	62.3	29.8	na	RT: 5 exercises x 2 sets x 12 repetitions Standard care	nr na	na	na	16 wk
	C	12 (66)	62.3	31.3	na	AT: cycle ergometer ns	75%HR _{max} nr	7	30	6 mo
Dobrosielski (2012)	AT+RT	51 (65)	57.0	33.0	nr	AT: treadmill, cycle ergometer, stepper RT: 7 exercises x 2 sets x 10–15 repetitions	na 60–90%HR _{max}	na	na	6 mo
	C	63 (59)	56.0	33.6	nr	Standard care	50%RM na	na	45 (total)	26 wk
								na	na	26 wk

Continues

Study	Group	n (% men)	Age, years	BMI, kg/m ²	T2D ₁ years	Intervention				
						Type	Intensity	Frequency	min / session	Duration
Fritz (2013)	AT	20 (65)	61.4	31.7	5.1	Nordic walking	SSOB, P	nr	5 h/wk	4 mo
	C	30 (67)	61.0	31.1	5.1	Standard care	na	na	na	4 mo
Fritz (2013) ^a	AT	14 (38)	59.1	32.0	na	Nordic walking	SSOB, P	nr	5 h/wk	4 mo
	C	21 (48)	61.8	30.8	na	Standard care	na	na	na	4 mo
Gordon (2008)	AT	77 (19.5)	63.9	nr	1–10	Walking, stretching, dancing, games,	8–10 RPE	4–5	60–120	24 wk
	C	77 (9.5)	63.6	nr	1–10	Standard care	na	na	na	24 wk
Gram (2010)	AT	22 (45)	62.0	31.4	>1	Nordic walking	>40%VO _{2max}	1–2	45	4 mo
	AT+RT	24 (58)	59.0	32.4	>1	AT: ns RT: 5 exercises x sets nr x repetitions nr	>40%VO _{2max} 13–14 RPE	1–2 (total)	45 (total)	4 mo
Hordern (2008)	C	22 (59)	61.0	32.8	>1	Standard care	na	na	na	4 mo
	AT+RT	68 (53)	57.1	32.3	5.0	AT: not specified RT: exercise nr x 2–3 sets x 12–15 repetitions	12–13 RPE 12–15 RM	2 (total)	60–90 (total)	4 wk
Kadoglou (2007)	C	64 (53)	65.8	30.9	4.0	Standard care	na	na	na	4 wk
	AT	30 (43)	59.3	32.1	6.9	Walking, running, cycle ergometer, calisthenics	50–75%VO _{2peak}	4	45–60	6 mo
Kadoglou (2010)	C	30 (40)	63.8	31.9	6.7	Standard care	na	na	na	6 mo
	AT	23 (35)	56.8	31.7	6.5	Walking + promoted to increase LTPA	50–70%VO _{2peak}	≥4	30–60	16 wk
Krousel-Wood (2008)	C	24 (29)	60.3	31.3	7.8	Standard care	na	na	na	16 wk
	AT+RT	37 (32)*	56.6*	38.2	nr	nr	3–6 MET	5 (total)	10–30 (total)	3 mo
Ku (2010)	C	39 (32)*	56.6*	37.0	nr	Standard care	150 min/wk	na	na	4 mo
	AT	15 (0)	55.7	27.1	6.6	General exercise, not specified	3.6–5.2 MET	5	60	12 wk
Lambers (2008)	RT	13 (0)	55.7	27.1	5.7	10 exercises x 3 sets x 15–20 repetitions	40–50%MEC	5	nr	12 wk
	C	16 (0)	57.8	27.4	5.8	Standard care	na	na	na	12 wk
Loimaala (2003)	AT	18 (89)	52.2	30.9	nr	Treadmill, cycle ergometer, stepper	60–85%HRR	3	60	12 wk
	AT+RT	17 (41)	55.8	28.9	nr	AT: Treadmill, cycle ergometer, stepper RT: 4 exercises x 3 sets x 10–15 repetitions	60–85%HRR 60–85%1RM	3 (total)	30	12 wk
Loimaala (2007)	C	11 (55)	57.5	30.4	nr	Standard care	na	na	na	12 wk
	AT+RT	24 (100)	53.6	29.3	<3	AT: Jogging, walking RT: 8 exercises x 3 sets x 10–12 repetitions	65–75%VO _{2max} 70–80%1RM	2	≥30	12 mo
Loimaala (2009)	C	25 (100)	54.0	29.8	<3	Standard care	na	na	na	12 mo

Continues

Study	Group	n (% men)	Age, years	BMI, kg/m ²	T2D, years	Intervention				
						Type	Intensity	Frequency	min / session	Duration
Marcus (2009) ^a	RT	10 (0)	56.3	28.5	na	Eccentric	7–13 RPE	3	5–30	12 wk
Middlebrook (2006)	C	6 (0)	53.2	32.2	na	Standard care	na	na	na	12 wk
	AT	22 (54)*	61.8	31.8	3.8	ns	70–80%HRR	3	30	6 mo
Oliveira (2012)	C	30 (54)*	64.6	29.9	4.9	Standard care	na	na	na	6 mo
	AT	11 (45)	52.0	29.3	5.5	Cycle ergometer	LT	3	20–50	12 wk
	RT	10 (40)	54.1	31.3	7.7	7 exercises x 2–4 steps x 10 repetitions	50%1RM	3	60	12 wk
Plotnikoff (2010)	AT+RT	10 (40)	57.9	31.2	7.3	AT: Cycle ergometer		3 (total)	10–25	12 wk
	C	12 (33)	53.4	30.0	5.3	RT: 7 exercises x 1–2 steps x 15 repetitions	50%1RM	3	nr	12 wk
Sigal (2007)	RT	27 (29)	55.0	35.0	nr	8 exercises x 2–3 sets x 8–12 repetitions	50–85%RM	3	nr	16 wk
	C	21 (38)	54.0	36.0	nr	Standard care	na	na	na	16 wk
Jennings (2009)	AT	60 (65)	53.9	35.6	5.1	Treadmill, cycle ergometer	60–75%HR _{max}	3	15–45	6 mo
	RT	64 (63)	54.7	34.1	6.1	7 exercises x 2–3 sets x 7–9 repetitions	7–9RM	3	nr	6 mo
Tudor-Locke (2004)	AT+RT	64 (43)	53.5	35.0	5.2	AT: Treadmill, cycle ergometer	60–75%HR _{max}	3	15–45	6 mo
	C	63 (65)	54.8	35.0	5.0	RT: 7 exercises x 2–3 sets x 7–9 repetitions	7–9RM	3	nr	6 mo
Van Rooijen (2004)	AT	24 (50)	52.8	34.1	>3 mo	Standard care	na	na	na	6 mo
	C	23 (61)	52.5	32.5	>3 mo	Walking	nr	nr	nr	16 wk
Wisse (2010)	AT	75 (0)	55	33	nr	Standard care	na	na	na	16 wk
	C	74 (0)	55.0	33.7	nr	Walking	12–14 RPE	nr	10–45	12 wk
Yates (2009) ^a	AT+RT	32 (62)	54.3	31.6	nr	Relaxations	na	na	na	12 wk
	C	29 (62)	51.3	35.2	nr	not specified	moderate	3	>160 min/wk (total)	24 mo
Yates (2010)	AT	29 (69)	66.0	28.7	nr	Standard care	na	na	na	24 mo
	C	29 (59)	65.0	29.8	nr	Walking	nr	nr	6000 or 9000 sid	12 mo
						Standard care	na	na	na	12 mo

Subjects have type 2 diabetes unless otherwise stated. BMI, body mass index; T2D, type 2 diabetes; AT, aerobic training; nr, not reported; s/d, steps per day; C, control; na, not applicable; HR_{max}, maximum heart rate; VO_{2peak}, peak oxygen uptake; RT, resistance training; RM, repetition maximum; AT+RT, combined aerobic and resistance training; VO_{2max}, maximum oxygen uptake; HRR, heart rate reserve; LIAM, low-impact aerobic movement; SSOB, slight shortness of breath; P, perspiration; RPE, rating of perceived exertion; LTPA, leisure-time physical activity; MET, metabolic equivalent; MEC, maximum exercise capacity; LT, lactate threshold. * Values are mean of all study participants.

resistance training only intervention (23%).

The effects of exercise on chronic hyperglycaemia have been investigated in most of the RCTs. Both aerobic (AT) and resistance training (RT) have been shown to decrease HbA_{1c} in people with type 2 diabetes (Castaneda et al., 2002; Sigal et al., 2007; Kadoglou et al., 2007; Kadoglou et al., 2010; Fritz et al., 2013). Current evidence indicates, however, that the combined training induces greater changes in HbA_{1c} compared to aerobic or resistance training alone (Sigal et al., 2007; Church et al., 2010). Church et al. (2010) found that when the total duration of exercise was kept similar across groups and the volume of aerobic exercises at the level of current clinical guidelines, the combined training decreased HbA_{1c} 0.34%-point compared to the control group, whereas no change was detected after solely aerobic or resistance training interventions. According to Sigal et al. (2007), combined training induced additional 0.46 and 0.59%-point decrease in HbA_{1c} compared to the aerobic or resistance training alone, respectively. In their study, however, the combined training intervention included full aerobic and resistance training programs, thus increasing the exercise dose substantially compared to the only aerobic or resistance training intervention. This difference in dose could also explain the marked difference in the total decrease in HbA_{1c} level compared to the study by Church et al. (2010), in which the doses were almost equal between the groups. Combined training has also been shown to prevent worsening of the HbA_{1c} levels (Dobrosielski et al., 2012). The mean decrease reported in the HbA_{1c} after exercise intervention seems to vary from approximately 0.3%-point (Church et al., 2010) to around 1.0%-point (Loimaala et al., 2003; Sigal et al., 2007). In some previous studies, exercise induced no significant decrease in HbA_{1c} compared to the control group, although the changes within the groups were significant (van Rooijen et al., 2004). While in other studies, no change in HbA_{1c} was detected (Araiza et al., 2006; Krousel-Wood et al., 2008; Cheung et al., 2009; Desch, 2010; Ku et al., 2010; Wisse et al., 2010; Gram et al., 2010). Altogether, 32% of the studies have reported a significant decrease in HbA_{1c} compared to the control group.

Four RCTs with aerobic exercise intervention (Kadoglou et al., 2007; Gordon et al., 2008; Yates et al., 2009; Kadoglou et al., 2010) and one study with combined exercise intervention (Cauza et al., 2006) have shown positive effects on fasting glucose. None of the 6 RCTs with only resistance training intervention reported significant decreases in fasting glucose levels (Castaneda et al., 2002; Marcus et al., 2009; Church et al., 2010; Plotnikoff et al., 2010; Ku et al., 2010; de Oliveira et al., 2012). Four studies have investigated the effect of exercise on glucose levels 2-hours after oral glucose tolerance test (Tudor-Locke et al., 2004; Yates et al., 2009; Desch, 2010; Fritz et al., 2013). Among those, only the study by Yates et al. (2009) reported significant decrease in the 2-h post challenge glucose levels compared to the control group. In their study, subjects with IGT were promoted to increase their walking activity with and without pedometer. In the pedometer group the change in 2-h glucose was 1.31%-point, whereas in the group without pedometer the decrease was only 0.34%-point.

Exercise has also been shown to reduce insulin levels after aerobic (Kadoglou et al., 2007; Desch, 2010) and resistance training intervention (Plotnikoff et al., 2010), but not after combined training intervention (Hordern et al., 2008; Church et al., 2010). The effect of exercise on insulin resistance estimated either by using homeostasis model assessment for insulin resistance (HOMA-IR) or with the clamp methods, has been inconsistent. Improved insulin sensitivity has been reported in 38% of the studies using HOMA-IR (Kadoglou et al., 2007; Brooks et al., 2007; Desch, 2010) or clamp methods (Boudou et al., 2003; Cuff et al., 2003; Baker et al., 2010). According to a recent review, it has been suggested that different types of physical exercise intervention, including aerobic, resistance, or high-intensity training (HIT), could all have beneficial effects on insulin resistance, although the authors concluded that large scale RCTs are still required (Roberts et al., 2013).

Few previous RCTs have also investigated the effect of exercise on adiponectin levels and inflammatory markers. Only one study has reported an increase in circulating adiponectin after resistance training intervention, which indicates that exercise could have anti-inflammatory effects (Brooks et al., 2007). Several studies have also reported a decrease in inflammatory markers, including hc-CRP or CRP (Kadoglou et al., 2007; Brooks et al., 2007; Kadoglou et al., 2010), leptin (Loimaala et al., 2009; Kadoglou et al., 2010), and retinol binding protein 4 (RBP4) (Ku et al., 2010). None of the RCTs, however, reported a significant decrease in TNF- α (Kadoglou et al., 2010), IL-6 (Middlebrooke et al., 2006; Yates et al., 2010), or gamma-glutamyl transpeptidase (γ -GT) (de Oliveira et al., 2012).

Like cytokines, the evidence about the beneficial effects of exercise on high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol concentrations has been inconsistent. According to Kadoglou et al. (2007) 6 month aerobic training for 45–60 minutes 4 times a week with an intensity of 50–75% of VO_{2max} , increased HDL and decreased LDL. Resistance training has also been shown to increase HDL in one study (Plotnikoff et al., 2010), while no change has been detected in LDL (Castaneda et al., 2002; Sigal et al., 2007; Plotnikoff et al., 2010; de Oliveira et al., 2012). In contrast, combined aerobic and resistance training intervention has been found to reduce LDL in two RCTs (Cauza et al., 2006; Gram et al., 2010), but no changes have been reported in HDL (Table 6).

Approximately one third of all the RCTs (26%) have reported a decreased total cholesterol level after aerobic training and combined training interventions (Cauza et al., 2006; Kadoglou et al., 2007; Gordon et al., 2008; Lambers et al., 2008; Kadoglou et al., 2010; Fritz et al., 2013). The effect of resistance training alone on total cholesterol has been studied only in one of the RCTs. In their study Oliveira et al. (2012) found no change in total cholesterol after 12 weeks of resistance training three times a week for 60 minutes with the intensity of 50% of one repetition maximum (1RM). Regarding blood lipids, triglycerides decreased after combined training (Cauza et al., 2006; Hordern et al., 2008), whereas no effect has been reported after aerobic or resistance training alone (Table 6).

Systolic blood pressure has been shown to decrease with aerobic training (Gordon et al., 2008), resistance training (Castaneda et al., 2002), and combined training (Loimaala et al., 2003). These studies, however, include only 17% of all RCTs that have investigated the effect of exercise on systolic blood pressure. In addition, Kadoglou et al (2010) have reported a decrease in the diastolic blood pressure after 16 weeks of walking at least 4 times a week for 30–60 minutes with an intensity of 50–70% VO_{2peak} . No such effect has, however, been reported in any of the other 20 RCTs (Table 6) investigating diastolic blood pressure.

Tremendous amount of studies have investigated the effect of exercise on body composition and obesity. Only in 3 of the 30 RCTs that have been summarized in Table 5 and 6 had no measures of excess body weight (Cauza et al., 2006; Gordon et al., 2008; Marcus et al., 2009). In all other studies, at least one indicator of excess body weight has been reported. Aerobic training is effective in decreasing total body weight (Cuff et al., 2003; Sigal et al., 2007; Ku et al., 2010), total body fat mass (Sigal et al., 2007; Gram et al., 2010), abdominal fat (Sigal et al., 2007; Church et al., 2010), and visceral fat (Boudou et al., 2003), without inducing significant increase in lean body mass (Sigal et al., 2007; Church et al., 2010). Resistance training on the other hand has been found to increase lean body mass (Castaneda et al., 2002) and decrease total body fat mass, abdominal fat (Church et al., 2010), or visceral fat (Ku et al., 2010), without significant reduction in body weight (Castaneda et al., 2002; Church et al., 2010; Ku et al., 2010). As can be expected, combined training could reduce body weight (Cuff et al., 2003; Hordern et al., 2008; Church et al., 2010; Dobrosielski et al., 2012), total body fat (Church et al., 2010; Dobrosielski et al., 2012), and central obesity (Church et al., 2010), while increasing lean body mass (Dobrosielski et al., 2012). These findings should be considered as general trends, as the evidence about the independent effect of exercise on body composition or excess adiposity is relatively inconsistent.

Physical capacity has been shown to increase with aerobic training (van Rooijen et al., 2004; Kadoglou et al., 2007; Jennings et al., 2009; Baker et al., 2010; Kadoglou et al., 2010; de Oliveira et al., 2012) and combined training (Loimaala et al., 2003; Hordern et al., 2008; Church et al., 2010; Dobrosielski et al., 2012), but not with resistance training only intervention (Jennings et al., 2009; Church et al., 2010; de Oliveira et al., 2012). Of all aerobic and combined exercise intervention studies, 43% have reported an improved VO_{2max} or VO_{2peak} after the intervention compared to the control group. In the previous meta-analysis of nine RCTs, it has been suggested that exercise induces approximately a 10% increase in VO_{2max} compared to the control group (Boule et al., 2003). Aerobic training (van Rooijen et al., 2004), resistance training (Marcus et al., 2009), and combined training (Lambers et al., 2008) have also consistently been shown to improve walking distance during a 6-minute walk test.

The effects of exercise on physical activity and dietary intake, which are the potential confounders of exercise response, have been studied in several RCTs. As shown in Table 6, none of the studies has detected a systematic change in dietary intake during the exercise intervention, although individual changes in dietary intake have been observed. The evidence related to physical activity has however

been more inconsistent, possibly due to the variety of methods applied to measure physical activity. Sigal et al. (2007) reported that daily number of steps measured by pedometer did not change substantially in an aerobic, resistance, combined training groups or in the control group. Similar results have also been reported in other previous RCTs (Krousel-Wood et al., 2008; Church et al., 2010). It has also been found that promoting subjects to increase their daily physical activity (Tudor-Locke et al., 2004) or walking activity (Araiza et al., 2006; Yates et al., 2009) significantly increased the number of daily steps. In the study by Araiza et al. (2006), there were no changes in daily steps in a control group, whereas in the study by Tudor-Locke et al. (2004), controls significantly decreased the number of daily steps. Yates et al. (2009) have reported an increased self-reported volume (MET-minutes) of walking activity and moderate/vigorous activity compared to the control group after a pragmatic programme aimed to increase walking activity. A resistance training program has been shown to increase the energy expenditure of self-reported LTPA and household physical activity, which did not include the physical activity related to training, compared to the control group (Castaneda et al., 2002). In contrast, Wisse et al. (2010) have found that the prescription of physical activity did not increase the self-reported volume (MET-h) of OPA or LTPA during the 2-year follow-up compared to the control group. In addition, Marcus et al. (2009) reported no change in daily steps after eccentric resistance training compared to the control group, in spite of the large within the group change. Furthermore, Fritz et al. (2013) have found that the number of subjects that reported taking high intensity activities increased among subjects with type 2 diabetes but not among subjects with IGT after a 4-month Nordic walking intervention.

2.4 SUMMARY OF PREVIOUS RESEARCH

Physical activity, which includes both the behavioral and physiological aspects of all daily movements, has been directly associated with a decreased risk of type 2 diabetes and other NCDs, albeit it may be less effective in decreasing the mortality or morbidity rates. The growing westernization of human population, including overnutrition, mechanical and technological advances, which have been suggested to decrease the dose of daily physical activity, has been proposed to be a driving force of worldwide rise in NCDs. To prevent the progression of type 2 diabetes, different types of exercise interventions have been recommended. The excess physical activity provided by exercise intervention may, however, result in decreased non-exercise physical activity, which could reduce the response to training. Although the effects of exercise on risk factors have been widely studied, the evidence from RCTs is somewhat inconsistent. Thus, the effects of exercise intervention on the dose of daily total physical activity and its subcategories and on the risk factors of type 2 diabetes remain to be determined.

3 AIMS OF THE STUDY

The general aims of this study were 1) to investigate the possibilities of structured exercise interventions to change total physical activity and its subcategories in respect to health and performance, and 2) to investigate the effect of structured exercise intervention on the risk factors for type 2 diabetes.

Specific aims of this study were as follows:

- 1 To determine the effect of in-patient physical rehabilitation intervention on the intensity and volume of total physical activity and its subcategories (I).
- 2 To determine the effect of structured Nordic walking (NW) and power type resistance training (RT) interventions on the intensity and volume of total physical activity and its subcategories (II).
- 3 To determine the intensity and volume of a 12-week NW and power type RT in relation to non-structured LTPA (III).
- 4 To determine the effect of NW and power-type RT on glucose control, liver enzymes metabolism, adipokines, body composition (IV), and physical capacity (IV and Wasenius et al. unpublished observation) in overweight or obese men with IGR.
- 5 To determine the effect of intensity and volume of non-structured LTPA on body composition and physical capacity responses to structured NW, structured power-type RT, and non-exercise control intervention (Wasenius et al. unpublished observation).

4 MATERIALS AND METHODS

This doctoral dissertation includes one cross-sectional study on subjects with chronic neck pain (I) and three studies from the randomized controlled Nordic walking and strength exercise program (NOWASTEP) trial including subjects with increased risk for type 2 diabetes (II–IV). In addition, some unpublished observations based on the NOWASTEP study sample are reported. The ethical committee of University of Jyväskylä (I) and the ethical committee of Hospital District of Helsinki and Uusimaa in Finland (II–IV) approved the study protocols. All subjects gave their written informed consent prior to the study (I–IV).

4.1 STUDY DESIGN AND SUBJECTS IN STUDY I

In this cross-sectional study, subjects with chronic neck pain were recruited from two 13-day multidisciplinary institutional inpatient neck rehabilitation programs conducted in Peurunka Rehabilitation Center (Laukaa, Finland) between March 2006 and June 2006. This population provided an exceptional chance to investigate the change in physical activity when the normal daily surroundings are replaced with an environment and surroundings that provides time and opportunities to be physically active. The inclusion criteria for the rehabilitation program were chronic neck or shoulder pain (>3 months), symptoms that repeatedly decreased their ability to work or function, work related physical overload or ergonomic issues, psychological stress, or radiating symptoms in upper arm as defined by the Social Insurance Institution of Finland (KELA). One woman was unwilling to participate in the study, thus 19 out of 20 eligible subjects (16 women, 3 men) were included in the study. No significant differences were found in the baseline characteristics between the men and the women (Table 7). The eligibility of the subjects was determined by the authorities (KELA) based on the individual applications and a recommendation from a treating physician.

4.2 STUDY DESIGN AND SUBJECTS IN STUDIES II–IV

A randomized controlled trial with two exercise groups and a non-exercising control group was conducted in two cities located in southern Finland (Helsinki and Turku) between November 2007 and December 2009. Altogether 144 overweight or obese middle-aged men with impaired glucose regulation were recruited. The recruitment was performed through newspaper advertisements and occupational health care centres. The eligible subjects, who fulfilled the following criteria; male, age 40–65 years, BMI 25.0–34.9 kg/m², increased risk for developing type 2 diabetes (>12 points on the Finnish diabetes risk test), passed medical examination, IFG (fasting plasma glucose 6.1–6.9 mmol·l⁻¹) and/or IGT (2

Table 7. Subject characteristics (I–IV).

Characteristics	Age (years)	BMI (kg/m ²)	Fat percent (%) ^{a,b}	VO _{2max} (ml·kg ⁻¹ ·min ⁻¹) ^{a,c}	METc (MET) ^a	VAS pain scale (0 - 10 cm)
Study I						
Women (n = 16)	48.6 (7.1)	25.9 (3.9)	30.0 (5.1)	25.4 (5.3)	7.2 (1.5)	4.9 (2.4)
Men (n = 3)	48.3 (4.0)	27.4 (2.9)	25.4 (0.4)	24.6 (2.1)	7.0 (0.6)	2.3 (3.2)
Study II						
Nordic walking (n = 7)	56.6 (8.3)	29.9 (3.5)	26.1 (3.7)	28.2 (4.7)		
Resistance training (n = 8)	55.0 (6.9)	33.3 (1.2)	24.3 (2.0)	28.8 (5.9)		
Control (n = 8)	58.1 (5.1)	27.6 (2.4)	20.4 (6.6)	32.9 (8.3)		
Study III and IV						
Nordic walking group (n = 39)	55.4 (6.2)	30.0 (3.4)	25.8 (5.9)	30.0 (7.6)		
Resistance training group (n = 36)	54.4 (6.1)	30.3 (3.2)	25.8 (4.5)	28.5 (5.0) ^d		
Control group (n = 40)	53.6 (7.3)	28.7 (3.0)	23.6 (5.0)	33.0 (5.0)		

Values are mean (standard deviation); VO_{2max}, maximum oxygen uptake (VO_{2peak} in studies II–IV); METc, Maximum oxygen consumption in MET-values; BMI, body mass index; VAS, visual analog scale (0 = no pain, 10 = maximum pain). ^an = 18, 15 women and 3 men; ^bn = 38 in the nordic walking group and n = 39 in the control group; ^cn = 29 in the resistance training group, n = 29 in the Nordic walking group, and n = 25 in the control group; ^d p = 0.023 compared to the control group; In study I there was no significant difference between men and women. Modified from Studies I, II and III.

hour plasma glucose 7.8–11.0 mmol·l⁻¹), were included in the study. The subjects were excluded from the study if they had been previously diagnosed with IGT and participated in any prescribed diet or exercise program, engaged in regular vigorous exercises, or used medication that affected glucose balance. The subjects were randomly assigned (1:1:1) to the Nordic walking (NW) group (n=48), power-type resistance training (RT) group (n=49), and non-exercise control (C) group (n=47). Randomization was performed by an independent person, who drew subject's number from a concealed envelope, to avoid bias. During the 12-week exercise intervention, 29 subjects dropped out from the study for variety of reasons and finally 115 subjects received the intervention as assigned (Figure 7). Baseline characteristics of subjects who were included in the studies II–IV are shown in Table 7 and in Table 9 in the results section. There were no significant differences between the those who completed the trial and those who dropped out (Table 8). Baseline pharmacotherapy received was similar between the RT-group, NW-group, and the C-group (Table 9).

4.3 PHYSICAL ACTIVITY INTERVENTIONS (I–IV)

4.3.1 REHABILITATION INTERVENTION (I)

All subjects in the study I participated in a regular 13-day group based inpatient rehabilitation program that was aimed to alleviate neck pain and related symptoms, reinforce pain coping strategies and subjects' ability to work and function, and promote self-directed rehabilitation methods and healthy lifestyle. The rehabilitation was organized by KELA according to their guidelines, and it was

Table 8. Comparison of baseline characteristics of study subjects and drop-outs (III–IV).

Characteristics	Completed			Drop-outs			Comparison		
	n	mean	SD	n	mean	SD	Difference	95% CI	p
Age (y)	115	54.5	(6.5)	28	52.8	(6.4)	1.6	–1.1 : 4.4	0.235
Height (cm)	115	178.6	(6.1)	26	179.6	(6.7)	–1.0	–3.7 : 1.7	0.452
Weight (kg)	115	94.6	(12.1)	25	94.5	(12.9)	0.1	–5.2 : 5.5	0.956
BMI (kg/m)	115	29.6	(3.3)	25	29.4	(3.7)	0.2	–1.3 : 1.7	0.782
Fat mass (kg)	113	24.2	(7.1)	25	23.2	(7.7)	1.0	–2.2 : 4.1	0.549
Fat percentage (%)	113	25.1	(5.2)	25	24.2	(5.9)	0.9	–1.4 : 3.2	0.451
Waist circumference (cm)	115	105.0	(9.4)	24	105.4	(9.2)	–0.4	–4.6 : 3.7	0.837

implemented in the Peurunka Rehabilitation Center. At baseline, a physician and a physiotherapist individually examined all subjects, and measurements of physical capacity were made. The physical capacity measurements were part of the normal rehabilitation and the results had no influence on the content of the program. Throughout the 13-day program, the subjects had also group discussions with the physiotherapist (3 x 60 min) and a psychologist (1 x 60 min), lectures on related topics (1 x 45 min and 1 x 30 min), massage (3 x 45 min), relaxation (3 x 45 min), ergonomic lectures and training (3 x 60 min), functional exercises (1 x 120 min), group physical exercise sessions [aerobic exercise (2 x 90 min and 1 x 60 min), and therapeutic exercises with (5 x 90 min) or without (1 x 75 min) stretching. The content of the program was unaffected by the research and it followed the normal clinical practice.

4.3.2 NORDIC WALKING INTERVENTION (II–IV)

In the NW-group, Nordic walking was performed in 60 min bouts, 3 times a week (non-consecutive days), for 12 weeks. Each exercise session was supervised by personal trainers, students of physiotherapy, or students of exercise physiology and performed in small groups mainly outside on walking pathways. The target HR was increased progressively in every four weeks of exercise (weeks 1–4 [50–60%HRR], weeks 5–8 [60–70%HRR], and weeks 9–12 [70–80%HRR]). The calculation of individual HRR was based on the estimated maximum HR ($210 - 0.65 \times \text{age}$) (Jones, 1988) and measured resting HR. During the exercise session each participant wore a heart rate monitor (Polar F4, Polar Electro Oy, Kempele, Finland) and were instructed to follow their heart rate during the session. After the session mean heart rate information was collected by the group supervisors. Resting HR was measured with the same heart rate monitor for 5 minutes in three consecutive mornings after a good night's sleep and before getting out of the bed. The mean of the three measurements was then calculated and applied in the calculation of HRR. In order to achieve the target HR in every four weeks, the walking speed or the number of hills were increased. For warm-up, each session was started with 5 min of walking and stretching of the muscles (trapezius, triceps,

Table 9. Distribution of therapeutic drug treatments between subjects (III–IV).

Target	ATC codes	RT (n = 36)	NW (n = 39)	C (n = 40)	Total (n = 115)	p-value
Cardiovascular system	C	15 (42)	13 (33)	17 (43)	45 (39)	0.680
Beta blocking agent	C07(AB02, AB07, AG02, FB02)	1 (3)	4 (10)	4 (10)	9 (8)	
Diuretics	C03AA03	0 (0)	0 (0)	1 (3)	1 (1)	
Calcium channel blockers	C08CA(01, 02)	3 (8)	0 (0)	0 (0)	3 (3)	
Lipid modifying agents	C10(AA01, AA04, AA05, AA07, AX09)	8 (22)	6 (15)	8 (20)	22 (19)	
Agents acting on renin-angiotensin system	C09(AA02, AA04, AA05, BA02, CA01, CA03, CA06, CA07, CA08)	8 (22)	5 (13)	8 (20)	21 (18)	
Antihypertensives	C02	1 (3)	2 (5)	2 (5)	5 (4)	
Blood and blood forming organs	B	5 (14)	4 (10)	4 (10)	13 (11)	0.871
Antianemic preparations	B03BA03	0 (0)	1 (3)	0 (0)	1 (1)	
Antithrombotic agents	B01AC(06, 07,30)	5 (14)	3 (8)	4 (10)	12 (10)	
Other		2 (6)	7 (18)	3 (8)	12 (10)	0.175
Alimentary tract and metabolism	A02BC02	0 (0)	0 (0)	1 (3)	1 (1)	
Genito urinary system and sex hormones	G04(CA02, CB01)	1 (3)	2 (5)	0 (0)	3 (3)	
Musculo-skeletal system	M01AX05	0 (0)	1 (3)	0 (0)	1 (1)	
Nervous system	N05AF01, N06(AB10, AG02, AX11, AX16)	0 (0)	2 (5)	1 (3)	3 (3)	
Respiratory system	R03(AK07, BA02)	0 (0)	4 (10)	2 (5)	6 (5)	
Systemic hormonal preparations	H03AA01	0 (0)	1 (3)	0 (0)	1 (1)	
Total		18 (50)	19 (49)	19 (48)	56 (49)	1.000

Values are number of subjects, n (%). Classification is based on the The Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology, 13 May 2014). RT, resistance training group, NW, Nordic walking group, C, control group. p-value is based on Chi square test.

pectoralis major, abdominals, quadriceps, hamstrings, and gastrocnemius and soleus). Stretching exercises were repeated after the sessions for cool-down.

4.3.3 POWER TYPE RESISTANCE TRAINING INTERVENTION (II–IV)

In the RT-group, power-type resistance training exercises, including leg press, bench press, leg extension, lateral pull-down, leg flexion, and shoulder flexion, were performed with ordinary training machines, barbells, and dumbbells. The intervention program also included exercises with subjects own body weight (leg squats, squat jumps, standing calf jumps or heel raises, push-ups, abdominal flexions, and back extensions). Exercises were performed with maximal

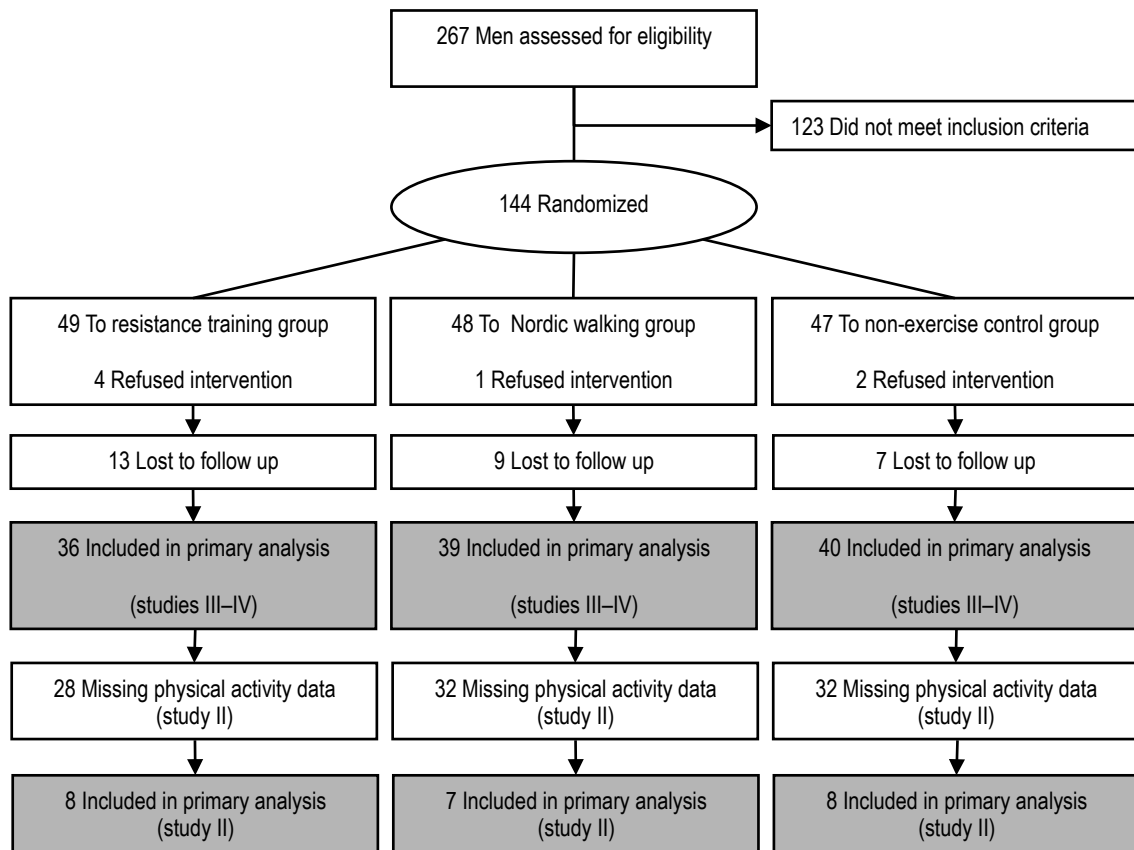


Figure 7. Participant flow through the study (II–V).

contraction velocity and each session lasted 60 min and was performed 3 times a week (non-consecutive days) for 12 weeks. Each exercise session was supervised by personal trainers, students of physiotherapy, or students of exercise physiology and performed in small groups in a gym. Individual exercises were performed 1–3 times a week and the number of sets varied from 1 to 4 and the number of repetitions varied from 3 to 10. The intensity of the exercise increased progressively from 50% to 85% of the estimated maximal strength during the intervention. The maximal strength was estimated with a repetition maximum test with equation $[(-4.18 \cdot \text{Repetition maximum of load}) + 103]$ (McDonagh and Davies, 1984). The goal was to find an external load, which corresponded to 5 repetitions maximum (RM), but we accepted the closest number of repetitions (2–7 RM), if 5 RM could not be achieved. The numbers of repetition for abdominal flexions and back extensions were determined by a performance capacity test. During the test subjects performed as many repetitions as possible with equal pace, according to the supervisor’s observation, without the time limit. The achieved number of repetitions was considered to reflect performance maximum (100%), which was then used to determine the number of repetitions performed in each set of exercises. The progressivity of the performance capacity followed that

of the repetition maximum test. The tests were repeated in the seventh training week to control the progression and adjust the external loads.

4.3.4 NON-EXERCISE CONTROL INTERVENTION (II–IV)

Before the intervention, subjects in the C-group participated in a general lecture together with all other study subjects. The lecture included information about the lifestyle and metabolic disorders. The subjects randomized into the C-group participated in the baseline and 12-week follow-up measurements similarly as the subjects randomized into the exercise groups. Subjects were also instructed to continue their habitual physical activity and diet during the 12-week intervention period. The subjects were, however, allowed to modify their lifestyle if they wanted and no explanation or additional notice was required.

4.4 MEASUREMENTS

4.4.1 PHYSICAL ACTIVITY (I–IV)

Conduction of measurement and analysis of physical activity in studies I–IV has been described in Figure 8. In studies I–II, physical activity in different subcategories (OPA, CPA, LTPA, MHPA, sleep) was measured for four weeks before the interventions with a questionnaire that asked about the type, duration, frequency, distance travelled (meters), terrain geometry (leveled, moderate uphill, vigorous uphill), and RPE of the activity. One-week data was reported. The questionnaires were completed in four-week periods. During the first measurement week, subjects were asked to complete the questionnaire accurately in a diary manner. During the next three weeks, subjects were asked to recall and report weekly physical activity with the help of the first week questionnaire. The same questionnaire, with addition of intervention activity, was also employed to measure the physical activity during the whole 13-day rehabilitation intervention (I) and the 12-week exercise intervention (II). In study I, the questionnaire filled during the rehabilitation was modified so that the CPA included transition from inpatient accommodation to rehabilitation center and OPA subcategory was replaced by the objectively measured rehabilitation intervention physical activity (RIPA), which lasted each day approximately 8 hours. In study II, in addition to verbal guidance (group lecture) subjects received also detailed written (one A4 paper sheet) instructions on how to fill in the questionnaire. It was specifically emphasized that the goal of the questionnaire is to collect data for the whole week (24 hours per day). Furthermore, subjects were encouraged to ask themselves “What have I done?” while filling in the questionnaire to diminish the subjective evaluation of their physical activity level. The reliability of similar questionnaires that apply the same analysis program (see chapter 4.4.2) has been acceptable ($\kappa = 0.48–0.78$) (Mälkiä, 1996) and intraclass correlation coefficient (ICC) = 0.91–0.94 for all activities and ICC = 0.62–0.76 for LTPA (Sjögren, 2006).

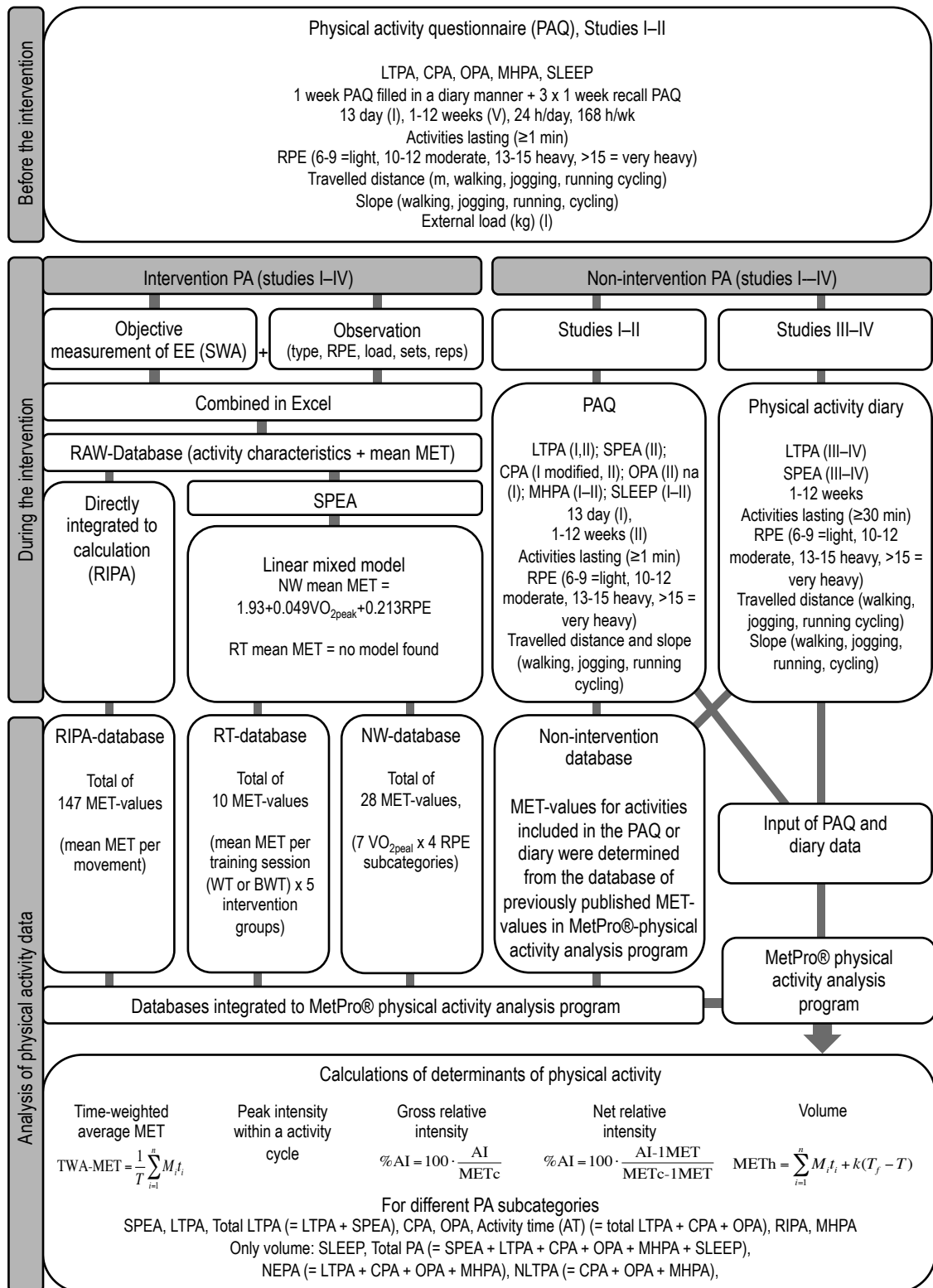


Figure 8. Flow of physical activity measurement (I–IV). RPE, rating of perceived exertion; PA, physical activity; EE, energy expenditure; SWA, SenseWear Armband; MET, metabolic equivalent of task; RIPA; rehabilitation intervention PA; SPEA, structured physical exercise activity; LTPA, leisure-time PA; CPA, commuting PA; OPA, occupational PA; MHPA, miscellaneous home PA; NW, Nordic walking; RT, resistance training; WT, weight training, BWT, Body WT; AI, absolute intensity; NEPA, non-exercise PA; NLTPA, non-LTPA PA.

The intensity and duration of all RIPA (I) activities was measured with SenseWear Armband pro₂ (SWA, BodyMedia Inc., Pittsburgh, PA 15222, USA). During the measurement a researcher observed subjects while logging the information about the type of activities performed, external load used (during applicable exercises), and RPE. Likewise, in the studies II–IV the intensity of the NW and RT interventions were determined with SWA (SWA pro₃) measurements, but the duration was based on the self-reported values. The goal was to measure at least one day (I) or one exercise session (II–IV) from each participant and the measurement day was randomly assigned for each subject. The validity and reliability of SWA to measure energy expenditure has been at least moderate as has been reviewed in the pages 24–25. The SWA seems to be at least as good as other multisensor devices and 3-axis accelerometers, that are most accurate in estimating energy expenditure in free living conditions compared to the gold standard methods (double labeled water or indirect calorimetry) (Van Remoortel et al., 2012).

In studies III–IV, the type, duration, distance travelled (meters), and RPE of structured physical exercise activity (SPEA = NW or RT) and LTPA was measured with a diary throughout the 12-week exercise interventions. In case of missing values, subjects (n = 3 in the RT-group, n = 1 in the NW-group, and n = 8 in the C-group) were contacted by telephone to complete data on average 6 months after the intervention. In addition, for one subject in the RT-group, who completed the study, no information on physical activity was received. For the analysis, RPE was classified into four categories (1 = light or 6–9; 2 = moderate or 10–12; 3 = heavy or 13–16; and 4 = very heavy or 17–20) and only activities that lasted 30 min or longer were included.

4.4.2 ANALYSIS OF PHYSICAL ACTIVITY DATA (I–IV)

The data from SWA was converted into MET-values by dividing the measured energy expenditure (kcal) with a subject's estimated resting energy expenditure (kcal) (study I) or by using directly the MET values from the SWA (II–V). The mean MET for each type of activity performed by the subjects, as logged during the measurement by the researcher, was calculated. This database that included the type of activity and its intensity (MET) was integrated into MetPro® physical activity analysis program (MetPro®, Kuntoväline Ltd, Helsinki, Finland). For the NW and RT exercise activities, a statistical analysis was conducted before constructing the database for MetPro®. With a linear mixed model, the significant independent factors of mean MET of a single session of NW were determined. It was found that VO_{2peak} and RPE were independently associated with the intensity of NW ($\text{MET} = 1.93 + 0.049\text{VO}_{2\text{peak}} + 0.213 \text{RPE}$) and they were used to construct the database for MetPro® program (III). No significant factors were found to explain the MET of a single session of RT. Thus, the mean MET was used as described in the study III.

The intensity of activities other than those related to the intervention (rehabilitation or SPEA) was determined from the existing MetPro®-database.

This database includes previously published MET-values for approximately 2000 different activities, including those published by Ainsworth et al. (1993; 2000b) and International Organization for Standardization (2004).

With MetPro® program the time-weighted average MET (TWA-MET), peak or maximum MET (Peak-MET), and MET_h were calculated by the equations described in studies I and III. The relative intensity was also calculated by dividing the TWA-MET or Peak-MET with the MET capacity (MET_c). MET_c indicates the maximum physical capacity of the subjects (VO_{2max} or VO_{2peak}) in MET values. In study I, net relative intensity was also calculated. To calculate the MET_h, the missing time was calculated by multiplying it by 1 MET (I, II) or by 1.5 MET (II–IV). It was estimated that in the studies including total physical activity (24h) (I, II), the missing time included mostly resting type of activities, whereas in the studies including only LTPA (III–IV), the missing time included mostly light physical activities like those performed during MHPA, hence the 1.5 MET. In addition, the calculations of MET_h of LTPA (III) were standardized for time. The standard timeframe (STF) of measurement was defined by the longest reported time used on the SPEA or LTPA by subjects during a 4-week period (III). This standardization had no effect on other determinants of physical activity.

4.4.3 PHYSICAL CAPACITY (I–IV)

In study I, maximum oxygen uptake (VO_{2max}) was measured with direct maximal cycle ergometry (Ergoline 900, Ergo-line GmbH + Co KG, Ergometriesysteme, Bitz, Germany). The power of the initial stage was set to 25–50 W and increased by 25–50 W every three minutes until exhaustion. In studies II–IV, the peak oxygen uptake (VO_{2peak}) was measured with direct maximal cycle ergometer test (breath-by-breath method, Oxycone Pro ergospirometry, CareFusion Germany 234 GmbH CareFusion, Hoechberg, Germany) until exhaustion or subjective maximum (RPE = 18 or higher) with RER at least 1.10. For some subjects, the test had to be stopped because of the excessive elevation of blood pressure. After the first stage (50 W), the power was increased 25 W per 1 min stage. The UKK 2-km walk test was also performed to estimate VO_{2max} (UKK fitness index). Walking speed was determined from the walk test results by dividing the distance (2000 m) with time.

4.4.4 DIETARY INTAKE (II–IV)

Energy (kcal/day), fat (E%), saturated fat (E%), carbohydrate (E%), protein (E%), alcohol (E%), and fiber (g/1000 kcal) intake was assessed with a continuous three-day (2 week day and 1 weekend day) food diary (Haapa et al., 1985; Pietinen et al., 1988) and analysed with a specific analysis program (Ovaskainen et al., 1996). Subjects were advised to fill in the diary during a time period (from Thursday to Saturday or from Sunday to Tuesday) which corresponded most closely with their habitual intake.

4.4.5 ANTHROPOMETRICS AND BODY COMPOSITION (I–IV)

Body composition was assessed with electrical bioimpedance method (Inbody 3.0, Biospace, Seoul, Korea) (I–V). In studies II–V, body height was determined to the nearest 0.5 cm. Body weight of bare-footed subjects wearing light clothing was defined to the nearest 0.1 kg with calibrated scales. Waist circumference was measured between the lower rib and iliac crest. BMI was calculated by dividing the body weight with height in meters squared (kg/m^2).

4.4.6 BLOOD PRESSURE (II–IV)

Systolic and diastolic blood pressures were measured two times (one minute break between the measurements) from a right arm with automated Omron M4-I (Omron Healthcare Europe BV, Hoofddorp, The Netherlands) measurement device using standard procedures. Measurements were taken between 7 am and 10 am. Subjects were advised to avoid strenuous exercise two days and morning before the tests. Before the test, subjects sat for 20 minutes of which last 5 minutes in total rest. Cuff was selected to match the circumference of the subjects arm. Same measurement devices were used at baseline and follow-up. If large variation existed between the two measurements, additional measurements were taken. The mean of two measurements was reported.

4.4.7 BLOOD SAMPLES AND CLINICAL ANALYSIS (II–IV)

Blood plasma and serum samples were drawn from the brachial vein after overnight fast (12 hours) and tubes were centrifuged at $2200 \times g$ for 10 min. Subjects were advised to avoid alcohol use, intensive exercise, and painkillers 2 days before the samples were taken. In addition, subjects were instructed to follow habitual carbohydrate intake for 3 days prior the collection of the samples.

Plasma glucose level was measured with enzymatic photometric method with Konelab Glucose HK reagent. HbA_{1c} and serum hs-CRP was determined with immunoturbidimetry (Konelab 20i analyser, Thermo Clinical Labsystems Oy, Konelab, Finland) and serum insulin with chemiluminescence-immunoassay (Immu- lite 1000 analyser, Siemens Medical Solutions, Espoo, Finland). Plasma gamma glutamyltransferase (γ -GT), total cholesterol, HDL cholesterol, LDL cholesterol, triacylglycerols, and uric acid were measured with enzymatic photometric methods with commercial kits (Thermo Clinical Labsystems Oy, Espoo, Finland) using a Konelab 20i analyser (Lehtonen et al., 2010). Plasma adiponectin, leptin, $\text{TNF-}\alpha$, and serum chemerin and retinol binding protein 4 (RBP4) were measured with commercial kits (Millipore, Billerica, MA). The plasma samples were analyzed with BioRad Bio-Plex 200 System (Bio-Rad Laboratories, Espoo, Finland) and serum samples with Thermo Multiskan (Thermo Clinical Labsystems Oy, Konelab, Finland). In addition, HOMA-IR (Matthews et al., 1985) and fatty liver index (FLI) (Bedogni et al., 2006) were calculated.

4.5 STATISTICAL ANALYSIS (I–IV)

In the exercise intervention study, the adequacy of sample size was determined with power calculations: If there is at least 34 subjects per group and the change in plasma glucose concentration is ± 0.2 mmol/l after intervention, the result is statistically significant compared to the control group ($p < 0.05$). In the rehabilitation intervention, no power calculation was performed.

The data is expressed as mean (standard deviation, SD; standard error, SE; or 95% CI) and median (interquartile range, IQR). The normal distribution of the variables was tested with Shapiro-Wilk Statistics ($n < 50$) or Kolmogorov-Smirnov ($n > 50$) statistics. The normality was accepted if skewness or kurtosis values were within twice the standard error (I).

The statistical comparisons of small samples or non-parametric data were performed with Wilcoxon signed-rank test and independent samples Mann-Whitney U test. Multiple comparisons of non-parametric data were conducted Kruskal-Wallis test (independent samples) or with a Friedman's test (dependent samples). Mann-Whitney U test or Wilcoxon Signed-rank test with Bonferroni correction were used as post-hoc test for independent and dependent samples, respectively (I–III).

Analysis of variance (ANOVA) was applied for between the groups comparison at baseline (III, Wasenius et al. unpublished observation). Analysis of covariance (ANCOVA), adjusted for baseline values, was used to compare the effect of exercise intervention (IV). In study IV, total cholesterol, LDL cholesterol, chemerin, fatty liver index, and leptin were rank-transformed before ANCOVA due to the non-normal distribution of the variables. In Wasenius et al. (unpublished observations), the extreme outliers ($3 \times SD$) were removed from the analysis. Post-hoc analysis of significant multiple comparison tests (ANOVA and ANCOVA) was conducted with Bonferroni correction (III, Wasenius et al. Unpublished observations) or with least significant difference (LSD) (IV).

The association between variables was tested with Pearson's correlation coefficient (II, Wasenius et al. unpublished observations). In study II, linear mixed models adjusted for individual variation in the intercept were developed to investigate the association between the weekly change in the volume of SPEA and NEPA or LTPA and NLTPA. Separate models were developed for each group. In addition, the investigation of associations between the dose variables of physical activity and change in outcomes (response) were performed with multiple linear regression analysis that was adjusted for possible confounders and the intervention group (Wasenius et al. unpublished). Only either absolute or relative intensity values were accepted for the regression model analysis according to the best-fit basis. For multivariate linear regression analysis and for linear mixed model analysis extreme outliers ($3 \times SD$) that can have detrimental effect on such analyses were removed based on the distribution of residuals. This method was chosen to make the definition of outliers more objective and to avoid bias related to subjectivity. Subjects were categorized as responders if the change in outcome was greater than >0 in the direction of health benefit (eg. 1.0 kg decrease in fat

mass) or non-responders if the change in outcome was greater than >0 in the direction of adverse effect (1.0 kg increase in fat mass) (Wasenius et al. Unpublished observation). Subjects that had no change in outcome were defined into a no change group. Analyses were performed with Statistical Package for Social Sciences, SPSS versions 15.0, 20.0 and 21.0 (IBM Corp., Armonk, New York, USA). Statistical significance was determined with p -value < 0.05 .

5 RESULTS

5.1 THE EFFECT OF REHABILITATION INTERVENTION ON DAILY PHYSICAL ACTIVITY (I)

The rehabilitation intervention was completed fully by all subjects (100%). The RIPA accounted on average for 20% (SD 1.9) of the volume of total physical activity performed during the intervention period. In addition, physical exercises accounted for the major proportion of the volume of RIPA (69%, SD 0.1). The volume of specific exercises accounted for 22% (SD 0.1) and the volume of other mainly aerobic type physical exercise accounted for 78% (SD 0.1) of the total volume of physical exercises performed during RIPA.

The volume of total physical activity decreased significantly during the in-patient rehabilitation program compared to everyday life (290.2 METh·wk⁻¹, SD 33.8 vs. 265.8 METh·wk⁻¹, SD 18.8, $p < 0.05$). No significant difference was observed between the rehabilitation and everyday life in the volume of physical activity when only the activities that exceeded the intensity level of $\geq 50\%$ of VO_{2max} were compared (62.3 6 METh·wk⁻¹, SD 21.1 vs. 62.6 METh·wk⁻¹, SD 43.8, $p = 0.435$). In rehabilitation, however, the volume of activities performed with an intensity of $\geq 50\%$ of VO_{2max} increased significantly in the LTPA and decreased in MHPA compared to everyday-life (Figure 9). In addition, the volume of CPA and LTPA increased and the volume of OPA/RIPA and MHPA decreased in rehabilitation compared to everyday life (Figure 10).

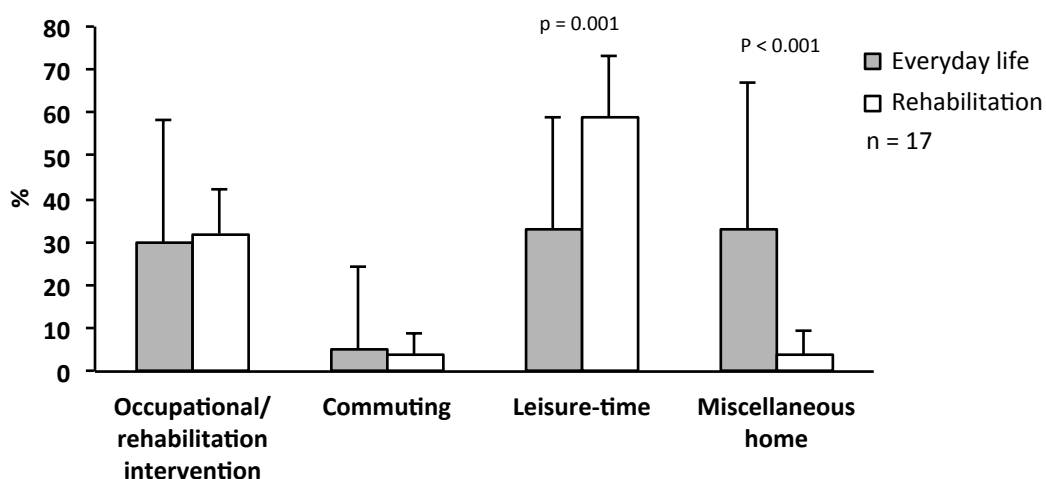


Figure 9. The mean proportional distribution of volume of physical activities performed at the intensity 50% of maximum oxygen uptake or greater (I). Error bars indicate standard deviation.

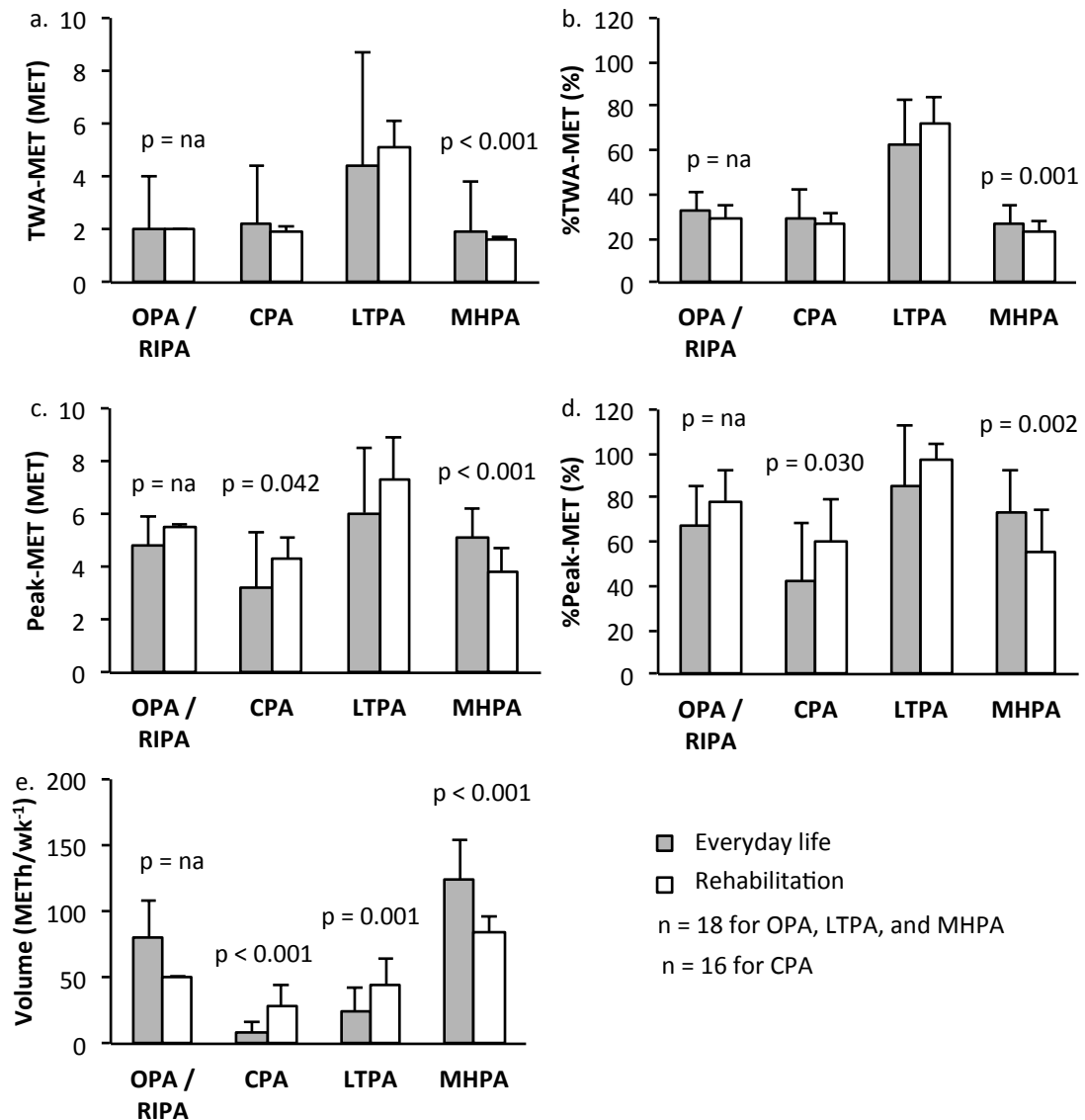


Figure 10. The mean absolute and relative time-weighted average intensity (TWA-MET) (a. and b.), peak intensity (Peak-MET) (c. and d.), and volume (d.) of physical activity in different subcategories of physical activity in everyday life and rehabilitation (I). OPA, occupational physical activity; RIPA rehabilitation intervention physical activity; CPA, commute physical activity; LTPA, leisure-time physical activity; MHPA, miscellaneous physical activity; na, not applicable.

No significant differences were found between the rehabilitation and everyday life in TWA-MET (2.4 MET, SD 0.2 vs. 2.5 MET, SD 0.6, $p > 0.050$) or Peak-MET (7.2 MET, SD 1.9 vs. 6.4 MET, SD 1.8, $p > 0.050$) of activity time physical activity (ATPA), which includes OPA/RIPA, CPA, and LTPA. The TWA-MET and Peak-MET of MHPA were significantly lower in rehabilitation compared to everyday life. The Peak-MET of CPA and LTPA however were higher during the intervention than in everyday life. The changes in relative intensity followed

consistently the changes found in the absolute intensity (Figure 10). No other significant differences between everyday life physical activity and rehabilitation physical activity were found.

5.2 THE EFFECT OF STRUCTURE EXERCISE INTERVENTION ON DAILY PHYSICAL ACTIVITY (II–III)

5.2.1 ADHERENCE TO TRAINING AND PHYSICAL DOSE OF STRUCTURED EXERCISE INTERVENTIONS (III)

Subjects in the NW-group participated on average in 61% (22.1 / 36) of the scheduled exercise sessions, where as in the RT-group the compliance was 67% (24.3 / 36). There were no significant difference between the NW-group and RT-group in the median number of exercise sessions (25.4, IQR 36.0 vs. 27.1, IQR 34.0, $p = 0.208$), in the frequency (2.1 session·wk⁻¹, IQR 3.0 vs. 2.3, IQR 2.8, $p = 0.208$), or in the time used per session (62.6 min·session⁻¹, IQR 82.7 vs. 64.0 min·session⁻¹, IQR 92.5, $p = 1.000$). As described in Figure 11, the intensity and volume of the NW-group was approximately twice as high as in the RT-group.

5.2.2 THE EFFECT OF STRUCTURED EXERCISE INTERVENTION ON TOTAL PHYSICAL ACTIVITY (II)

At baseline, the physical activity profiles were similar between the groups ($p > 0.050$). No significant changes in volume of total physical activity, NEPA, or NLTPA were found between or within the intervention groups (Figure 12).

The mean change in the volume of total LTPA, which included both SPEA and LTPA, was significantly greater in the NW-group (22.5 METh·wk⁻¹, SD 14.7, $p = 0.001$) but not in the RT-group (2.0 METh·wk⁻¹, SD 19.1, $p = 0.105$) compared to the C-group (-11.1 METh·wk⁻¹, SD 16.9). Within the NW-group, the volume of physical activities that were $\geq 50\%$ of $VO_{2\text{ peak}}$ increased significantly, whereas no significant change was detected in the RT-group or C-group (Figure 12). In the C-group, the volume of LTPA decreased significantly during the intervention compared to baseline (Figure 12). No other significant differences were found in the volume of physical activity within or between the two exercise groups and the C-group.

No significant changes in the TWA-MET or %TWA-MET of OPA, CPA, LTPA, MHPA or ATPA were found between or within the NW-group, the RT-group, or the C-group. The mean TWA-MET or %TWA-MET of total LTPA decreased significantly in the RT-group compared to baseline (-0.6 MET [SD 0.6], $p = 0.039$ or -7% [SD 8], $p = 0.039$, respectively). No significant change in the TWA-MET or %TWA-MET of total LTPA was found in the NW-group (0.1 MET [SD 0.5], $p = 1.000$ or 0% [SD 17], $p = 1.000$, respectively) or C-group (-0.5 MET [SD 1.3], $p = 0.313$ or -5% [SD 15], $p = 0.383$, respectively).

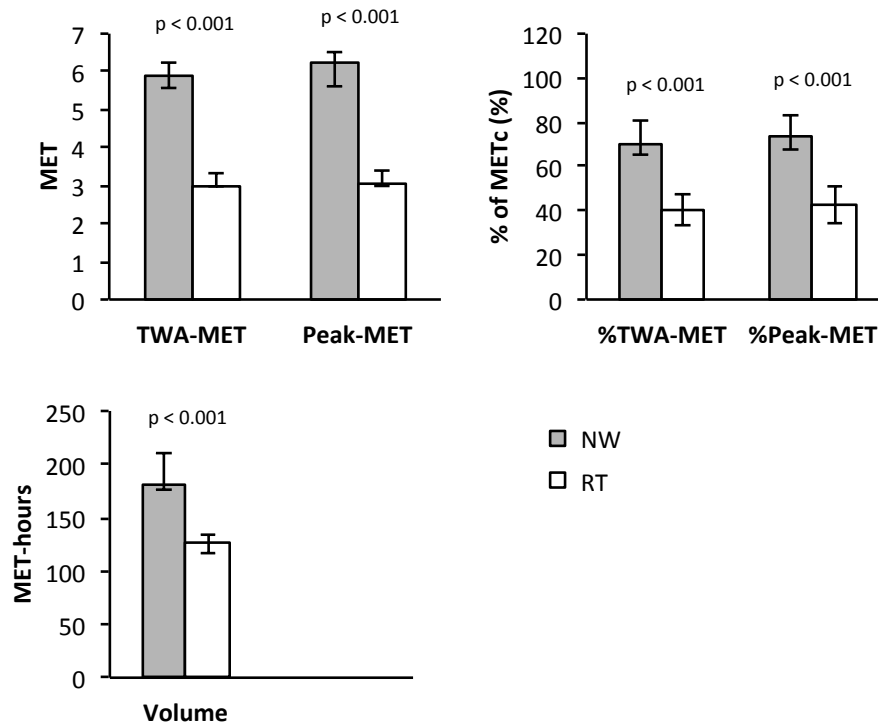


Figure 11. The median time-weighted average intensity (TWA-MET) and peak intensity (Peak-MET) expressed in absolute figures and relative to maximum physical capacity (METc) and the volume of structured physical exercise activity in the Nordic walking (NW) group and in the power-type resistance training (RT) group (II). Error bars indicate interquartile range.

There was a large inter-individual variability in the weekly change of volume of physical activity. When adjusted for individual variation in the intercept, an inverse association was found between the change in the volume of total LTPA and NLTPA. In the NW-group, one METH increase in the volume of total LTPA was associated with a decrease of -0.56 METH (95% CI, -0.68 : -0.44 ; $p < 0.001$) in the volume of NLTPA. Similarly, in the RT-group, one METH increase in the volume of total LTPA was significantly associated with a decrease of -0.24 METH (95% CI, -0.45 : -0.02 ; $p = 0.030$) in the volume of NLTPA. The weekly volume of SPEA was, however, not associated with the change in NEPA either in the NW group (estimate = 0.085 , 95% CI, -0.859 : 1.029 , $p = 0.858$) or in the RT-group (estimate = 0.929 , 95% CI, -0.925 : 2.783 , $p = 0.322$).

5.2.3 THE CORRELATES OF CHANGE IN PHYSICAL ACTIVITY DURING STRUCTURED EXERCISE INTERVENTION (II)

In the RT-group, significant correlations were found between the absolute and relative TWA-MET of total LTPA and baseline BMI ($r = 0.742$, $p = 0.035$ and $r = 0.795$, $p = 0.018$, respectively). No other significant correlations were found. No significant correlations were found between the intensity (TWA-MET or %TWA-

MET) or volume of SPEA and change in intensity or volume of other physical activity subcategories.

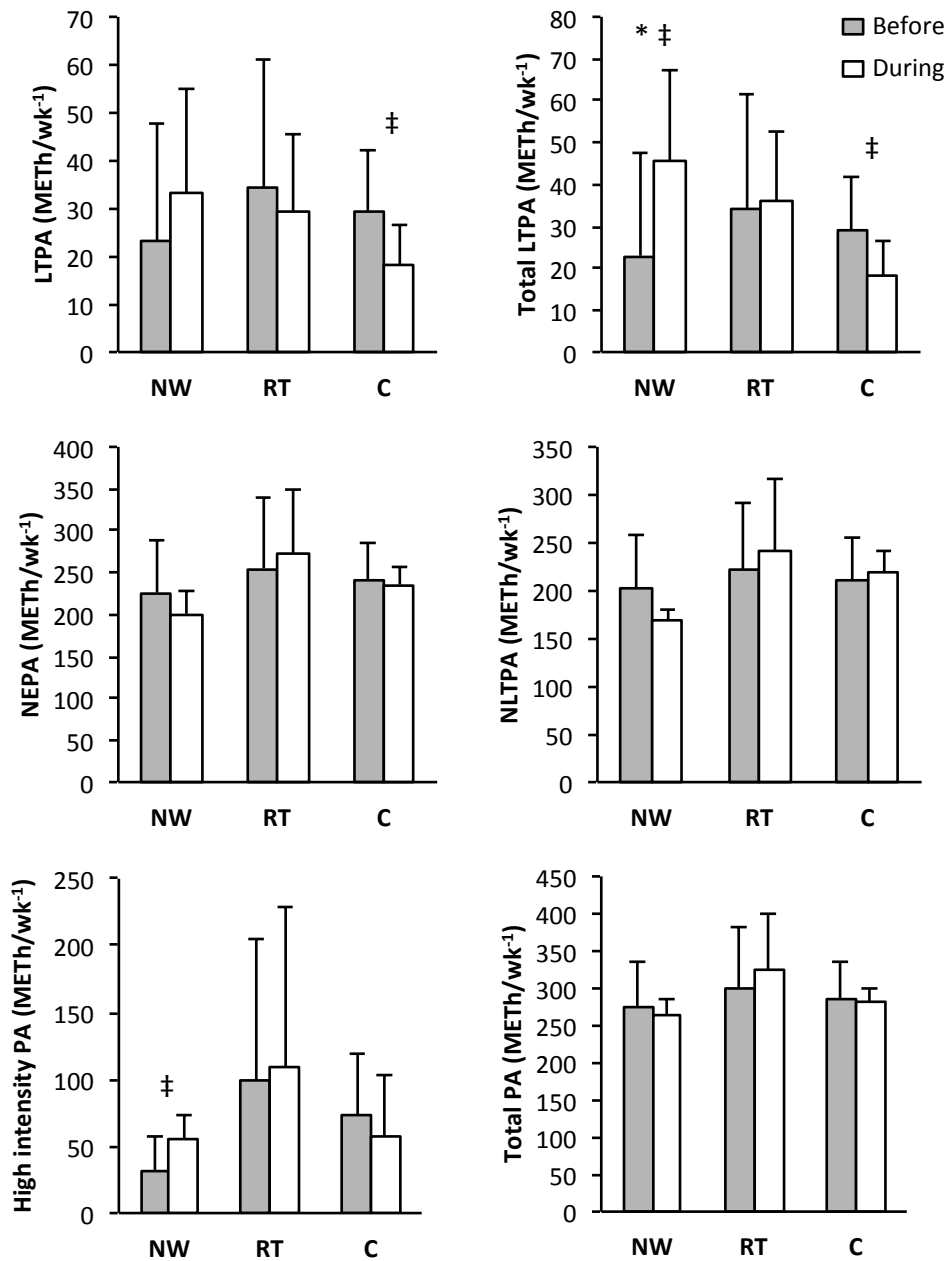


Figure 12. Mean volume of physical activity before and during the 12-week Nordic walking (NW), resistance training (RT), or non-exercise control (C) intervention (II). LTPA, leisure-time physical activity, total LTPA, LTPA + structured exercise, high intensity PA, all physical activities $\geq 50\%$ of $VO_{2\text{ peak}}$; NEPA, non-exercise physical activity; NLTPA, non-LTPA. ‡ p = before vs. during, *change in NW vs. change in C.

5.2.4 BETWEEN THE GROUP COMPARISON OF LEISURE-TIME PHYSICAL ACTIVITY DURING EXERCISE INTERVENTION (III)

The median frequency of LTPA was lower in the NW-group compared to the C-group (2.4 session·wk⁻¹, IQR 7.4 vs. 4.0 sessions·wk⁻¹, IQR 10.0; $p = 0.006$). In the RT-group, median frequency of total LTPA was greater than in the C-group (4.8 session·wk⁻¹, IQR 10.8 vs. 4.0 sessions·wk⁻¹, IQR 10.0; $p = 0.034$). No other significant differences were found between the groups in the frequency or median time used for one session of LTPA, SPEA, or total LTPA ($p > 0.050$).

The median TWA-MET of total LTPA was significantly lower in the RT-group (3.91 MET, IQR 3.89) compared to the NW-group (5.47 MET, IQR 2.87, $p < 0.001$) or the C-group (5.11, IQR 10.40). There was no significant difference in TWA-MET between the NW-group and the C-group. The median %TWA-MET of total LTPA was also significantly lower in the RT-group than in the NW-group (51 %METc, IQR 47 vs. 68 %METc, IQR 56, $p < 0.001$), but not compared to the C-group (59 %METc, IQR 88, $p = 0.140$). Median %TWA-MET of total LTPA was significantly higher in the NW-group than in the C-group ($p = 0.049$). No significant difference was found between the groups for Peak-MET in LTPA or total LTPA.

No significant difference was found between the groups for TWA-MET of LTPA during the weeks 1–4, weeks 5–8, or weeks 9–12 of the intervention (Figure 13). The TWA-MET of total LTPA was, however, significantly lower throughout the intervention in the RT-group compared to the C-group. In contrast, the median TWA-MET of total LTPA tended to be higher in the NW-group than in the C-group in all three phases of the intervention, although a significant difference was found only in weeks 5–9.

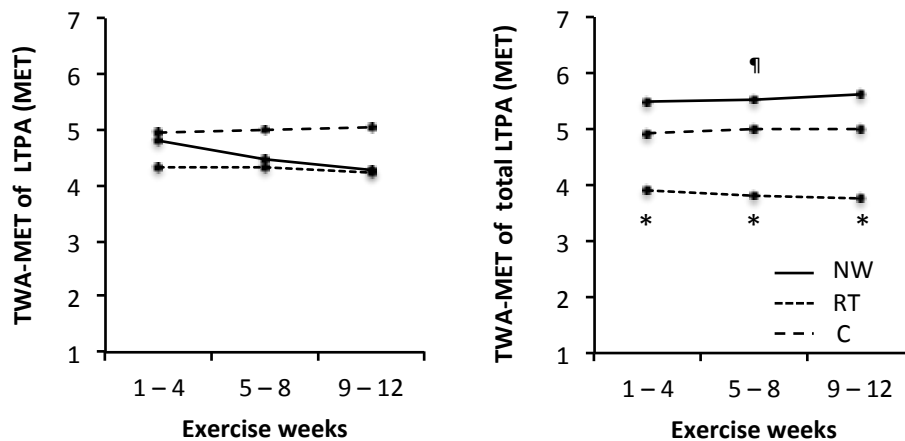


Figure 13. Time-weighted average intensity (TWA-MET) of leisure-time physical activity (LTPA) and total LTPA in different phases of exercise (III). * $p < 0.050$ Resistance training (RT) group vs. control (C) group; † $p < 0.050$ Nordic walking (NW) group vs. C.

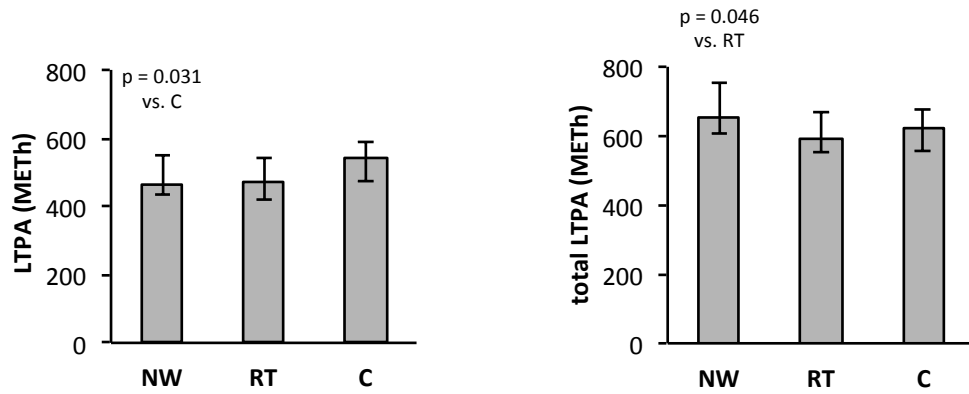


Figure 14. The median leisure-time physical activity during 12-week Nordic walking (NW), power-type resistance training (RT), or non-exercise control (C) interventions (III). Error bars indicate interquartile range.

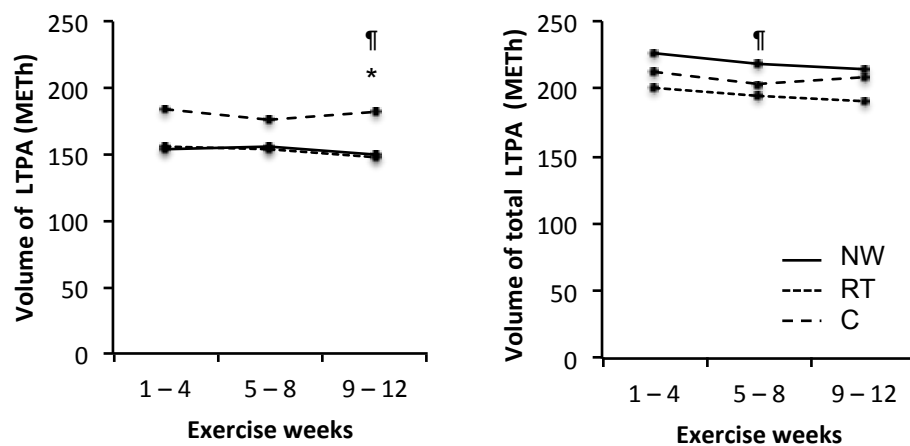


Figure 15. Volume of leisure-time physical activity (LTPA) and total LTPA in different phases of exercise (III). * $p < 0.050$ Resistance training (RT) group vs. control (C) group; ¶ $p < 0.050$ Nordic walking (NW) group vs. C.

The median volume of LTPA during the 12-week exercise intervention was significantly lower in the NW-group compared to the C-group, but not compared to the RT-group (Figure 14). No significant difference was found between the exercise groups and the C-group in the volume of total LTPA (Figure 14). The volume of total LTPA was, however, significantly higher in the NW-group compared to the RT-group.

During the different phases of the exercise intervention (weeks 1–4, weeks 5–8, and weeks 9–12) the median volume of LTPA was similar in the NW and RT-group (Figure 15). The median volume of LTPA seemed to be higher in the C-group than in the two exercise groups throughout the study, although the groups

differed significantly only in the last phase of the training (weeks 9–12). The median volume of total LTPA tended to be higher in the NW-group compared to the C-group. A significant difference between the NW-group and the C-group was found only in weeks 5–8. There was no significant difference between the RT and the C-group in the volume of total LTPA. The median values, however, tended to be lower among subjects in the RT-group compared to the subjects in the C-group.

5.3 EFFECT OF EXERCISE INTERVENTION ON RISK FACTORS FOR TYPE 2 DIABETES (IV)

5.3.1 BASELINE DATA (IV)

Subjects' baseline characteristics have been described in Table 8. At baseline the fasting insulin and leptin were significantly higher in the NW and the RT-groups compared to the C-group. In the NW-group, the baseline 2-hour insulin, chemerin, and IL-6 were also higher than in the C-group. In the RT-group, the VO_{2peak} (Wasenius et al. unpublished observation), UKK fitness index, and carbohydrate intake were lower compared to the C-group (IV). Otherwise, baseline characteristics were similar between the groups.

5.3.2 BETWEEN THE GROUP COMPARISON (IV)

In the NW-group, body weight, BMI, fat percentage, , plasma leptin, and serum chemerin decreased and UKK fitness index increased significantly compared to the C-group (Table 8). In the RT group, only serum chemerin decreased significantly compared to the C-group. In addition to UKK fitness index, there were no significant between the group differences in other physical capacity measures (Wasenius et al. unpublished observation). No other significant differences were found between the exercise groups and the C-group.

An analysis of covariance, in which the baseline value and baseline body fat percentage were set as a covariate, was performed on rank-transformed variables to investigate the effect of body fat on chemerin and leptin, total cholesterol, LDL cholesterol, and fatty liver index values. After these adjustments, the improvements in leptin ($p = 0.002$), chemerin ($p = 0.040$), total cholesterol ($p = 0.034$), LDL-cholesterol ($p = 0.015$), and fatty liver index ($p = 0.012$) were significantly larger in the NW-group compared to the C-group. In the RT-group, only the change in chemerin ($p = 0.019$) remained significant, whereas no significant differences were found in leptin ($p = 0.174$), total cholesterol ($p = 0.698$), LDL-cholesterol ($p = 0.814$), or fatty liver index ($p = 0.495$) compared to the C-group.

Table 10. Baseline characteristics and change in risk factors of type 2 diabetes after a 12-week structured exercise intervention (IV).

Variable	Resistance training group		Nordic walking group		Control group	
	Baseline	Change	Baseline	Change	Baseline	Change
Body composition						
Weight (kg)	96.7 (12.3)	-0.2 (2.2)	95.1 (11.7)	-2.3 (2.5) ^a	92.2 (12.4)	-0.8 (2.1)
Fat percentage (%)	25.8 (4.5)	-0.5 (2.0)	25.8 (5.9)	-1.9 (2.6) ^a	23.6 (5.0)	-0.4 (1.5)
Waist circumference (cm)	107 (9.6)	-1.5 (3.2)	106 (9.6)	-1.9 (3.3)	102 (8.6)	-0.6 (3.2)
Fat free mass (kg)	67.7 (7.2)	0.3 (1.9)	65.0 (12.5)	0.1 (1.9)	64.9 (12.9)	-0.1 (1.2)
Glucose metabolism						
Glucose (mmol/l) ^c	6.1 (0.1)	-0.1 (0.1)	6.2 (0.1)	-0.0 (0.1)	6.1(0.1)	-0.2(0.1)
2-hour glucose (mmol/l) ^c	6.6 (0.3)	-0.3 (0.3)	6.8 (0.3)	-0.5 (0.3)	6.1(0.2)	-0.3 (0.3)
Insulin (mIU/ml) ^c	12.9 (0.7)	-0.8 (1.0)	12.6 (1.2)	-1.7 (1.0)	7.7 (0.7)	1.0 (0.9)
2-hour insulin (mIU/ml) ^c	63.0(8.2)	-4.2 (4.8)	80.7 (10.1)	-15.9 (6.4)	48.9 (6.7)	-9.1 (3.9)
HbA _{1c} (%) ^c	5.4 (0.1)	0.1 (0.1)	5.5 (0.1)	0.0 (0.1)	5.4 (0.1)	0.2 (0.1)
HOMA-IR	3.6 (0.5)	-0.3 (0.3)	3.5 (0.4)	-0.5 (0.3)	2.1 (0.2)	0.3 (0.3)
Lipid metabolism						
Total Chol (mmol/l) ^c	4.8 (0.2)	0.2 (0.1)	5.3 (0.2)	-0.2 (0.1)	5.2 (0.2)	0.1(0.1)
HDL-cholesterol (mmol/l) ^c	1.2 (0.1)	0.1 (0.0)	1.2 (0.1)	0.0 (0.0)	1.2 (0.1)	0.1 (0.0)
LDL-cholesterol (mmol/l) ^c	2.9 (0.1)	0.2 (0.1)	3.4 (0.1)	-0.2 (0.1)	3.3 (0.1)	0.1 (0.1)
Triacylglycerols (mmol/l) ^c	1.9 (0.3)	0.0 (0.2)	1.9 (0.2)	-0.3 (0.2)	1.6 (0.2)	-0.1 (0.2)
Liver enzymes metabolism						
hs-CRP (mg/l) ^c	1.6 (0.3)	0.3 (0.4)	2,2 (0.4)	-0.5 (0.4)	1.4 (0.2)	-0.1 (0.3)
γ-GT (IU/l) ^c	65 (10)	8 (7)	59 (7)	-7 (2)	55 (6)	-2 (3)
Fatty liver index (FLI) ^c	75.6 (2.9)	-1.0 (1.2)	77.6 (2.9)	-9.2 (2.6)	73.8 (2.8)	-3.4 (1.5)
Uric acid (μmol/l) ^c	427 (12)	3 (9)	420 (11)	-3 (7)	398 (10)	18 (9)
Adipocytokines						
Adiponectin (μg/ml) ^c	10.4 (1.1)	0.9 (0.6)	11.2 (1.3)	0.0 (0.8)	12.1 (1.5)	0.2 (0.7)
Chemerin (μg/ml) ^c	58.4 (3.8)	-1.1 (3.8) ^a	64.4 (3.9)	-1.6 (2.7) ^a	55.3 (4.1)	8.1 (2.6)
Interleukin-6 (pg/ml) ^c	7.6 (2.3)	0.3 (0.5)	11.5 (3.3)	-0.4 (0.9)	4.0 (1.1)	0.7 (0.8)
Leptin (μg/ml) ^c	11.5 (1.4)	-0.9 (0.9)	14.1(2.8)	-3.8 (1.2) ^a	7.6 (1.3)	-0.2 (0.9)
RBP-4 (ng/ml) ^c	19.2 (2.0)	-0.9 (1.8)	16.3 (0.8)	0.5 (0.5)	16.5 (0.6)	1.3 (0.5)
TNF-α (pg/ml) ^c	5.5 (0.8)	-0.2 (0.4)	5.6 (0.4)	-0.2 (0.3)	4.6 (0.3)	0.5 (0.2)
Blood pressure						
Systolic pressure	144 (15.7)	-4.1 (14.2)	147(13.9)	-6.7(11.1)	142 (17.6)	-2.9 (12.6)
Diastolic pressure	86 (7.3)	-2.8(6.4)	85 (9.3)	-3.8 (6.0)	84 (11.7)	-2.7(7.5)
Energy intake (kcal/day)						
Alcohol (E%)	5.5 (6.6)	2.0 (6.1)	4.9 (5.9)	-0.3 (4.3)	5.5 (6.3)	-1.4 (8.4)
Carbohydrates (E%)	41.7 (8.7)	-0.1 (7.8)	46.0 (7.7)	-3.3 (6.9)	46.6 (7.3)	-1.8 (7.1)
Dietary fiber (g /1000 kcal)	11.6 (4.5)	-1.5 (4.8)	11.2 (3.8)	-0.4 (3.2)	11.8 (4.4)	0.5 (4.0)
Protein (E%)	18.2 (2.6)	-0.7 (3.0)	17.6 (2.7)	0.6 (3.2)	17.2 (2.9)	0.8 (3.4)
Fat (E%)	34.6 (7.3)	-1.2 (6.8)	31.5 (6.4)	3.0 (6.2)	30.7 (5.9)	2.4 (5.9)
Saturated Fat (E%)	11.6 (3.2)	0.2 (2.5)	11.1 (3.4)	1.0 (2.7)	10.7 (2.8)	1.1 (2.6)
Physical capacity						
UKK fitness index	68.9 (21.1)	10.2 (9.6)	74.0 (23.2)	14.4 (16.3) ^a	80.2 (18.7)	6.0 (13.5)
Walking speed (m/s) ^b	1.84 (0.17)	0.05 (-0.04-0.13)	1.91 (0.19)	0.07 (-0.10-0.16)	1.94 (0.17)	na
Peak oxygen uptake (ml/kg/min) ^b	28.5 (5.0)	-0.1 (-1.6-1.4)	30.0 (7.6)	0.4 (-1.1-1.9)	33 (5.0)	na
Peak oxygen uptake (l/min) ^b	2.7 (0.5)	0.0 (-0.1-0.2)	2.8 (0.7)	0.0 (-0.1-0.1)	2.8 (0.4)	na

Values are mean (standard deviation) unless otherwise stated. BMI, body mass index; HbA_{1c}, glycated haemoglobin; HOMA-IR, Homeostasis model assessment for insulin resistance; hs-CRP, high sensitive C-reactive protein; γ-GT, gamma-glutamyl transpeptidase; RBP-4, retinol binding protein 4; TNF-α, tumor necrosis factor alpha. ^ap < 0.050 vs. control group, ^bchange values are mean difference between the exercise group and the control group (95% confidence interval, according to analysis of covariance adjusted for the baseline value) (Wasenius et al. unpublished observation), ^cvalues are mean (standard error).

5.4 INDEPENDENT PREDICTORS OF BODY COMPOSITION AND PHYSICAL CAPACITY RESPONSES TO EXERCISE INTERVENTION (UNPUBLISHED)

Large inter-individual variability was found in the changes of outcomes (Table 9). The associations between the responses in physical fitness or body composition and determinants of non-structured LTPA varied between the intervention groups. In the NW-group, the volume of non-structured LTPA correlated with a change in waist circumference ($r = -0.33$, $P = 0.038$) and in walking speed ($r = 0.44$, $P = 0.012$). In the RT-group, the TWA-MET of non-structured LTPA was associated with a change in BMI ($r = -0.34$, $P = 0.04$), body weight ($r = -0.35$, $P = 0.036$), and walking speed ($r = 0.40$, $P = 0.028$). In the C-group, the TWA-MET of

Table 11. The mean and range of individual changes in outcomes and the prevalence of responders.

Change in outcome	% of responders (n)	% of no change (n)	% of non-responders (n)	Minimum	Maximum	Mean (95% CI)
Nordic walking group						
Body mass index (kg/m ²)	82.1 (32)	2.6 (1)	15.4 (6)	-4.5	0.4	-0.7 (-1.0;-0.4)
Weight (kg)	82.1 (32)	2.6 (1)	15.4 (6)	-14.3	1.1	-2.2 (-3.1;-1.4)
Total fat mass (kg)	89.5 (34)	0 (0)	10.5 (4)	-14.1	0.5	-2.4 (-3.2;-1.5)
Total body fat (%)	76.3 (29)	0 (0)	23.7 (9)	-11.9	0.8	-1.9 (-3.0;-1.1)
Waist circumference (cm)	71.8 (28)	12.8 (5)	15.4 (6)	-15.0	5.0	-1.9 (-3.0;-0.9)
VO _{2peak} (l/min)	44.8 (13)	37.9 (11)	17.2 (5)	-0.1	0.7	0.1 (0.0:0.1)
VO _{2peak} (ml/kg/min)	62.1 (18)	10.3 (3)	27.6 (8)	-1.2	7.9	1.3 (0.6:2.1)
Walking speed (m/s)	83.9 (26)	0 (0)	16.1 (5)	-0.2	0.5	0.2 (0.1:0.2)
Resistance training group						
Body mass index (kg/m ²)	47.2 (17)	5.6 (2)	47.2 (17)	-1.9	1.4	0.0 (-0.3:0.2)
Weight (kg)	47.2 (17)	5.6 (2)	47.2 (17)	-7.0	4.1	-0.2 (-0.9:0.6)
Total fat mass (kg)	55.6 (20)	2.8 (1)	41.7 (15)	-10.7	3.1	-0.6 (-1.4:0.3)
Total body fat (%)	61.1 (22)	0 (0)	38.9 (14)	-6.9	3.5	-0.5 (-1.1:0.2)
Waist circumference (cm)	55.6 (20)	13.9 (5)	30.6 (11)	-9.0	3.0	-1.6 (-2.6;-0.5)
VO _{2peak} (l/min)	55.2 (16)	24.1 (7)	20.7 (6)	-0.3	0.7	0.1 (0.0:0.2)
VO _{2peak} (ml/kg/min)	75.9 (22)	0 (0)	24.1 (7)	-3.5	8.3	0.9 (0.1:1.8)
Walking speed (m/s)	93.3 (28)	0 (0)	6.7 (2)	-0.1	0.4	0.1 (0.1:0.2)
Control group						
Body mass index (kg/m ²)	60.0 (24)	2.5 (1)	37.5 (15)	-1.9	1.2	-0.2 (-0.4:0.0)
Weight (kg)	60.0 (24)	2.5 (1)	37.5 (15)	-7.1	3.9	-0.8 (-1.4;-0.1)
Total fat mass (kg)	59.0 (23)	2.6 (1)	38.5 (15)	-7.7	2.3	-0.7 (-1.3:0.0)
Total body fat (%)	59.0 (23)	2.6 (1)	38.5 (15)	-5.2	2.1	-0.5 (-1.1:0.0)
Waist circumference (cm)	47.5 (19)	12.5 (5)	40.0 (16)	-7.0	6.0	-0.6 (-1.6:0.4)
VO _{2peak} (l/min)	52.0 (13)	32.0 (8)	16.0 (4)	-0.3	0.6	0.1 (-0.0:0.1)
VO _{2peak} (ml/kg/min)	68.0 (17)	0 (0)	32.0 (8)	-4.1	8.2	0.8 (-0.2:1.8)
Walking speed (m/s)	65.7 (23)	2.9 (1)	31.4 (11)	-0.4	0.3	0.1 (0.0:0.1)

CI, confidence interval; VO_{2peak}, peak oxygen uptake.

Table 12. Determinants of change in body weight, body mass index, and walking speed.

Predictor	beta	95% CI	p-value	Partial R ²	Model R ²	Model
Change in body weight (n = 79)						
(Constant)	6.0	2.63 : 9.34	0.001			
Intensity of non-structured LTPA (MET)	-0.25	-0.45 : -0.06	0.012	0.088		
Baseline Weight (kg)	-0.06	-0.09 : -0.03	0.001	0.154		
Change in energy intake (kcal)	0.001	0.0001 : 0.001	0.028	0.068		
Nordic walking group	-1.4	-2.28 : -0.60	0.001	0.144		
Resistance training group	0.6	-0.30 : 1.50	0.190	0.024		
Change in fiber density (g/1000g)	0.04	-0.09 : 0.16	0.559	0.005		
Change in carbohydrate intake (%E)	0.05	-0.03 : 0.13	0.227	0.021		
Change in fat intake (%E)	-0.02	-0.10 : 0.05	0.519	0.006		
Change in protein intake (%E)	0.2	0.08 : 0.32	0.001	0.142	0.474	<0.001
Change in body mass index, BMI (n = 80)						
(Constant)	1.38	0.15 : 2.60	0.028			
Relative intensity of non-structured LTPA (%)	-0.01	-0.01 : -0.001	0.030	0.065		
Baseline BMI (kg/m ²)	-0.04	-0.08 : -0.001	0.045	0.056		
Change in energy intake (kcal)	0.0003	0.00004 : 0.001	0.024	0.070		
Nordic walking group	-0.43	-0.71 : -0.14	0.004	0.111		
Resistance training group	0.18	-0.12 : 0.49	0.239	0.020		
Change in fiber density (g/1000g)	0.01	-0.03 : 0.05	0.629	0.003		
Change in carbohydrate intake (%E)	0.02	-0.01 : 0.04	0.211	0.022		
Change in fat intake (%E)	-0.01	-0.03 : 0.02	0.700	0.002		
Change in protein intake (%E)	0.07	0.02 : 0.11	0.003	0.121	0.389	<0.001
Change in walking speed (n = 95)						
(Constant)	0.053	-0.36 : 0.46	0.796			
Intensity of non-structured LTPA (MET)	0.023	0.01 : 0.04	0.002	0.100		
Nordic walking group	0.071	0.01 : 0.13	0.025	0.055		
Resistance training group	0.042	-0.02 : 0.11	0.191	0.019		
Baseline walking speed (m/s)	-0.128	-0.28 : 0.02	0.086	0.033		
Age (years)	0.003	-0.001 : 0.01	0.128	0.026	0.195	0.001

LTPA, leisure-time physical activity; MET, metabolic equivalent of task. P < 0.05 statistically significant.

non-structured LTPA was associated with a change in fat mass ($r = -0.36$, $P = 0.025$) and percentage of body fat ($r = -0.43$, $P = 0.006$). Both in NW and RT-group, the associations remained relatively unchanged when the combined effect of dose of non-structured LTPA and SPEA was investigated. In addition, no significant correlations were found between the intensity or volume of SPEA and the changes in outcomes either in the NW-group or the RT-group.

Multivariate linear regression analyses were performed on the pooled group data (Table 10) for those outcome variables (change in body weight, BMI, and walking speed) that were found to be correlated with the dose determinants of non-structured LTPA, SPEA, or total LTPA. The forced entry models were adjusted for the baseline value of the dependent variable, intervention group, and the confounding factors. One MET increase in the TWA-MET of non-structured LTPA was associated with a decrease of -0.25 kg (95% CI, -0.45 :

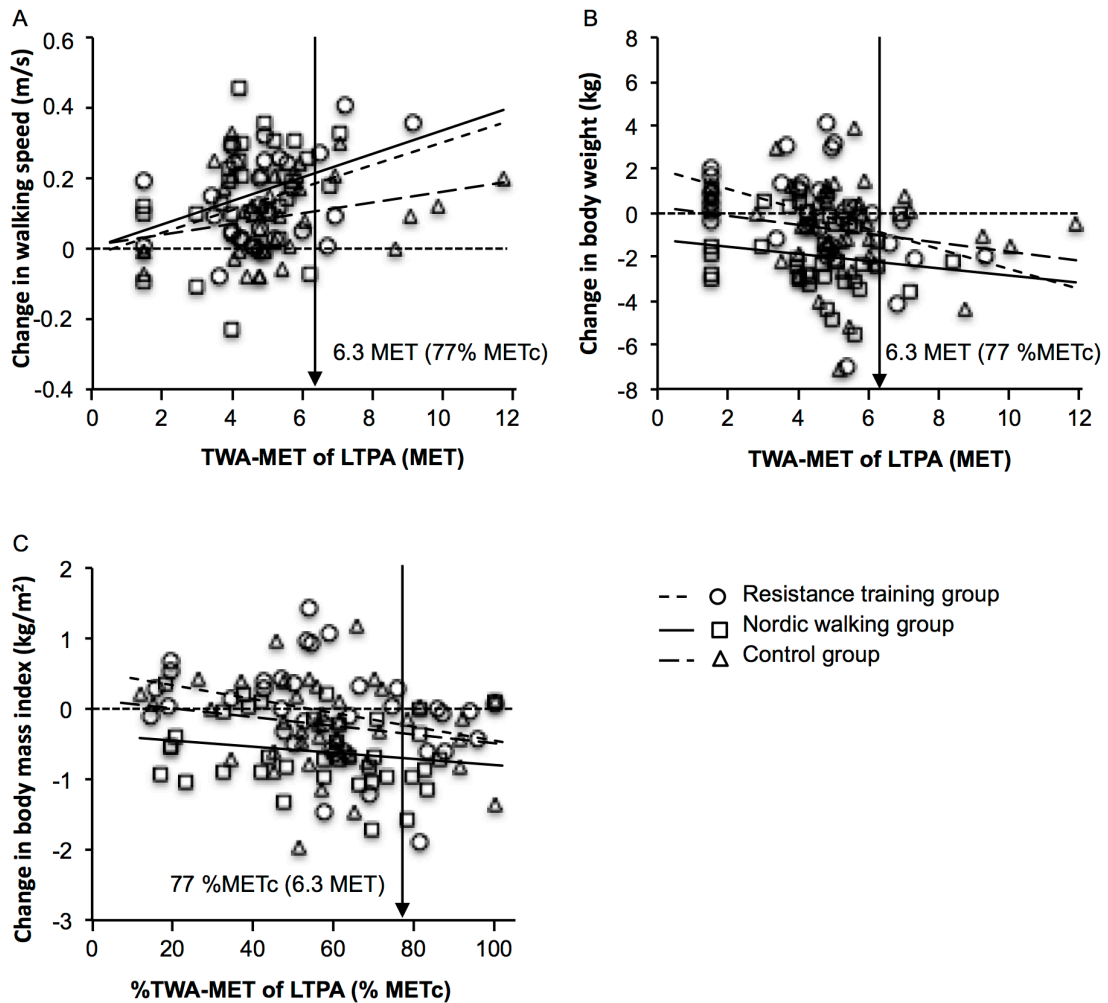


Figure 16. The change in walking speed (A), body weight (B), and body mass index (C) in relation to the time-weighted average intensity (TWA-MET) or relative TWA-MET (%TWA-MET) of non-structured leisure-time physical activity (LTPA) in different intervention groups and plausible effective thresholds. MET, metabolic equivalents of task; METc, peak oxygen uptake expressed in MET.

-0.06, $p = 0.012$) in body weight and an increase of $0.023 \text{ m}\cdot\text{s}^{-1}$ (95% CI, 0.01: 0.04, $p = 0.002$) in walking speed. After adjustments, TWA-MET explained 10% of the total variance of change in walking speed and 9% of the total variance of change in body weight. In addition, one percentage point increase in %TWA-MET was inversely associated with a decrease of $-0.01 \text{ kg}/\text{m}^2$ (95% CI, -0.01 : -0.001 , $p = 0.030$) in BMI. %TWA-MET accounted for 7% of the total variance in the BMI response to exercise intervention. In all three variables, the percentage of responders increased significantly after the intensity of non-structured LTPA was greater than 6.3 MET or 77% of METc, which can indicate a possible effective threshold for increase in walking speed or decrease in body weight or BMI (Figure 16).

6 DISCUSSION

6.1 MAIN FINDINGS

The present study investigated: 1) the effects of a 13-day rehabilitation or a 12-week exercise intervention on total daily physical activity and its subcategories (I-II), 2) the dose of RT and NW in relation to dose of non-structured LTPA (III), 3) the effect of structured NW or RT interventions on risk factors of type 2 diabetes (IV), and 3) the effect of non-structured LTPA on body composition and physical capacity responses to exercise (Wasenius et al. unpublished observation).

Both rehabilitation and Nordic walking exercise intervention increased the volume of total LTPA from baseline. During the exercise intervention the volume of total LTPA level was, however, similar between the exercise groups and the control group. No increase in the volume of total physical activity was detected with rehabilitation, NW, or RT intervention.

The 12-week structured NW intervention resulted in decreased circulating chemerin, leptin, adiposity, and increased fitness index compared to the non-exercising controls, whereas RT intervention decreased only circulating chemerin. The large inter-individual variability found in body composition and physical capacity responses to exercise was found to be associated with the intensity of non-structured LTPA. The intensity of non-structured LTPA explained 10%, 9%, and 7% of the change in walking speed, body weight, and BMI during the structured exercise intervention. The results of this study also suggest that the effect of non-structured LTPA becomes more evident when the intensity threshold of 6.3 MET (77% of METc) is exceeded (Wasenius et al. unpublished observations).

6.2 INTERPRETATION OF THE RESULTS

6.2.1 THE EFFECT OF REHABILITATION INTERVENTIONS ON HIGHER INTENSITY PHYSICAL ACTIVITY (I)

The active in-patient rehabilitation program resulted in an increased volume of LTPA. The increase in LTPA was, however, compensated by decrease in the volume of MHPA and OPA. In this type of full board rehabilitation intervention, subjects are free from occupational and mandatory domestic physical activities, thus providing more time for rest and LTPA. The shift of physical activities from one subcategory to another was also supported by the distribution of physical activities performed with an intensity of $\geq 50\%$ METc in different subcategories. In everyday life, 63% of such were performed in OPA and MHPA, while during the rehabilitation intervention 59% of such activities were accounted by LTPA (I).

It could have been expected that the fatigue induced by the exercises performed during the official structured rehabilitation program might have limited the subjects' capacity or willingness to exercise during the non-structured hours. However, it seems that the lack of compulsory daily living activities of everyday life outweighs the physical demand of the official program. In fact, in-patient rehabilitation intervention may have positive influence on several factors that may enhance the performance exercises. By decreasing mandatory OPA and MHPA activities, more time is available for exercise. Lack of time has been one of the leading factors that prevent people from exercising (Brownson et al., 2001; Mier et al., 2007). This can be especially important among women who generally are more engaged in domestic activities and childcare than men. Subjects may also experience that the physical stress and strain of a physically demanding occupation provides sufficient workout and no further recreational activity is required (Brownson et al., 2001). Thus, the lack of physical demands of OPA during in-patient rehabilitation may activate the greater daily level of LTPA, especially among subjects with physically strenuous occupations. From a psychological and sociological perspective, group based rehabilitation may provide a safe and motivating environment and also social connections that support the performance of LTPA (Hays and Clark, 1999; Kamphuis et al., 2008). Moreover, the exercise facilities of the rehabilitation center (e.g. gym, pool, dancing, lake, walking pathways in the forest) were readily available for subjects. Several previous studies have reported that the lack of facilities or insufficient space at home can prevent people from exercising (Brownson et al., 2001; Mier et al., 2007; Skowron et al., 2008; Piana et al., 2013). A rehabilitation center, which provides good facilities, can encourage people to perform more daily LTPA or it can inspire subjects to try new types or modes of recreational activities.

6.2.2 THE EFFECT OF EXERCISE INTERVENTIONS ON HIGHER INTENSITY PHYSICAL ACTIVITY (I)

During the exercise intervention, the volume of LTPA was lower in the NW-group compared to the randomly assigned non-exercise C-group, whereas no difference was found in the volume of total LTPA (LTPA + SPEA) (III). The volume of total LTPA was also similar between the RT-group and the C-group. These findings seems to suggest that the exercise intervention induced a compensatory decrease in the daily LTPA, if it is assumed that the randomization procedure was powerful enough to equally distribute the confounding factors between the treatment groups and the control group. Theoretically the mean LTPA should have been equal across randomized groups both before and during the intervention, and the difference in the volume of total LTPA should have been no less or greater than the dose of SPEA. In the present study, the baseline volume of LTPA was similar between the groups according to the sample of the subjects included in the study II. Within the subsamples, it was possible to investigate the actual change in total LTPA from baseline. In contrast to the whole sample analysis, this analysis revealed that the 12-week Nordic walking intervention increased the volume of

total LTPA compared to the C-group. Whether or not this finding applies to the whole sample cannot be determined. It is possible that the subsample selectively included only those subjects who were especially motivated for lifestyle change. Due to the selection bias and differences in the physical activity measurement methods, it is emphasized that the results of the two studies are not comparable. It could, however, be possible that the inclusion of the baseline data and analyzing the true change in physical activity gives a more definitive picture of the change in physical activity.

6.2.3 THE EFFECT OF PHYSICAL ACTIVITY INTERVENTIONS ON TOTAL PHYSICAL ACTIVITY (I–II)

In spite of the increased volume of total LTPA with both the rehabilitation and exercise intervention, no increase in the volume of total physical activity was observed (I, II). In fact, the volume of total physical activity decreased with rehabilitation intervention. These findings indicate that in rehabilitation the RIPA or LTPA were unable to compensate the lack of OPA and “obligatory” MHPA activities. While in exercise intervention, the results indicate that individuals were prone to compensate the change in volume of total LTPA by decreasing the volume of other physical activities (II).

Together, these findings paint a disappointing picture. The intervention that liberates more time by decreasing the amount of obligatory activities and offers extensive facilities to exercise, does not provide an increase in total physical activity. Unfortunately, neither does the exercise intervention that is aimed to decrease sedentary behavior during leisure hours. Interestingly, the volume of activities that reached the intensity of $\geq 50\% \text{METc}$ was also unchanged with rehabilitation intervention and resistance training but increased with Nordic walking. Taken into account the constancy in physical activity, it would seem that people are programmed to function at a specific physical activity level, which is hard to overcome, as suggested by the ActivityStat hypothesis (Gomersall et al., 2013). Whether this resistance to change is mediated by genetic, physiological, psychological, environmental or other possible factors cannot be determined in the present study. According to a recent review by Baumann et al. (2012), the human physical activity is regulated by multiple related factors. Their roles are, however, poorly understood. For a long-lasting behavioral change, it may be necessary that the intervention is able to induce adaptive neuroplasticity in the brain (Peterson, 2012). Peterson (2012) has hypothesized that a longer intervention may be required to achieve a sustainable new level of physical activity. This suggestion is supported by the fact that compensatory behavior is more commonly observed with shorter interventions as reviewed in chapter 2.2.3. The mechanisms concerning neuroplastic changes and physical activity are, however, a relatively unexplored area (Peterson, 2012). Possibly the most successful interventions are such that activate dopaminergic pathways of the brain, as these pathways has been associated with the regulation of physical activity. The dopamine system regulates reward behavior, addictive behavior,

motivation, and motor control, for example by increasing the transcription and function of dopamine receptors or related neuropeptides (Knab and Lightfoot, 2010). Longer interventions could also enable greater dose of intervention due to the progression of exercise program. This could ultimately have a greater beneficial effect on total physical activity profile and hence the health indicators.

The fact that no increase in the volume of total physical activity was observed with exercise intervention indicates a presence of compensatory behavior. In this study, a weekly change in the volume of total LTPA was inversely associated with a weekly change in the volume of NLTPA, which supports compensatory behavior in both exercise groups (NW and RT) (II). There was however, no such association found between the weekly volume of SPEA and weekly change in NEPA. These findings would suggest that structured exercise could modulate daily physical activity in multiple ways. For example, participation in structured NW intervention can increase the volume of daily higher intensity activities, but simultaneously it can decrease the volume of low intensity physical activities. This finding is supported by a previous study by Colley et al. (2010), in which an 8-week walking intervention increased the amount of vigorous physical activities while no change in total energy expenditure was observed. In contrast, in spite of evident compensation, no change in time spent on leisure and sport activities was found in elderly people (mean age 63 years) after 14 weeks of cycling training performed at the intensity of 50% of VO_{2max} with high intensity intervals exceeding of the lactate threshold (Morio et al., 1998). It is likely that the interval cycling was relatively more strenuous than the Nordic walking in the present study or the walking in the study by Colley et al. (2010). In addition, the post exercise recovery may be disturbed by age (Deschenes et al., 2006). Thus, both the physical demands of the exercise intervention and the individual's ability to recover from it can predict the individual's willingness to perform additional high intensity physical activities during physical activity intervention.

Moreover, the proportion of this types of exercise interventions are small compared to the volume of total physical activity, thus it is reasonable to expect that their effect on total physical activity is marginal. Although the mean intensity of exercises, especially aerobic type, usually exceeds those of the daily activities, the time used for such activities accounts for only few hours (e.g. 3 x 1 hours per week) of total weekly hours (168 hours) or 2%. Thus, smaller intensity variations in daily activities can allow greater changes in the total energy expenditure simply as the result of amount of time used for such activities (Tremblay et al., 2007). In addition, time to perform newly prescribed structured exercises has to be taken from some other types of activities as shown in Figure 17, which further decreases possibilities of exercise to increase the volume of total physical activity. Therefore, the exercise induced increase in daily physical activity is directly proportional to the net difference between the dose of structured exercise and the dose of replaced activities as shown in Figure 17. It is generally recommended or assumed that the prescribed exercises will replace resting type low intensity activities of daily living, thus maximizing the net increase in energy expenditure (Figure 17, example C). This type of recommendation was also given to all subjects in the present exercise

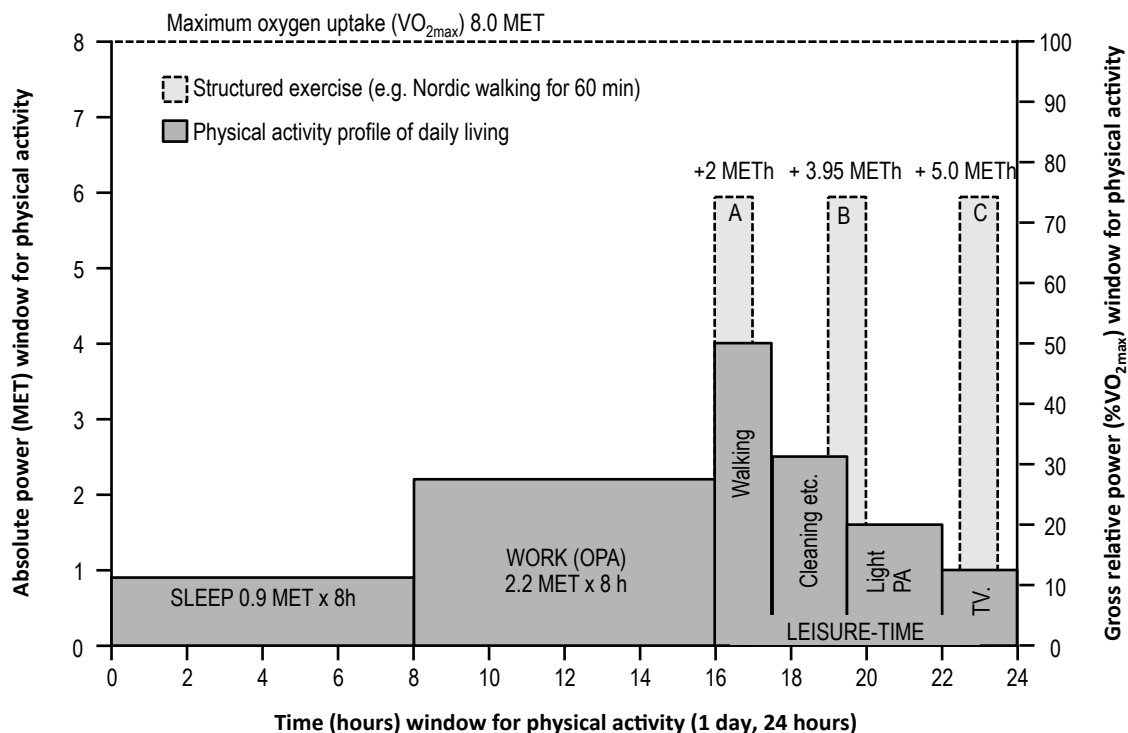


Figure 17. Different possibilities (A, B, C) to replace and increase daily physical activities with structured exercise.

intervention study. It is, however, possible that the exercises replace some other types of higher intensity activities (Figure 17, examples A and B), thus diminishing the net change in energy expenditure.

After exercise, there are most likely multiple metabolic, physiological, psychological, behavioral, and sociological factors and genetic pathways activated that determine the post-exercise susceptibility for compensatory behavior (King et al., 2007; Knab and Lightfoot, 2010; Bauman et al., 2012; Pedersen et al., 2012). Possibly, the most common factors that have been associated with compensation are reward behavior and fatigue. Goran and Poehlman (1992) found no increase in the total energy expenditure among elderly subjects who performed cycling exercise three times a week for 8 weeks with an intensity of 60–85% of VO_{2max} until 150–300 kcal of energy per session was expended. It was suggested by the authors that the intensity of the intervention could have been too strenuous for subjects during the final weeks of the training when the measurements were performed, which may have induced severe fatigue and compensatory decrease in NEAT. On the other hand, Colley et al. (2010) have reported similar compensatory decrease in NEAT with intervention, in which obese middle aged women were instructed to walk four times a week with mean heart rate of 129–137 bpm. In addition, interval cycling with an intensity varying between 50% of VO_{2max} and lactate threshold also resulted in compensation (Morio et al., 1998). Thus, it would seem that exercise induced fatigue is not the only factor explaining the compensatory behavior. Reward behavior, which is often linked to feeding and

energy balance regulation, may also be a factor for physical activity. Involvement with exercise may encourage subjects to reward themselves with extra rest or opt out of the daily high intensity physical activities and replace them with lower intensity physical activities. The pathways and factors that regulate compensation and their relationships remain unknown, but they are possibly related to the regulation of body's homeostasis, energy balance, motivation, and reward behavior. The findings of the present study suggest that compensatory behavior to exercise varies between individuals. It is also possible that these factors vary within individuals and clinical groups as a function of time due to adaptive neuroplastic responses and other individual and environmental factors.

The subjects in this study represented two different clinical groups (chronic pain patients and prediabetics), which could have altered physical activity (compensation or activation) response to exercise types of interventions. The association between the chronic pain and physical activity may be reciprocal. Previous studies have reported that chronic pain is associated with decreased physical activity (Patel et al., 2013; Hallman et al., 2013; Soysal et al., 2013; Dansie et al., 2014). While Pinto et al. (2014) have reported that higher baseline physical activity was associated with less pain and disability during a one-year follow-up in patient with low back pain. The inactivity associated with chronic pain could result from the fear-avoidance of pain, although the evidence is inconsistent for general physical activity (Leeuw et al., 2007). As suggested by Leeuw et al. (2007) it seems more likely that people with chronic pain avoid only those types of activities that they associate with pain aggravation. Interestingly, it has been hypothesized that dopamine may be related to initiation of avoidance behavior (Becker et al., 2013). These findings could suggest that the regulation or response to physical activity or exercise intervention could be different between chronic pain and pain-free patient from the neuropeptide level onwards.

Furthermore, in exercise intervention study the subjects were most likely leptin resistant (peripheral and/or central) (Maffei et al., 1995; Pan et al., 2014). Decreased leptin sensitivity could decrease physical activity energy expenditure (Pelleymounter et al., 1995; Salbe et al., 1997). In addition, leptin resistance could also reduce function of orexin – a hypothalamic neuropeptide which is a possible regulator of NEAT (Kotz et al., 2012). NEAT is a major component of exercise related compensation (Levine et al., 1999). There may be also other factors (genetic or environmental) that had detrimental effects on physical activity and predisposed subjects for a particular clinical condition. Therefore, the modification of daily physical activity of these clinical groups may differ from that of the healthy individuals.

6.2.4 THE EFFECT OF STRUCTURED EXERCISE ON RISK FACTORS OF TYPE 2 DIABETES (IV)

In the present study, Nordic walking seemed to be more effective than power-type resistance training in inducing beneficial effects on risk factors for type 2 diabetes. The physical dose of interventions were identical in the sense of duration and

frequency, however, the intensity in the NW-group, and hence volume, was almost twice as high as in the RT-group.

Both types of interventions reduced serum chemerin concentrations. These findings are consistent with other studies (Saremi et al., 2010; Stefanov et al., 2013; Neuparth et al., 2014). The decreased levels of chemerin can imply increased insulin sensitivity especially in the liver or prevention of progression of non-alcoholic fatty liver disease (NAFLD). The latter explanation seems more fitting in the present study, as no change in HOMA-IR was found. The plasma leptin level also decreased in the NW-group but not in the RT-group, which supports the previous evidence on people with IGR (Loimaala et al., 2009; Ku et al., 2010). In a study by Boudou et al. (Boudou et al., 2003), however, no change in leptin was found after 8-weeks of aerobic training. The leptin level is closely associated with the size and number of adipocytes. Thus, the change in leptin could have mirrored the change in body fat or it could also indicate an improved leptin sensitivity. Reduced leptin resistance can also have health effects, including increased peripheral fatty acid oxidation that limit the accumulation of triglycerides in tissues, decreased energy intake, or increased energy expenditure.

In the NW-group, but not in the RT-group, a significant decrease in adiposity was observed. In both groups, the fat-free mass remained unchanged. The amount of weight reduction in the NW-group is comparable with the amount commonly found with aerobic exercise (Boutcher and Dunn, 2009). The resistance training effect on adiposity has been suggested to result mainly from increased basal metabolic rate due to the increased muscle mass (Donnelly et al., 2009). The duration of the current resistance training intervention was probably too short to induce substantial increase in muscle mass. In addition, the type of resistance training program applied was not aimed for increasing muscle mass, but rather activating type IIb muscle fibers. Some evidence suggests that greater percentage of type IIb is directly associated with obesity and inversely associated with insulin resistance in humans (Lillioja et al., 1987; Tanner et al., 2002). Resistance training could have resulted in greater muscle specific physical stress and strain, but due to the intermittent nature of resistance training, the continuous Nordic walking resulted in greater total energy expenditure. In addition, the relative intensity of Nordic walking (median 73% of METc) was close to 47–64% of VO_{2max} level at which the maximum fat oxidation per unit of energy expended is achieved (Achten and Jeukendrup, 2004). On the other hand, in the RT-group, a greater proportion of energy for exercises was most likely derived from high-energy phosphates and glycolysis due to the short bursts of maximal velocity movements. Furthermore, 12-weeks of aerobic training, but not resistance training, increased the feeling of fullness in fasting and postprandial states, which could support weight loss (Guelfi et al., 2013). These differences in interventions could explain why weight loss response to NW excelled that of the RT.

From all physical capacity or performance related parameters, only UKK fitness index increased in the NW-group, whereas no change was found in the RT-group. These findings suggest that Nordic walking intervention can improve individuals' functional capacity related to walking without altering VO_{2peak} .

Improved functional capacity together with reduced body weight could have enabled in part the observed increase in volume of high intensity physical activities.

6.2.5 LEISURE-TIME PHYSICAL ACTIVITY AND RESPONSE TO EXERCISE (UNPUBLISHED)

In the last part of this study, the effect on non-structured LTPA on adiposity and physical capacity was explored. The individual variability in response to training was large in both the body composition variable and in the physical capacity variables, which is consistent with previous findings (Bouchard and Rankinen, 2001; Hautala et al., 2006; King et al., 2008; Church et al., 2009; Hautala et al., 2009). The intensity of non-structured LTPA, especially after 6.3 MET (77% of METc) threshold, explained 10.0% of walking speed, 9% of body weight, and 7% of BMI response. The observed association would suggest that the intensity of non-structured LTPA changed with intervention, albeit we were unable to measure the actual change in daily physical activity.

The evidence concerning the effect of non-exercise physical activity on physical capacity variables is limited. In the present study, no association was found with the non-exercise physical activity and the change in VO_{2peak} . In contrast, Hautala et al. (2012) have reported that the greater volume of habitual physical activity during a high to very high intensity aerobic training intervention was associated with the change in VO_{2max} in physically active men. Their analysis, however, included total physical activity, physically more demanding intervention and more fit subjects, which could explain the differing results. High intensity training has also been shown to increase walking speed in stroke patients (Kuys et al., 2011) and walking distance in Parkinson's disease patients (Rose et al., 2013) during a 6 minute walk test. These findings would support the suggestion that high intensity non-structured LTPA could have increased the functional capacity of the subjects. It is also intriguing to infer that increased functional capacity could also have resulted in greater energy expenditure in daily living and thereby have positive effects on metabolic health.

To support our findings, exercise induced change in non-exercise physical activity energy expenditure has been associated with a change in body weight (Goran and Poehlman, 1992). In the present study, however, non-structured LTPA was not associated with a change in fat mass. Albeit, the change in fat mass has previously been associated with a change in non-exercise energy expenditure (Manthou et al., 2010). To support our findings, a change in fat mass has not been associated with a change in time used for higher intensity physical activity (Barwell et al., 2009). According to Manthou et al. (2010), a change in non-exercise energy expenditure explained 13% of the variance of change in fat mass. Taken together with the present findings, it seems that non-exercise physical activity, either intensity or volume, can account for approximately 5–15% of the change in adiposity response to training.

The proportion explained by the intensity of non-structured LTPA of the inter-individual variability in response to training was close to that of the other possible confounders included in the multivariate models. Especially the proportion explained by change in energy intake of the body weight (7%) and BMI (7%) response was surprisingly similar. Dietary intake may have been modified by the intensity of non-structured LTPA. Intensive exercises have been shown to suppress feeling of hunger, decrease orexigenic (appetite stimulant) hormone ghrelin concentration, and increase anorexigenic (appetite suppressor) hormone peptide YY concentration (Broom et al., 2007; Broom et al., 2009; King et al., 2010; Crabtree et al., 2014), all of which can decrease post-exercise energy intake. The recent meta-analysis on 29 studies, however, suggests that intensive exercise does not affect 0–2-hour post exercise dietary intake, thereby resulting in negative energy balance (Schubert et al., 2013). The negative energy balance may have been increased by excess post exercise oxygen consumption (EPOC), which has been shown to increase with exercise intensity (LaForgia et al., 2006). In a review by LaForgia (2006), EPOC was estimated to increase energy expenditure by 7–14% of that of the exercise. With the NW intervention, as applied here, EPOC could induce approximately 1.5 kg fat loss in a year (LaForgia et al., 2006). Thus, the effect of EPOC on weight loss during a 12-week intervention is marginal. Furthermore, the possible increase in higher intensity of non-structured LTPA and EPOC together with stable dietary intake could have induced a negative energy balance that resulted in weight loss as described in Figure 17.

Interestingly, the volume of non-structured exercise was not found to explain the adiposity response to exercise, which supports some previous findings (Bond Brill et al., 2002; Church et al., 2007). Some studies have reported that greater volume of exercise with similar intensity (50% of VO_{2peak} or 70% maximum heart rate) has not resulted in greater reduction of body weight or fat percentage in overweight or obese postmenopausal women with elevated systolic blood pressure (Church et al., 2007; Donnelly et al., 2013). Similarly, increasing the duration of walking exercise with diet has not resulted in increased weight loss over diet alone intervention (Bond Brill et al., 2002). In contrast, Nybo et al. (2010) have suggested that running exercise that includes near maximal intervals is less effective than prolonged training in decreasing adiposity. In their study, however, the volume of exercise was not controlled (Nybo et al., 2010). When the volume of exercise has been controlled, a 12-week low-intensity (40–50% of VO_{2max}) and high-intensity (70–75% VO_{2max}) training resulted in similar weight reduction in obese Korean women with sedentary lifestyles (Cho et al., 2011).

Intensity of non-structured LTPA seems also to have a similar or larger influence on training response than the baseline value of the dependent variable, age, sex, race, or genetic inheritance (Bouchard and Rankinen, 2001; Mori et al., 2009; Bouchard et al., 2011; Rankinen et al., 2012). Although combining susceptible genetic variants increases their contribution (Bouchard et al., 2011; Rankinen et al., 2012). In the present study, we were able to investigate the association of intensity and volume of non-structured LTPA, change in energy and macronutrient intake, the baseline value of the dependent variable in a same sex,

race, and aged sample. However, the lack of genetic information may have affected the present associations, especially due to its interaction with physical activity (Li et al., 2010; Ahmad et al., 2013).

Furthermore, the challenge of measuring and quantifying true change in the response variable may have affected the results; particularly, the phenomenon known as regression to mean (RTM) (Davis, 1976). RTM means that a group of subjects selected for intervention based on the single measurement of high (e.g. overweight or obesity) or low (e.g. physical capacity) baseline value in outcome will get, even without intervention, a lower or higher value in second (follow-up) measurement (Davis, 1976; Yudkin and Stratton, 1996). The effect of RTM can be decreased by measuring the response variable multiple times before (2–4 times) and after the intervention and then calculate the difference between the mean values (Davis, 1976). In the present study, we were unable to perform a genetic analysis or multiple measurements due to the financial and practical limitations.

6.3 METHODOLOGICAL CONSIDERATIONS

In the exercise intervention study, the power of the samples was estimated to be sufficient to detect a 0.2 mmol/L change in glucose levels. The size of the sample may have been insufficiently powered to detect a change in physical activity and that may have affected the results of the studies (II, III, Wasenius et al. unpublished observations). No power calculations were performed in the rehabilitation intervention study, as the goal was not to investigate the effectiveness of the intervention, but rather to measure the change in physical activity from a physiological point of view. This reasoning is also applicable for study II. Based on the present findings, it is clear that the individual variation, when it comes to change in physical activity, is large and that substantially larger sample sizes may have been required for significant results.

The study designs were appropriate for both rehabilitation and exercise intervention studies. A RCT study design, which is the most robust design to study causal relationships, was applied for the exercise intervention study. Although, the dropouts may have somewhat affected the randomization and thereby influenced the results. In addition, the lack of blinding, especially blinding of the subjects, which is almost impossible to achieve in exercise studies, may have influenced their physical activity.

In the rehabilitation group, the estimates could have been improved by the addition of a control group. It would have not, however, been possible to randomly allocate subjects into intervention or control group, because the selection of subjects was made by experts in KELO. The researchers could not influence this selection procedure. Therefore, the sample consisted of volunteers and a selected group of subjects, which diminishes the generalization of the findings. In the exercise intervention, the generalization of the findings may also have been affected by the partial volunteer sample.

The physical activity measurements in this study were largely based on self-reports, either diaries or questionnaires. Self-reports by subjects with higher fat percentage and by men have been shown to be associated with greater over-reporting of high intensity physical activity and under-reporting of low physical activity (Buchowski et al., 1999). Several other studies have also reported that self-reports (questionnaires and physical activity logs) are associated with over-reporting of moderate to vigorous physical activity compared to accelerometers (Macfarlane et al., 2006; Troiano et al., 2008; Boon et al., 2010) or heart rate measurements (Macfarlane et al., 2006). The discrepancy between the methods may somewhat be explained by the limited validity of waist accelerometers to measure lifestyle physical activities with upper body movement, load carriage, differing slope and surface of terrain (Jakicic et al., 1999; Hendelman et al., 2000). In addition, the validity of accelerometers' thresholds applied for moderate physical activity were based on walking and jogging activities, which were substantially larger (1952 counts and 2020 counts) than thresholds (190.7 counts and 574 counts) derived from field studies of lifestyle activities (Hendelman et al., 2000; Swartz et al., 2000). Applying lower or larger range for moderate physical activity is likely to increase the duration of such activities, thereby closing the gap between the objective measurements and self-reports. In another study, approximately 0.1 unit increase (from $r = 0.24$ to $r = 0.32$ or $r = 0.35$) in the correlation coefficient between the self-reports and accelerometer was found when the lifestyle activities based thresholds were used instead of those retrieved from walking and jogging activities (Ainsworth et al., 2000a). Therefore, a significant portion of the difference between the methods remains to be explained. According to Haskell (2012), it is possible that self-reports measure different or complementary aspects of physical activity compared to objective methods. In the present study, the possible over-reporting can be argued to have only minor influence on present findings, as the analyses were based on the comparison of groups with similar body weights and the investigation of change in physical activity.

Furthermore, the aim in both datasets was to measure physical activity continuously for several weeks, which limits the use of objective measures. In the present data, financial limitation but also the limited data saving capacity of objective monitors (accelerometers) and the limited battery life would have increased the burden on subjects and on researchers. In addition, burden on subjects due to wearing physical activity monitors continuously for several weeks and reporting the wear time, recharging batteries, and possibly uploading the saved file to a computer and sending the files to the researchers would have been tremendous. In addition, objective measurements should be complemented by some type of log or diary to obtain information about physical activity subcategories. Possibly due to these limitations, several previous studies have employed objective measures to measure 1–2 weeks of physical activity before the intervention and 1–2 weeks during the middle and/or last weeks of exercise intervention. This approach has also resulted in great number of incomplete

measurements and missing data in some clinical trials (Hollowell et al., 2009; Rangan et al., 2011).

In the present study, objective measurements with SWA were applied to validate the MET-value estimations of the interventions. The applicability of this method in clinical environment was first tested in study I. In study I, also a heart rate based method was used, but it proved to be less reliable and more complicated to analyze than SWA. Thus, the SWA was chosen also for the exercise intervention study. MET-values for NW and RT training were similar to the previous studies (Phillips and Ziuraitis, 2003; Phillips and Ziuraitis, 2004; Hansen and Smith, 2009; Jurimae et al., 2009; Schiffer et al., 2009; Schiffer et al., 2011). However, the mean MET-values used for the calculation of RT dose were unable to account for the anaerobic, EPOC, and sinusoidal (exercise to recovery to exercise) nature of RT energy expenditure, which may have affected the results of the present studies (International Organization For Standardization, 2004; Scott, 2011). The accuracy of the multiple individual activities measured during the rehabilitation intervention may have also increased the risk of error due to the limitation in SWA validation studies for individual activities. Furthermore, the average of all subjects was used to estimate the RIPA, which may have affected the individual data. The RIPA was, however, a group based rehabilitation, in which all subjects went through the same program.

The risk factors of type 2 diabetes were measured with standard methods. However, in the exercise intervention study, VO_{2peak} estimation was based on the one-minute steps with an increase of 25 W until the end-point of the test was achieved. The increase may have been too steep for some subjects in order to reach steady state in each step. The non-steady state exercise may have induced exhaustion of the working muscles before the true VO_{2max} was achieved. The test was, however, performed similarly before and after the intervention, which allowed a comparison of the results. Albeit, it is possible that the physiological nature of the test did not reflect well the physiological nature of the NW, which could partially explain why no significant change in VO_{2peak} was observed. Inconsistently, structured exercise has been shown to induce 12% increase in VO_{2max} among subjects with type 2 diabetes in a previous meta-analysis (Boule et al., 2003).

Statistical methods applied in this study followed the current tradition. ANCOVA may have been more robust than non-parametric tests for change score to detect significant between the group differences in risk factors of type 2 diabetes (IV) (Jamieson, 1999; Fitzmaurice, 2001). The non-normal distribution of the data, however, enabled the use of this approach even after data transformation. Furthermore, we did not impute the missing response data, because the goal of this study was not to investigate the effectiveness of the intervention. Therefore, the inclusion of dropouts from the trial by means of imputation would have biased the exercise effect, albeit the estimates of clinical effectiveness would have been more accurate.

Moreover, the inclusion of the baseline value of the dependent variable into the regression analyses (Wasenius et al. unpublished observations) for change, as in

the previous studies (Bouchard and Rankinen, 2001; Nikander et al., 2006), may have biased the interpretation. In this approach, the baseline value is included on both sides of the regression equation ($Y_2 - \underline{Y}_1 = b_0 + bX_1 + b\underline{Y}_1 + e$) making it correlated with the error term. On the other hand, exercise response is widely reported as a change score ($Y_2 - Y_1$) and it is well known that the baseline value will have an effect on it. Thus, it would have been contradictory not to include the baseline value to the model. In the present study, several multiple linear regression analyses were performed with and without the baseline value as a predictor, and the one showing most consistency and best fit was reported. The best-fit model was estimated based on the proportion variation explained (R^2), lack of multicollinearity, normality, and heteroskedasticity of the residuals.

6.4 STRENGTHS AND WEAKNESSES OF THE STUDY

The major strength of the exercise intervention study was the randomized controlled study design to investigate the effect of structured exercise on risk factors of type 2 diabetes. There are many previous RCTs to investigate the independent effect of exercise on the risk factors of type 2 diabetes (see Table 5). The majority of these studies have been conducted on subjects with type 2 diabetes, whereas only few good quality trials have been performed on subjects with IFG or IGT. Therefore, this study increases, albeit through surrogate measures, current knowledge of the prevention of type 2 diabetes with structured exercises alone interventions.

The present study also provides information about the effect of two different types of physical activity interventions on total physical activity profile. Especially, the strength of this study was the inclusion of intensity, both absolute and relative, and volume of physical activity in different subcategories. Albeit intensity and volume are related, they could independently contribute to different health indicators. A vast majority of previous studies have focused solely on the energy expenditure or duration of the exercise. Furthermore, physical activity measured in MET-values and expressed in different subcategories of physical activity enables the clinical applicability of the results beyond the general instructions that motivate subjects to get involved in more exercise for health benefits.

A great emphasis was made in physical activity data analysis to achieve physiological comparability of the results by imputation of the missing values. The imputation was done with 1.5 MET or with 1.0 MET. It can be rightfully argued that the imputation procedure was inadequate and inaccurate. We reasoned, however, that a greater weakness would have been not to impute at all. Due to the restriction in the data, it would have been overly complicated to use more advanced imputations such as multiple imputation.

The percentage of completed structured exercise sessions was relatively low in both the NW-group (61%) and the RT-group (67%). With greater adherence, possibly more prominent effect could have been seen. This could have also influenced findings on physical activity. In study III, the diary used to measure

LTPA included only activities that were performed more than 30 minutes. Although such activities are comparable with the exercise intervention activities, the influence of shorter bouts of activity may have affected the results. Furthermore, this study is somewhat limited in its ability to determine the effect of exercise intervention on total physical activity and its subcategories due to the small number of subjects with complete data. Therefore, the results should be cautiously interpreted. The small and heterogeneous sample in study I may also have influenced the results. These findings, however, indicate real life clinical conditions, where group based intervention is applied to a group of individuals.

6.5 IMPLICATIONS OF THE FINDINGS

Clinicians and scientists worldwide are struggling to find ways to increase physical activity among risk populations. The results of the present study suggest that physical activity interventions performed in a controlled environment or in a form of structured exercise can result in increased volume of higher intensity activities, without changing the volume of total physical activity. This may result in health benefits, although the inter-individual variation is large. Approximately 5–10%, which can be an underestimation, of this variation can be accounted for by the dose of non-exercise physical activity. Thus, the dose of on non-exercise physical activity should be taken into account when prescribing or evaluating the independent effect of exercise on risk factors for type 2 diabetes.

The physical activity questionnaires employed in this study could be directly applied in a clinical environment, however, an electronic or web-based form with built-in computing could be more efficient. Especially the subjects in the exercise intervention study were requesting electronic questionnaires, which we were unable to provide in the present study. The development of cost-effective and sufficiently accurate tools for assessing the intensity and the volume of total physical activity and its subcategories in clinical settings is required. The exercise instructions and content of exercise programs should be based on these measurements and on the full understanding of the limitations and possibilities of the individual physical activity profile. Focusing solely on whether or not an individual meets the current physical activity guidelines seems to be insufficient as it includes only few percentages of the total physical activity. Thus, the total potential of physical activity to induce health benefits remains unused. The accumulation of evidence of health benefits of lower intensity physical activity supports this conclusion (Hamilton et al., 2007; Katzmarzyk, 2010).

According to the present study, NW is a safe and easy exercise mode for middle-aged men and it can have beneficial health effects in overweight or obese men with IGR. NW seems to be more effective than RT to induce health effects, albeit the health benefits of RT may require longer interventions and muscle hypertrophy. The lean body mass remained unchanged in the present study in all intervention groups. Thus, based on the current findings, NW can be recommended as an alternative mode of exercise for men with impaired glucose

regulation. In both the NW and the RT intervention, the adherence to training was relatively low. Health care providers should focus on improving commitment to physical activity change. in addition to effective dosage of exercise and physical activity

6.6 IMPLICATIONS FOR FURTHER STUDIES

An overwhelming number of physical exercise and health related studies are conducted annually. The basic assumption in exercise science is that the observed responses to training are causal to training. The effect of prescribed exercise intervention on total physical activity has been most often overlooked. The investigation of causality has been based on the RCT study design and comparison of group mean values to determine effect sizes. This is possible only if the one and only difference between the groups is the intervention, which is idealistic. For example, subjects randomly assigned into the exercise group, but not into the non-exercise control group, are forced to change their time usage due to the 24-hour limit (Figure 17). Furthermore, if all subjects in the randomized group are not replacing physical activities of similar intensity, the net physical activity change induced by structured intervention is different. Thus, it is clear that even with the RCT study design, the independent effect of exercise is affected by confounding factors. Thus, the future dose-response studies should include the analysis of change in intensity and volume of total physical activity and its subcategories. This would enlighten the influence of NEPA on response to exercise.

The two types of interventions investigated in this study were not able to increase the volume of total physical activity. In the future, interventions that try to increase the intensity and volume of physical activity should be conducted. These studies should be aimed for the total 24 hour period of the day rather than to be limited in traditional exercise. To enable such studies, physical activity measurement methods that allow feasible, reliable and valid ways to measure intensity and volume of physical activity in the long-term should be developed. In addition, analytical methods that can be used to investigate the associations between the multifaceted inter-correlated physical activity data and individual exercise responses should be developed. Generally, future exercise studies should be more focused on clarifying the effect of exercise on the dose of daily physical activity and its subcategories and the underlying regulative mechanisms. Better understanding of such mechanisms is the only way to achieve effective personalized prescriptions for both the intensity and volume of physical activity in the future.

7 CONCLUSIONS AND FUTURE DIRECTIONS

The present study investigated the effect of a 13-day in-patient physical active rehabilitation and a 12-week exercise intervention on intensity and volume of daily physical activity. In addition, the effect of exercise intervention on risk factors of type 2 diabetes and the effect of intensity and volume of non-structured LTPA on body composition and the physical capacity responses to training were studied.

Full board in-patient rehabilitation intervention that provides time and extensive facilities for physical activity and exercise increased the volume of LTPA. However, it resulted in a decreased volume of total physical activity. In the exercise intervention study, NW, but not RT, increased the volume of total LTPA (structured exercise + non-structured LTPA) from baseline compared to the non-exercise control group. Neither NW nor RT, however, induced an increase in the volume of total physical activity (24 hours per day). Both NW and RT intervention can decrease circulating chemerin levels, while only NW was effective in decreasing circulating plasma leptin, body weight and fat percentage. At least in the short term, NW may result in greater health benefits than RT in overweight or obese middle aged men with IGR, although the individual differences in response were large. Intensity of non-structured LTPA during structured exercise intervention can explain 10%, 9%, and 7% of the variation of walking speed, body weight, and BMI response to exercise, respectively. These associations were independent of the randomized groups and other confounders. The effect of non-structured LTPA seemed to systematically increase after exceeding the intensity threshold of 6.3 MET (77% of METc). In addition, predictability of non-structured LTPA of exercise response seems to be comparable to other predictors.

This study provides evidence that physical activity intervention can result in increased volume of total LTPA in overweight or obese middle-aged men with IGR; however, it does not at least systematically increase the volume of total physical activity. The increased volume of total LTPA seemed to be associated with a compensatory decrease in non-LTPA physical activity.

In the future, there is a great need for studies that further elaborate the possibilities of intervention to increase physical activity. Furthermore, the factors that regulate the dose of daily physical activity as a response to the intervention should be determined. This would enable personalized prescription of intensity and volume of physical activity and possibly a more effective treatment.

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REFERENCES

- Achten J, Jeukendrup AE. Optimizing fat oxidation through exercise and diet. *Nutrition* 2004; 20: 716-727.
- Adams SA, Matthews CE, Ebbeling CB, Moore CG, Cunningham JE, Fulton J, Hebert JR. The effect of social desirability and social approval on self-reports of physical activity. *Am J Epidemiol* 2005; 161: 389-398.
- Ades PA, Savage PD, Brochu M, Tischler MD, Lee NM, Poehlman ET. Resistance training increases total daily energy expenditure in disabled older women with coronary heart disease. *J Appl Physiol* 2005; 98: 1280-1285.
- Adolph EF, Molnar GW. Exchanges of heat and tolerances to cold in men exposed to outdoor weather. *Am J Physiol* 1946; 146: 507-537.
- Ahmad S, Rukh G, Varga TV, Ali A, Kurbasic A, Shungin D, Ericson U, Koivula RW, Chu AY, Rose LM, Ganna A, Qi Q, Stancakova A, Sandholt CH, Elks CE, Curhan G, Jensen MK, Tamimi RM, Allin KH, Jorgensen T, Brage S, Langenberg C, Aadahl M, Grarup N, Linneberg A, Pare G, InterAct Consortium, DIRECT Consortium, Magnusson PK, Pedersen NL, Boehnke M, Hamsten A, Mohlke KL, Pasquale LT, Pedersen O, Scott RA, Ridker PM, Ingelsson E, Laakso M, Hansen T, Qi L, Wareham NJ, Chasman DI, Hallmans G, Hu FB, Renstrom F, Orho-Melander M, Franks PW. Gene x physical activity interactions in obesity: Combined analysis of 111,421 individuals of european ancestry. *PLoS Genet* 2013; 9: e1003607.
- Ainslie PN, Campbell IT, Lambert JP, MacLaren DP, Reilly T. Physiological and metabolic aspects of very prolonged exercise with particular reference to hill walking. *Sports Med* 2005; 35: 619-647.
- Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. The compendium of physical activities tracking guide. <https://sites.google.com/site/compendiumofphysicalactivities/> (accessed 6 September 2013). Healthy Lifestyles Research Center, College of Nursing & Health Innovation, Arizona State University. 2011.
- Ainsworth BE, Bassett DR, Jr, Strath SJ, Swartz AM, O'Brien WL, Thompson RW, Jones DA, Macera CA, Kimsey CD. Comparison of three methods for measuring the time spent in physical activity. *Med Sci Sports Exerc* 2000a; 32: S457-64.
- Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr, Montoye HJ, Sallis JF, Paffenbarger RS, Jr. Compendium of physical activities: Classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993; 25: 71-80.
- Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Jr, Schmitz KH, Emplaincourt PO, Jacobs DR, Jr, Leon AS. Compendium of physical activities: An update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000b; 32: S498-504.
- Alahmadi MA, Hills AP, King NA, Byrne NM. Exercise intensity influences nonexercise activity thermogenesis in overweight and obese adults. *Med Sci Sports Exerc* 2011; 43: 624-631.
- Allen FM. Note concerning exercise in the treatment of severe diabetes. *Bost Med Surg J* 1915; 173: 743-744.
- Allen FM, Stillman E, Fitz R. Total dietary regulation in the treatment of diabetes. monographs of the rockefeller institute for medical research no. 11. New York. The Rockefeller Institute for Medical Research. 1919: 646 p.
- American Academy of Pediatrics. Committee on Public Education. American academy of pediatrics: Children, adolescents, and television. *Pediatrics* 2001; 107: 423-426.
- American society of heating, refrigerating and air-conditioning engineers (ASHRAE). ANSI/ASHRAE standard 55-2010: Thermal environmental conditions for human occupancy. Atlanta. ASHRAE. 2010: 1-37 p.
- Andersen LG, Angquist L, Gamborg M, Byberg L, Bengtsson C, Canoy D, Eriksson JG, Eriksson M, Jarvelin MR, Lissner L, Nilsen TI, Osler M, Overvad K, Rasmussen F, Salonen MK, Schack-Nielsen L, Tammelin TH, Tuomainen TP, Sorensen TI, Baker JL, NordNet Study Group. Birth weight in relation to

- leisure time physical activity in adolescence and adulthood: Meta-analysis of results from 13 nordic cohorts. *PLoS One* 2009; 4: e8192.
- Araiza P, Hewes H, Gashetewa C, Vella CA, Burge MR. Efficacy of a pedometer-based physical activity program on parameters of diabetes control in type 2 diabetes mellitus. *Metabolism* 2006; 55: 1382-1387.
- Archer E, Shook RP, Thomas DM, Church TS, Katzmarzyk PT, Hebert JR, McIver KL, Hand GA, Lavie CJ, Blair SN. 45-year trends in women's use of time and household management energy expenditure. *PLoS One* 2013; 8: e56620.
- Asmussen E, Hohwü Christensen E. Einfluss der blutverteilung auf den kreislauf bei körperlicher arbeit. *Skan Arch Physiol* 1939; 82: 185-192.
- Asmussen E, Hohwü Christensen E, Nielsen M. IV. die bedeutung der körperstellung für die pulsrequenz bei arbeit. *Skan Arch Physiol* 1939; 82: 225-233.
- Åstrand I. Aerobic work capacity in men and women with special reference to age. *Act Physiol Scan* 1960; 49: 1-92.
- Åstrand I. Degree of strain during building work as related to individual aerobic work capacity. *Ergonomics* 1967; 10: 293-303.
- Åstrand I. Estimating the energy expenditure of housekeeping activities. *Am J Clin Nutr* 1971; 24: 1471-1475.
- Åstrand P-, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *J Appl Physiol* 1954; 7: 218-221.
- Åstrand PO, Saltin B. Maximal oxygen uptake and heart rate in various types of muscular activity. *J Appl Physiol* 1961; 16: 977-981.
- Atwater WO, Benedict FG. Experiments on the metabolism of matter and energy in the human body, 1900-1902. Washington, D.C. United States Government Printing Office. 1903.
- Atwater WO, Benedict FG. A respiration calorimeter with appliances for the direct determination of oxygen. Washington, D. C. The Carnegie Institution of Washington. 1905: 193 p.
- Atwater WO, Rosa EB. A new respiration calorimeter and experiments on the conservation of energy in the human body. I. *Phys Rev* 1899a; 9: 129-166.
- Atwater WO, Rosa EB. A new respiration calorimeter and experiments on the conservation of energy in the human body. II. *Phys Rev* 1899b; 9: 214-251.
- Atwater WO, Woods CD. The chemical composition of american food materials. Washinton, DC. Government printing office. 1896: 47 p.
- Australian Government. Physical activity guidelines. <http://www.health.gov.au/internet/main/publishing.nsf/Content/health-publth-strateg-phys-act-guidelines> (accessed 15 January 2014). Australian Government, The Department of Health. 2013.
- Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982; 36: 936-942.
- Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Cholerton BA, Plymate SR, Fishel MA, Watson GS, Duncan GE, Mehta PD, Craft S. Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for alzheimer's disease. *J Alzheimers Dis* 2010; 22: 569-579.
- Bakewell S. Medical gymnastics and the cyriax collection. *Med Hist* 1997; 41: 487-495.
- Balke B. The effect of physical exercise on the metabolic potential, a crucial measure of physical fitness. 1960: 73-81.
- Baranowski T. Validity and reliability of self report measures of physical activity: An information-processing perspective. *Res Q Exerc Sport* 1988; 59: 314-327.
- Barwell ND, Malkova D, Leggate M, Gill JM. Individual responsiveness to exercise-induced fat loss is associated with change in resting substrate utilization. *Metabolism* 2009; 58: 1320-1328.

- Bassett DR, Jr, Ainsworth BE, Leggett SR, Mathien CA, Main JA, Hunter DC, Duncan GE. Accuracy of five electronic pedometers for measuring distance walked. *Med Sci Sports Exerc* 1996; 28: 1071-1077.
- Bassett DR, Jr, Ainsworth BE, Swartz AM, Strath SJ, O'Brien WL, King GA. Validity of four motion sensors in measuring moderate intensity physical activity. *Med Sci Sports Exerc* 2000; 32: S471-80.
- Bassett DR, Jr, Howley ET, Thompson DL, King GA, Strath SJ, McLaughlin JE, Parr BB. Validity of inspiratory and expiratory methods of measuring gas exchange with a computerized system. *J Appl Physiol* 2001; 91: 218-224.
- Bassett DR, Jr, Rowlands A, Trost SG. Calibration and validation of wearable monitors. *Med Sci Sports Exerc* 2012; 44: S32-8.
- Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW, Lancet Physical Activity Series Working Group. Correlates of physical activity: Why are some people physically active and others not? *Lancet* 2012; 380: 258-271.
- Becker S, Ceko M, Louis-Foster M, Elfassy NM, Leyton M, Shir Y, Schweinhardt P. Dopamine and pain sensitivity: Neither sulpiride nor acute phenylalanine and tyrosine depletion have effects on thermal pain sensations in healthy volunteers. *PLoS One* 2013; 8: e80766.
- Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C. The fatty liver index: A simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006; 6: 33.
- Bellinger L, Sculley DV, Langley-Evans SC. Exposure to undernutrition in fetal life determines fat distribution, locomotor activity and food intake in ageing rats. *Int J Obes (Lond)* 2006; 30: 729-738.
- Bellisari A. Evolutionary origins of obesity. *Obes Rev* 2008; 9: 165-180.
- Benedict FG, Carpenter TM. Respiration calorimeters for studying the respiratory exchange and energy transformations of man. Washington, D. C. The Carnegie Institution of Washington. 1910: 102 p.
- Benzinger TH, Kitzinger C. Direct calorimetry by means of the gradient principle. *Rev Sci Instrum* 1949; 20: 849-860.
- Berggren G, Hohwü Christensen E. Heart rate and body temperature as indices of metabolic rate during work. *Arbeitsphysiologie* 1950; 14: 255-260.
- Bevegård S, Freyschuss U, Strandell T. Circulatory adaptation to arm and leg exercise in supine and sitting position. *J Appl Physiol* 1966; 21: 37-46.
- Blaak EE, Westerterp KR, Bar-Or O, Wouters LJ, Saris WH. Total energy expenditure and spontaneous activity in relation to training in obese boys. *Am J Clin Nutr* 1992; 55: 777-782.
- Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: An analysis of 574 doubly-labelled water measurements. *Eur J Clin Nutr* 1996; 50: 72-92.
- Blair SN, LaMonte MJ, Nichaman MZ. The evolution of physical activity recommendations: How much is enough? *Am J Clin Nutr* 2004; 79: 913S-920S.
- Bock AV, Vancaulaert C, Dill DB, Folling A, Hurxthal LM. Studies in muscular activity: III. dynamical changes occurring in man at work. *J Physiol* 1928; 66: 136-161.
- Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol* 1985; 248: E286-91.
- Bond Brill J, Perry AC, Parker L, Robinson A, Burnett K. Dose-response effect of walking exercise on weight loss. how much is enough? *Int J Obes Relat Metab Disord* 2002; 26: 1484-1493.
- Bonjer FH. Relationship between working time, physical working capacity and allowable caloric expenditure. *Muskelarbeit und muskelttraining*. Stuttgart. A.W. Genter Verlag. 1968: 86-98 p.
- Boon RM, Hamlin MJ, Steel GD, Ross JJ. Validation of the new zealand physical activity questionnaire (NZPAQ-LF) and the international physical activity questionnaire (IPAQ-LF) with accelerometry. *Br J Sports Med* 2010; 44: 741-746.
- Booth FW, Chakravarthy MV, Spangenburg EE. Exercise and gene expression: Physiological regulation of the human genome through physical activity. *J Physiol* 2002; 543: 399-411.

- Booth FW, Laye MJ. Lack of adequate appreciation of physical exercise's complexities can pre-empt appropriate design and interpretation in scientific discovery. *J Physiol* 2009; 587: 5527-5539.
- Booth FW, Laye MJ. The future: Genes, physical activity and health. *Acta Physiol (Oxf)* 2010; 199: 549-556.
- Boothby WM. A determination of the circulation rate in man at rest and at work. *Am J Physiol* 1915; 37: 383-417.
- Booyens J, Hervey GR. The pulse rate as a means of measuring metabolic rate in man. *Can J Biochem Physiol* 1960; 38: 1301-1309.
- Borg G. Borg's perceived exertion and pain scales. Champaign (IL): Human Kinetics, 1998: 104-38.
- Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377-381.
- Borodulin K, Jousilahti P. Liikunta vapaa-ajalla, työssä ja työmatkalla 1972-2012. tutkimuksesta tiiviisti 5. Helsinki. Terveiden ja hyvinvoinnin laitos. 2012.
- Borodulin K, Laatikainen T, Juolevi A, Jousilahti P. Thirty-year trends of physical activity in relation to age, calendar time and birth cohort in finnish adults. *Eur J Public Health* 2008; 18: 339-344.
- Bottini P, Tantucci C, Scionti L, Dottorini ML, Puxeddu E, Reboldi G, Bolli GB, Casucci G, Santeusanio F, Sorbini CA. Cardiovascular response to exercise in diabetic patients: Influence of autonomic neuropathy of different severity. *Diabetologia* 1995; 38: 244-250.
- Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc* 2001; 33: S446-51; discussion S452-3.
- Bouchard C, Sarzynski MA, Rice TK, Kraus WE, Church TS, Sung YJ, Rao DC, Rankinen T. Genomic predictors of the maximal O₂ uptake response to standardized exercise training programs. *J Appl Physiol (1985)* 2011; 110: 1160-1170.
- Bouchard C, Tremblay A, Leblanc C, Lortie G, Savard R, Theriault G. A method to assess energy expenditure in children and adults. *Am J Clin Nutr* 1983; 37: 461-467.
- Bouchardat A. De l'entraînement ou de l'exercice forcé appliqué au traitement de la glycosurie. *Annuaire De Thérapeutic De Matière De Médicale De Pharmacie Et De Toxicologie* 1865: 291-336.
- Boudou P, Sobngwi E, Mauvais-Jarvis F, Vexiau P, Gautier JF. Absence of exercise-induced variations in adiponectin levels despite decreased abdominal adiposity and improved insulin sensitivity in type 2 diabetic men. *Eur J Endocrinol* 2003; 149: 421-424.
- Boule NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia* 2003; 46: 1071-1081.
- Boutcher SH, Dunn SL. Factors that may impede the weight loss response to exercise-based interventions. *Obes Rev* 2009; 10: 671-680.
- Bowen RS, Turner MJ, Lightfoot JT. Sex hormone effects on physical activity levels: Why doesn't jane run as much as dick? *Sports Med* 2011; 41: 73-86.
- Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor actiheart. *Eur J Clin Nutr* 2005; 59: 561-570.
- Branson RD, Johannigman JA. The measurement of energy expenditure. *Nutr Clin Pract* 2004; 19: 622-636.
- Breyer MK, Breyer-Kohansal R, Funk GC, Dornhofer N, Spruit MA, Wouters EF, Burghuber OC, Hartl S. Nordic walking improves daily physical activities in COPD: A randomised controlled trial. *Respir Res* 2010; 11: 112-9921-11-112.
- Brooks N, Layne JE, Gordon PL, Roubenoff R, Nelson ME, Castaneda-Sceppa C. Strength training improves muscle quality and insulin sensitivity in hispanic older adults with type 2 diabetes. *Int J Med Sci* 2007; 4: 19-27.
- Broom DR, Batterham RL, King JA, Stensel DJ. Influence of resistance and aerobic exercise on hunger, circulating levels of acylated ghrelin, and peptide YY in healthy males. *Am J Physiol Regul Integr Comp Physiol* 2009; 296: R29-35.
- Broom DR, Stensel DJ, Bishop NC, Burns SF, Miyashita M. Exercise-induced suppression of acylated ghrelin in humans. *J Appl Physiol (1985)* 2007; 102: 2165-2171.

- Brownson RC, Baker EA, Housemann RA, Brennan LK, Bacak SJ. Environmental and policy determinants of physical activity in the united states. *Am J Public Health* 2001; 91: 1995-2003.
- Buchowski MS, Townsend KM, Chen KY, Acra SA, Sun M. Energy expenditure determined by self-reported physical activity is related to body fatness. *Obes Res* 1999; 7: 23-33.
- Bureau international des poids et mesures. The international system of units (SI). France. Bureau International des Poids Mesures. 2006: 92 p.
- Buskirk ER, Harris D, Mendez J, Skinner J. Comparison of two assessments of physical activity and a survey method for calorie intake. *Am J Clin Nutr* 1971; 24: 1119-1125.
- Butler PJ, Green JA, Boyd IL, Speakman JR. Measuring metabolic rate in the field: The pros and cons of the doubly labelled water and heart rate methods. *Funct Ecol* 2004; 18: 168-183.
- Butler AA, Marks DL, Fan W, Kuhn CM, Bartolome M, Cone RD. Melanocortin-4 receptor is required for acute homeostatic responses to increased dietary fat. *Nat Neurosci* 2001; 4: 605-611.
- Butte NF, Ekelund U, Westerterp KR. Assessing physical activity using wearable monitors: Measures of physical activity. *Med Sci Sports Exerc* 2012; 44: S5-12.
- Butte NF, Wong WW, Adolph AL, Puyau MR, Vohra FA, Zakeri IF. Validation of cross-sectional time series and multivariate adaptive regression splines models for the prediction of energy expenditure in children and adolescents using doubly labeled water. *J Nutr* 2010; 140: 1516-1523.
- Butterick TA, Billington CJ, Kotz CM, Nixon JP. Orexin: Pathways to obesity resistance? *Rev Endocr Metab Disord* 2013; 14: 357-364.
- Byrne NM, Hills AP, Hunter GR, Weinsier RL, Schutz Y. Metabolic equivalent: One size does not fit all. *J Appl Physiol* 2005; 99: 1112-1119.
- Campbell WW, Crim MC, Young VR, Evans WJ. Increased energy requirements and changes in body composition with resistance training in older adults. *Am J Clin Nutr* 1994; 60: 167-175.
- Canadian Society for Exercise Physiology. Canadian physical activity guidelines. Canadian sedentary behaviour guidelines. www.csep.ca/guidelines (accessed 15 January 2014). Ottawa. Canadian Society for exercise physiology. 2014: 29 p.
- Caperchione CM, Kolt GS, Mummery WK. Physical activity in culturally and linguistically diverse migrant groups to western society: A review of barriers, enablers and experiences. *Sports Med* 2009; 39: 167-177.
- Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. the nurses' health study. *Am J Epidemiol* 1997; 145: 614-619.
- Carlson LD, Honda N, Sasaki T, Judy WV. A human calorimeter. *Proc Soc Exp Biol Med* 1964; 117: 327-331.
- Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: A 20-year follow-up of the finnish twin cohort study. *Diabetes Care* 2003; 26: 2785-2790.
- Carnethon MR, Sternfeld B, Schreiner PJ, Jacobs DR, Jr, Lewis CE, Liu K, Sidney S. Association of 20-year changes in cardiorespiratory fitness with incident type 2 diabetes: The coronary artery risk development in young adults (CARDIA) fitness study. *Diabetes Care* 2009; 32: 1284-1288.
- Carroll D, Turner JR, Prasad R. The effects of level of difficulty of mental arithmetic challenge on heart rate and oxygen consumption. *Int J Psychophysiol* 1986; 4: 167-173.
- Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Rep* 1985; 100: 126-131.
- Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care* 2002; 25: 2335-2341.
- Cauza E, Hanusch-Enserer U, Strasser B, Kostner K, Dunky A, Haber P. The metabolic effects of long term exercise in type 2 diabetes patients. *Wien Med Wochenschr* 2006; 156: 515-519.
- Cavagna G, Saibene F, Margaria R. A three-directional accelerometer for analyzing body movements. *J Appl Physiol* 1961; 16: 191.

- Cavalli-Sforza LL, Menoffi P, Piazza A. The history and geography of human genes. New Jersey. Princeton University Press. 1994: 541 p.
- Centers for Disease Control and Prevention (CDC). Prevalence of no leisure-time physical activity--35 states and the district of columbia, 1988-2002. *MMWR Morb Mortal Wkly Rep* 2004; 53: 82-86.
- Centers for Disease Control and Prevention (CDC). Prevalence of regular physical activity among adults--united states, 2001 and 2005. *MMWR Morb Mortal Wkly Rep* 2007; 56: 1209-1212.
- Chaffin DB, Couto Hde A. Correlation of aerobic capacity of brazilian workers and their physiologic work requirements. *J Occup Med* 1986; 28: 509-513.
- Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994; 17: 961-969.
- Chappuis P, Pittet P, Jequier E. Heat storage regulation in exercise during thermal transients. *J Appl Physiol* 1976; 40: 384-392.
- Chasens ER, Umlauf MG, Weaver TE. Sleepiness, physical activity, and functional outcomes in veterans with type 2 diabetes. *Appl Nurs Res* 2009; 22: 176-182.
- Chauveau MA, Kaufman M. Expériences pour la détermination du coefficient de l'activité nutritive et respiratoire des muscles en repos et en travail. *Comptes Rendus De L'Académie Des Sciences* 1887: 1126-1132.
- Chen KY, Bassett DR, Jr. The technology of accelerometry-based activity monitors: Current and future. *Med Sci Sports Exerc* 2005; 37: S490-500.
- Chen KY, Janz KF, Zhu W, Brychta RJ. Redefining the roles of sensors in objective physical activity monitoring. *Med Sci Sports Exerc* 2012; 44: S13-23.
- Cheung NW, Cinnadaio N, Russo M, Marek S. A pilot randomised controlled trial of resistance exercise bands in the management of sedentary subjects with type 2 diabetes. *Diabetes Res Clin Pract* 2009; 83: e68-71.
- Cho JK, Lee SH, Lee JY, Kang HS. Randomized controlled trial of training intensity in adiposity. *Int J Sports Med* 2011; 32: 468-475.
- Christensen EH. Physiological valuations of work in nykroppa iron works. Symposium on fatigue. London. H.K.Lewis & Co. Ltd. 1953: 93-108 p.
- Christensen EH. Physical working capacity of old workers and physiological background for work tests and work evaluations. *Bull World Health Organ* 1955; 13: 587-593.
- Church TS, Blair SN, Cocreham S, Johannsen N, Johnson W, Kramer K, Mikus CR, Myers V, Nauta M, Rodarte RQ, Sparks L, Thompson A, Earnest CP. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: A randomized controlled trial. *JAMA* 2010; 304: 2253-2262.
- Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: A randomized controlled trial. *JAMA* 2007; 297: 2081-2091.
- Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN. Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women. *PLoS One* 2009; 4: e4515.
- Church TS, Thomas DM, Tudor-Locke C, Katzmarzyk PT, Earnest CP, Rodarte RQ, Martin CK, Blair SN, Bouchard C. Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. *PLoS One* 2011; 6: e19657.
- Cindy Ng LW, Mackney J, Jenkins S, Hill K. Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis. *Chron Respir Dis* 2012; 9: 17-26.
- Colberg SR, Swain DP, Vinik AI. Use of heart rate reserve and rating of perceived exertion to prescribe exercise intensity in diabetic autonomic neuropathy. *Diabetes Care* 2003; 26: 986-990.
- Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995; 122: 481-486.

- Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990; 132: 501-513.
- Cole SA, Butte NF, Voruganti VS, Cai G, Haack K, Kent JW, Jr, Blangero J, Comuzzie AG, McPherson JD, Gibbs RA. Evidence that multiple genetic variants of MC4R play a functional role in the regulation of energy expenditure and appetite in hispanic children. *Am J Clin Nutr* 2010; 91: 191-199.
- Colley RC, Hills AP, King NA, Byrne NM. Exercise-induced energy expenditure: Implications for exercise prescription and obesity. *Patient Educ Couns* 2010; 79: 327-332.
- Consolazio CF, Johnson HL. Measurement of energy cost in humans. *Fed Proc* 1971; 30: 1444-1453.
- Cordain L, Gotshall RW, Eaton SB, Eaton SB, 3rd. Physical activity, energy expenditure and fitness: An evolutionary perspective. *Int J Sports Med* 1998; 19: 328-335.
- Corder K, Brage S, Ekelund U. Accelerometers and pedometers: Methodology and clinical application. *Curr Opin Clin Nutr Metab Care* 2007; 10: 597-603.
- Crabtree DR, Chambers ES, Hardwick RM, Blannin AK. The effects of high-intensity exercise on neural responses to images of food. *Am J Clin Nutr* 2014; 99: 258-267.
- Crawford A. Experiments and observations on animal heat, and the inflammation of combustible bodies. being an attempt to resolve these phenomena into a general law of nature. Philadelphia. printed for Thomas Dobson, in second street, between market and Chesnut-street. 1787: 94 p.
- Crouter SE, Churilla JR, Bassett DR, Jr. Estimating energy expenditure using accelerometers. *Eur J Appl Physiol* 2006a; 98: 601-612.
- Crouter SE, Churilla JR, Bassett DR, Jr. Accuracy of the actiheart for the assessment of energy expenditure in adults. *Eur J Clin Nutr* 2008; 62: 704-711.
- Crouter SE, Clowers KG, Bassett DR, Jr. A novel method for using accelerometer data to predict energy expenditure. *J Appl Physiol* 2006b; 100: 1324-1331.
- Crouter SE, Schneider PL, Karabulut M, Bassett DR, Jr. Validity of 10 electronic pedometers for measuring steps, distance, and energy cost. *Med Sci Sports Exerc* 2003; 35: 1455-1460.
- Crucza R. Body heat balance in man subjected to endogenous and exogenous heat load. *Eur J Appl Physiol* 1983; 51: 419-433.
- Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. *Diabetes Care* 2003; 26: 2977-2982.
- Current Clinical Guidelines. Liikunta.
<http://www.kaypahoito.fi/web/kh/suosituksset/naytaartikkeli/tunnus/hoi50075?hakusana=liikunta#s4>
 (accessed 15 January, 2014). The Finnish Medical Society Duodecim. 2012.
- Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M, Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: Systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011; 378: 31-40.
- Dansie EJ, Turk DC, Martin KR, Van Domelen DR, Patel KV. Association of chronic widespread pain with objectively measured physical activity in adults: Findings from the national health and nutrition examination survey. *J Pain* 2014; 15: 507-515.
- Dauncey MJ, Murgatroyd PR, Cole TJ. A human calorimeter for the direct and indirect measurement of 24 h energy expenditure. *Br J Nutr* 1978; 39: 557-566.
- Dauncey MJ. Activity and energy expenditure. *Can J Physiol Pharmacol* 1990; 68: 17-27.
- Davis CE. The effect of regression to the mean in epidemiologic and clinical studies. *Am J Epidemiol* 1976; 104: 493-498.
- De Moor MH, Liu YJ, Boomsma DI, Li J, Hamilton JJ, Hottenga JJ, Levy S, Liu XG, Pei YF, Posthuma D, Recker RR, Sullivan PF, Wang L, Willemsen G, Yan H, De Geus EJ, Deng HW. Genome-wide

- association study of exercise behavior in dutch and american adults. *Med Sci Sports Exerc* 2009; 41: 1887-1895.
- de Oliveira VN, Bessa A, Jorge ML, Oliveira RJ, de Mello MT, De Agostini GG, Jorge PT, Espindola FS. The effect of different training programs on antioxidant status, oxidative stress, and metabolic control in type 2 diabetes. *Appl Physiol Nutr Metab* 2012; 37: 334-344.
- de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a dutch population: The hoorn study. *JAMA* 2001; 285: 2109-2113.
- de Vilhena e Santos DM, Katzmarzyk PT, Seabra AF, Maia JA. Genetics of physical activity and physical inactivity in humans. *Behav Genet* 2012; 42: 559-578.
- DECODE Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care* 2003; 26: 688-696.
- Deighton T. A study of the metabolism of fowls. I. A calorimeter for the direct determination of the metabolism of the fowls. *J Agricult Sci* 1939; 29: 431-451.
- Desch SS. Effects of physical exercise versus rosiglitazone on endothelial function in coronary artery disease patients with prediabetes. *Diabetes Obes Metab* 2010; 12: 825-825.
- Deschenes MR, Carter JA, Matney EN, Potter MB, Wilson MH. Aged men experience disturbances in recovery following submaximal exercise. *J Gerontol A Biol Sci Med Sci* 2006; 61: 63-71.
- Dietary reference intakes. DRI: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids / panel on macronutrients, panel on the definition of dietary fiber, subcommittee in upper reference levels on nutrients, subcommittee on interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary reference intakes, food and nutrition board. Washington, D.C. National Academies Press. 2005: 1331 p.
- Dill DB. The economy of muscular exercise. *Physiol Rev* 1936; 16: 263-291.
- Dishman RK, Washburn RA, Schoeller DA. Measurement of physical activity. *Quest* 2001; 53: 295-309.
- Dishman RK. Gene-physical activity interactions in the etiology of obesity: Behavioral considerations. *Obesity (Silver Spring)* 2008; 16 Suppl 3: S60-5.
- Dishman RK, Sallis JF, Orenstein DR. The determinants of physical activity and exercise. *Public Health Rep* 1985; 100: 158-171.
- Dobrosielski DA, Gibbs BB, Ouyang P, Bonekamp S, Clark JM, Wang NY, Silber HA, Shapiro EP, Stewart KJ. Effect of exercise on blood pressure in type 2 diabetes: A randomized controlled trial. *J Gen Intern Med* 2012; 27: 1453-1459.
- Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK, American College of Sports Medicine. American college of sports medicine position stand. appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* 2009; 41: 459-471.
- Donnelly JE, Honas JJ, Smith BK, Mayo MS, Gibson CA, Sullivan DK, Lee J, Herrmann SD, Lambourne K, Washburn RA. Aerobic exercise alone results in clinically significant weight loss for men and women: Midwest exercise trial 2. *Obesity (Silver Spring)* 2013; 21: E219-28.
- Douglas CG. A method for determining the total respiratory exchange in man. *J Nutr* 1911; 42: 17-18.
- Droumaguet C, Balkau B, Simon D, Caces E, Tichet J, Charles MA, Eschwege E, DESIR Study Group. Use of HbA1c in predicting progression to diabetes in french men and women: Data from an epidemiological study on the insulin resistance syndrome (DESIR). *Diabetes Care* 2006; 29: 1619-1625.
- Du Bois EF. Clinical calorimetry: Thrity-fifth paper. A graphic representation of the respiratory quotient and the percentage of calories from protein, fat, and carbohydrate. *J Biol Chem* 1924; 59: 43-49.
- Dufour DL, Piperata BA. Energy expenditure among farmers in developing countries: What do we know? *Am J Hum Biol* 2008; 20: 249-258.

- Dugas LR, Harders R, Merrill S, Ebersole K, Shoham DA, Rush EC, Assah FK, Forrester T, Durazo-Arvizu RA, Luke A. Energy expenditure in adults living in developing compared with industrialized countries: A meta-analysis of doubly labeled water studies. *Am J Clin Nutr* 2011; 93: 427-441.
- Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes. A prospective population-based study. *Diabetes Care* 1996; 19: 1097-1102.
- Ebersole KE, Dugas LR, Durazo-Arvizu RA, Adeyemo AA, Tayo BO, Omatade OO, Brieger WR, Schoeller DA, Cooper RS, Luke AH. Energy expenditure and adiposity in nigerian and african-american women. *Obesity (Silver Spring)* 2008; 16: 2148-2154.
- Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Utility of hemoglobin A1c in predicting diabetes risk. *J Gen Intern Med* 2004; 19: 1175-1180.
- Edington D,W., Edgerton V,R. The biology of physical activity. Boston. Houghton Mifflin Company. 1976: 371-5 p.
- Epstein LH, Wing RR. Aerobic exercise and weight. *Addict Behav* 1980; 5: 371-388.
- Ericson U, Sonestedt E, Gullberg B, Hellstrand S, Hindy G, Wirfalt E, Orho-Melander M. High intakes of protein and processed meat associate with increased incidence of type 2 diabetes. *Br J Nutr* 2013; 109: 1143-1153.
- Eriksson KF. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. the 6-year malmö feasibility study. *Diabetologia* 1991; 34: 891.
- Esparza J, Fox C, Harper IT, Bennett PH, Schulz LO, Valencia ME, Ravussin E. Daily energy expenditure in mexican and USA pima indians: Low physical activity as a possible cause of obesity. *Int J Obes Relat Metab Disord* 2000; 24: 55-59.
- Evans WJ, Winsmann FR, Pandolf KB, Goldman RF. Self-paced hard work comparing men and women. *Ergonomics* 1980; 23: 613-621.
- FAO/WHO. Energy and protein requirements: Report of a joint FAO/WHO ad hoc expert committee. WHO technical report series no. 522. Geneva. FAO and WHO. 1973: 1-118 p.
- FAO/WHO/UNU. Energy and protein requirements: Report of an joint FAO/WHO/UNU expert consultation. WHO technical report series no. 724. Geneva. WHO. 1985: 1-96 p.
- FAO/WHO/UNU. Human energy requirements: Report of a joint FAO/WHO/UNU expert consultation. FAO food and nutrition technical report series no. 1. Rome. FAO/WHO/UNU. 2001: 1-96 p.
- Faulconbridge LF, Wadden TA, Rubin RR, Wing RR, Walkup MP, Fabricatore AN, Coday M, Van Dorsten B, Mount DL, Ewing LJ, Look AHEAD Research Group. One-year changes in symptoms of depression and weight in overweight/obese individuals with type 2 diabetes in the look AHEAD study. *Obesity (Silver Spring)* 2012; 20: 783-793.
- Feldman R, Sender AJ, Siegelaub AB. Difference in diabetic and nondiabetic fat distribution patterns by skinfold measurements. *Diabetes* 1969; 18: 478-486.
- Fenby DV. Heat: Its measurement from galileo to lavoisier. *Pure Appl Chem* 1987; 59: 91-100.
- Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, Rimm E, Colditz GA. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001; 161: 1581-1586.
- Fitzmaurice G. A conundrum in the analysis of change. *Nutrition* 2001; 17: 360-361.
- Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* 2007; 56: 1010-1013.
- Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: Findings from a national cohort of US adults. *Am J Epidemiol* 1997; 146: 214-222.
- Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, Wadden TA, Kelley D, Wing RR, Pi-Sunyer FX, Reboussin D, Kuna ST, Sleep AHEAD Research Group of Look AHEAD Research Group. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: The sleep AHEAD study. *Arch Intern Med* 2009; 169: 1619-1626.

- Fox CS, Pencina MJ, Meigs JB, Vasan RS, Levitzky YS, D'Agostino RB S. Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: The framingham heart study. *Circulation* 2006; 113: 2914-2918.
- Foy CG, Lewis CE, Hairston KG, Miller GD, Lang W, Jakicic JM, Rejeski WJ, Ribisl PM, Walkup MP, Wagenknecht LE, Look AHEAD Research Group. Intensive lifestyle intervention improves physical function among obese adults with knee pain: Findings from the look AHEAD trial. *Obesity (Silver Spring)* 2011; 19: 83-93.
- Frankenfield DC. On heat, respiration, and calorimetry. *Nutrition* 2010; 26: 939-950.
- Frayn KN. Calculation of substrate oxidation rates in vivo from gaseous exchange. *J Appl Physiol* 1983; 55: 628-634.
- Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: Depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab* 1998; 83: 847-850.
- Fritz T, Caidahl K, Krook A, Lundstrom P, Mashili F, Osler M, Szekeres FL, Ostenson CG, Wandell P, Zierath JR. Effects of nordic walking on cardiovascular risk factors in overweight individuals with type 2 diabetes, impaired or normal glucose tolerance. *Diabetes Metab Res Rev* 2013; 29: 25-32.
- Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC. Plasma glucose and prediction of microvascular disease and mortality: Evaluation of 1997 american diabetes association and 1999 world health organization criteria for diagnosis of diabetes. *Diabetes Care* 2000; 23: 1113-1118.
- Gagge AP, Burton AC, Bazett HC. A practical system of units for the description of the heat exchange of man with his environment. *Science* 1941; 94: 428-430.
- Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, American College of Sports Medicine. American college of sports medicine position stand. quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Med Sci Sports Exerc* 2011; 43: 1334-1359.
- Gibbs-Smith C, Rees G. *The inventions of leonardo da vinci*. Oxford. Phaidon Press Limited. 1978: 110-84 p.
- Goldman RF. Energy expenditure of soldiers performing combat type activities. *Ergonomics* 1965; 8: 321-327.
- Gomersall SR, Rowlands AV, English C, Maher C, Olds TS. The ActivityStat hypothesis: The concept, the evidence and the methodologies. *Sports Med* 2013; 43: 135-149.
- Good DJ, Coyle CA, Fox DL. Nhlh2: A basic helix-loop-helix transcription factor controlling physical activity. *Exerc Sport Sci Rev* 2008; 36: 187-192.
- Goran MI, Poehlman ET, Johnson RK. Energy requirements across the life span: New findings based on measurements of total energy expenditure with doubly labeled water. *Nutr Res* 1995; 15: 115-150.
- Goran MI, Poehlman ET. Endurance training does not enhance total energy expenditure in healthy elderly persons. *Am J Physiol* 1992; 263: E950-7.
- Gordon LA, Morrison EY, McGrowder DA, Young R, Fraser YT, Zamora EM, Alexander-Lindo RL, Irving RR. Effect of exercise therapy on lipid profile and oxidative stress indicators in patients with type 2 diabetes. *BMC Complement Altern Med* 2008; 8: 21.
- Government of United Kingdom. UK physical activity guidelines. <https://www.gov.uk/government/publications/uk-physical-activity-guidelines> (accessed 16 January 2014). London. Government of United Kingdom, Department of Health. 2011.
- Gram B, Christensen R, Christiansen C, Gram J. Effects of nordic walking and exercise in type 2 diabetes mellitus: A randomized controlled trial. *Clin J Sport Med* 2010; 20: 355-361.
- Green JA. The heart rate method for estimating metabolic rate: Review and recommendations. *Comp Biochem Physiol A Mol Integr Physiol* 2011; 158: 287-304.

- Green RM. A translation of galen's hygiene (de sanitate tuenda). Springfield. Charles C Thomas. 1951: 277 p.
- Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. atherosclerosis risk in communities study. *N Engl J Med* 2000: 342: 905-912.
- Guelfi KJ, Donges CE, Duffield R. Beneficial effects of 12 weeks of aerobic compared with resistance exercise training on perceived appetite in previously sedentary overweight and obese men. *Metabolism* 2013; 62: 235-243.
- Gupta NK, Mueller WH, Chan W, Meiningner JC. Is obesity associated with poor sleep quality in adolescents? *Am J Hum Biol* 2002; 14: 762-768.
- Haapa E, Toponen T, Pietinen P, Räsänen L. *Annoskuvakirja*. Helsinki. Painokaari Oy. 1985.
- Hallal PC, Wells JC, Reichert FF, Anselmi L, Victora CG. Early determinants of physical activity in adolescence: Prospective birth cohort study. *BMJ* 2006; 332: 1002-1007.
- Hallman DM, Ekman AH, Lyskov E. Changes in physical activity and heart rate variability in chronic neck-shoulder pain: Monitoring during work and leisure time. *Int Arch Occup Environ Health* 2013.
- Hambraeus L, Sjodin A, Webb P, Forslund A, Hambraeus K, Hambraeus T. A suit calorimeter for energy balance studies on humans during heavy exercise. *Eur J Appl Physiol Occup Physiol* 1994; 68: 68-73.
- Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes* 2007; 56: 2655-2667.
- Hansen EA, Smith G. Energy expenditure and comfort during nordic walking with different pole lengths. *J Strength Cond Res* 2009; 23: 1187-1194.
- Harati H, Hadaegh F, Saadat N, Azizi F. Population-based incidence of type 2 diabetes and its associated risk factors: Results from a six-year cohort study in iran. *BMC Public Health* 2009; 9: 186-2458-9-186.
- Haskell WL. Physical activity by self-report: A brief history and future issues. *J Phys Act Health* 2012; 9 Suppl 1: S5-10.
- Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: Updated recommendation for adults from the american college of sports medicine and the american heart association. *Med Sci Sports Exerc* 2007; 39: 1423-1434.
- Hautala A, Martinmaki K, Kiviniemi A, Kinnunen H, Virtanen P, Jaatinen J, Tulppo M. Effects of habitual physical activity on response to endurance training. *J Sports Sci* 2012; 30: 563-569.
- Hautala AJ, Kiviniemi AM, Makikallio TH, Kinnunen H, Nissila S, Huikuri HV, Tulppo MP. Individual differences in the responses to endurance and resistance training. *Eur J Appl Physiol* 2006; 96: 535-542.
- Hautala AJ, Kiviniemi AM, Tulppo MP. Individual responses to aerobic exercise: The role of the autonomic nervous system. *Neurosci Biobehav Rev* 2009; 33: 107-115.
- Havelock C. R. Discussion on diabetes in tropics. *BMJ* 1907; 2: 1051-1064.
- Hawley JA. Molecular responses to strength and endurance training: Are they incompatible? *Appl Physiol Nutr Metab* 2009; 34: 355-361.
- Hayes M, Chustek M, Heshka S, Wang Z, Pietrobelli A, Heymsfield SB. Low physical activity levels of modern homo sapiens among free-ranging mammals. *Int J Obes (Lond)* 2005; 29: 151-156.
- Hays LM, Clark DO. Correlates of physical activity in a sample of older adults with type 2 diabetes. *Diabetes Care* 1999; 22: 706-712.
- Helakorpi S, Holstila, A-L., Virtanen, S., Uutela A. *Suomalaisen aikuisväestön terveystilanne ja terveys, kevät 2011*. Helsinki. Terveysten ja hyvinvoinnin laitos. 2012: 203-25 p.
- Helmerhorst HJ, Brage S, Warren J, Besson H, Ekelund U. A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *Int J Behav Nutr Phys Act* 2012; 9: 103-5868-9-103.

- Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 1991; 325: 147-152.
- Hendelman D, Miller K, Baggett C, Debold E, Freedson P. Validity of accelerometry for the assessment of moderate intensity physical activity in the field. *Med Sci Sports Exerc* 2000; 32: S442-9.
- Henderson Y, Haggard H, Dolley FS. The efficiency of the heart, and the significance of rapid and slow pulse rates. *Am J Physiol* 1927; 82: 512-524.
- Henderson Y, Prince AL. The oxygen pulse and the systolic discharge. *Am J Physiol* 1914; 35: 106-115.
- Hill K, Dolmage TE, Woon L, Goldstein R, Brooks D. Measurement properties of the SenseWear armband in adults with chronic obstructive pulmonary disease. *Thorax* 2010; 65: 486-491.
- Hilsted J, Galbo H, Christensen NJ, Parving HH, Benn J. Haemodynamic changes during graded exercise in patients with diabetic autonomic neuropathy. *Diabetologia* 1982; 22: 318-323.
- Holbrook TL, Barrett-Connor E, Wingard DL. The association of lifetime weight and weight control patterns with diabetes among men and women in an adult community. *Int J Obes* 1989; 13: 723-729.
- Holdy KE. Monitoring energy metabolism with indirect calorimetry: Instruments, interpretation, and clinical application. *Nutr Clin Pract* 2004; 19: 447-454.
- Hollowell RP, Willis LH, Slentz CA, Topping JD, Bhakpar M, Kraus WE. Effects of exercise training amount on physical activity energy expenditure. *Med Sci Sports Exerc* 2009; 41: 1640-1644.
- Hordern MD, Cooney LM, Beller EM, Prins JB, Marwick TH, Coombes JS. Determinants of changes in blood glucose response to short-term exercise training in patients with type 2 diabetes. *Clin Sci (Lond)* 2008; 115: 273-281.
- Horton ES, Danforth E, Jr. Energy metabolism and obesity. *Diabetes mellitus and obesity*. Baltimore. Williams and Wilkins. 1982: 261-268 p.
- Howley ET. Type of activity: Resistance, aerobic and leisure versus occupational physical activity. *Med Sci Sports Exerc* 2001; 33: S364-9; discussion S419-20.
- Howley ET. Errors in MET estimates of physical activities using 3.5 ml.kg⁻¹.min⁻¹ as the baseline oxygen consumption. *J Phys Act Health* 2011; 8: 141-2; author reply 143-4.
- Huerta JM, Tormo MJ, Chirlaque MD, Gavrilu D, Amiano P, Arriola L, Ardanaz E, Rodriguez L, Sanchez MJ, Mendez M, Salmeron D, Barricarte A, Burgui R, Dorronsoro M, Larranaga N, Molina-Montes E, Moreno-Iribas C, Quiros JR, Toledo E, Travier N, Gonzalez CA, Navarro C. Risk of type 2 diabetes according to traditional and emerging anthropometric indices in Spain, a Mediterranean country with high prevalence of obesity: Results from a large-scale prospective cohort study. *BMC Endocr Disord* 2013; 13: 7-6823-13-7.
- Hughes AL, Goldman RF. Energy cost of "hard work". *J Appl Physiol* 1970; 29: 570-572.
- Hunter GR, Wetzstein CJ, Fields DA, Brown A, Bamman MM. Resistance training increases total energy expenditure and free-living physical activity in older adults. *J Appl Physiol* 2000; 89: 977-984.
- Ikeda T, Mabuchi A, Fukuda A, Hiraoka H, Kawakami A, Yamamoto S, Machida H, Takatori Y, Kawaguchi H, Nakamura K, Ikegawa S. Identification of sequence polymorphisms in two sulfation-related genes, PAPSS2 and SLC26A2, and an association analysis with knee osteoarthritis. *J Hum Genet* 2001; 46: 538-543.
- Ilmarinen J. Job design for the aged with regard to decline in their maximal aerobic capacity: Part I - guidelines for the practitioner. *Int J Ind Ergonom* 1992; 10: 53-61.
- International Atomic Energy Agency. Assessment of body composition and total energy expenditure in humans using stable isotope techniques. *IAEA Human Health Series* 2009: 3.
- International Dietary Energy Consultancy Group. The doubly-labelled water method for measuring energy expenditure: A consensus report by the IDECG working group. technical recommendations for use in humans. Vienna. IDECG/IAEA, NAHRES-4. 1990.
- International Organization For Standardization. Ergonomics of the thermal environment – Determination of metabolic rate, 2nd. Geneva: ISO/FDIS 8996, 2004: 24.

- International physical activity questionnaire. Guidelines for data processing and analysis of the international physical activity questionnaire (IPAQ). <http://www.ipaq.ki.se/scoring.htm> (accessed 17 July 2013). 2005: 15 p.
- Jacobsen S, Johansen O, Garby L. A 24-m³ direct heat-sink calorimeter with on-line data acquisition, processing, and control. *Am J Physiol* 1985; 249: E416-32.
- Jakicic JM, Marcus M, Gallagher KI, Randall C, Thomas E, Goss FL, Robertson RJ. Evaluation of the SenseWear pro armband to assess energy expenditure during exercise. *Med Sci Sports Exerc* 2004; 36: 897-904.
- Jakicic JM, Winters C, Lagally K, Ho J, Robertson RJ, Wing RR. The accuracy of the TriTrac-R3D accelerometer to estimate energy expenditure. *Med Sci Sports Exerc* 1999; 31: 747-754.
- Jamieson J. Dealing with baseline differences: Two principles and two dilemmas. *Int J Psychophysiol* 1999; 31: 155-161.
- Jennings AE, Alberga A, Sigal RJ, Jay O, Boule NG, Kenny GP. The effect of exercise training on resting metabolic rate in type 2 diabetes mellitus. *Med Sci Sports Exerc* 2009; 41: 1558-1565.
- Jequier E, Acheson K, Schutz Y. Assessment of energy expenditure and fuel utilization in man. *Annu Rev Nutr* 1987; 7: 187-208.
- Jequier E, Schutz Y. Stable isotopic methods for measuring energy expenditure. classical respirometry and the doubly-labelled-water (2H₂(18)O) method: Appropriate applications of the individual or combined techniques. *Proc Nutr Soc* 1988; 47: 219-225.
- Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 1990; 13: 555-565.
- Jeukendrup AE, Wallis GA. Measurement of substrate oxidation during exercise by means of gas exchange measurements. *Int J Sports Med* 2005; 26 Suppl 1: S28-37.
- Jing E, Nillni EA, Sanchez VC, Stuart RC, Good DJ. Deletion of the Nhlh2 transcription factor decreases the levels of the anorexigenic peptides alpha melanocyte-stimulating hormone and thyrotropin-releasing hormone and implicates prohormone convertases I and II in obesity. *Endocrinology* 2004; 145: 1503-1513.
- John D, Freedson P. ActiGraph and actical physical activity monitors: A peek under the hood. *Med Sci Sports Exerc* 2012; 44: S86-9.
- Johnson ML, Burke BS, Mayer J. Relative importance of inactivity and overeating in the energy balance of obese high school girls. *Am J Clin Nutr* 1956; 4: 37-44.
- Jones NL. *Clinical Exercise Testing*, 3rd ed. Philadelphia: WB Saunders, 1988: 13-73.
- Jordan AB, Robinson TN. Children, television viewing, and weight status: Summary and recommendations from an expert panel meeting. *Ann Am Acad Polit Soc Sci* 2008; 615: 83-99.
- Jorgensen K. Permissible loads based on energy expenditure measurements. *Ergonomics* 1985; 28: 365-369.
- Joslin E. The prevention of diabetes mellitus. *JAMA* 1921; 76: 79-84.
- Joslin EP. The treatment of diabetes mellitus. *Can Med Ass J* 1916; 6: 673-684.
- Joslin EP, Dublin LI, Marks HH. Studies in diabetes mellitus: IV. etiology – part 2. *Am J Med Sci* 1936; 192: 9-23.
- Jozkow P, Slowinska-Lisowska M, Laczmanski L, Medras M. DRD2 C313T and DRD4 48-bp VNTR polymorphisms and physical activity of healthy men in lower silesia, poland (HALS study). *Ann Hum Biol* 2013; 40: 186-190.
- Jurimae T, Meema K, Karelson K, Purge P, Jurimae J. Intensity of nordic walking in young females with different peak O₂ consumption. *Clin Physiol Funct Imaging* 2009; 29: 330-334.
- Kadoglou NP, Iliadis F, Angelopoulou N, Perrea D, Ampatzidis G, Liapis CD, Alevizos M. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur J Cardiovasc Prev Rehabil* 2007; 14: 837-843.

- Kadoglou NP, Iliadis F, Sailer N, Athanasiadou Z, Vitta I, Kapelouzou A, Karayannacos PE, Liapis CD, Alevizos M, Angelopoulou N, Vrabas IS. Exercise training ameliorates the effects of rosiglitazone on traditional and novel cardiovascular risk factors in patients with type 2 diabetes mellitus. *Metabolism* 2010; 59: 599-607.
- Kadono M, Hasegawa G, Shigeta M, Nakazawa A, Ueda M, Fukui M, Yoshikawa T, Nakamura N. Joint effect of alcohol and usual sleep duration on the risk of dysglycemia. *Sleep* 2007; 30: 1341-1347.
- Kaiyala KJ, Ramsay DS. Direct animal calorimetry, the underused gold standard for quantifying the fire of life. *Comp Biochem Physiol A Mol Integr Physiol* 2011; 158: 252-264.
- Kamphuis CB, Van Lenthe FJ, Giskes K, Huisman M, Brug J, Mackenbach JP. Socioeconomic status, environmental and individual factors, and sports participation. *Med Sci Sports Exerc* 2008; 40: 71-81.
- Kannel WB, Sorlie P. Some health benefits of physical activity. the framingham study. *Arch Intern Med* 1979; 139: 857-861.
- Kaprio J, Koskenvuo M, Sarna S. Cigarette smoking, use of alcohol, and leisure-time physical activity among same-sexed adult male twins. *Prog Clin Biol Res* 1981; 69 Pt C: 37-46.
- Karam JH, Grodsky GM, Forsham PH. Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. *Diabetes* 1963; 12: 197-204.
- Karlqvist L, Leijon O, Harenstam A. Physical demands in working life and individual physical capacity. *Eur J Appl Physiol* 2003; 89: 536-547.
- Kashiwazaki H, Dejima Y, Orias-Rivera J, Coward WA. Energy expenditure determined by the doubly labeled water method in bolivian aymara living in a high altitude agropastoral community. *Am J Clin Nutr* 1995; 62: 901-910.
- Katzmarzyk PT. Physical activity, sedentary behavior, and health: Paradigm paralysis or paradigm shift? *Diabetes* 2010; 59: 2717-2725.
- Katzmarzyk PT, Craig CL, Gauvin L. Adiposity, physical fitness and incident diabetes: The physical activity longitudinal study. *Diabetologia* 2007; 50: 538-544.
- Katzmarzyk PT, Mason C. The physical activity transition. *J Phys Act Health* 2009; 6: 269-280.
- Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Depressive symptoms and occurrence of type 2 diabetes among japanese men. *Diabetes Care* 1999; 22: 1071-1076.
- Kawate R, Yamakido M, Nishimoto Y, Bennett PH, Hamman RF, Knowler WC. Diabetes mellitus and its vascular complications in japanese migrants on the island of hawaii. *Diabetes Care* 1979; 2: 161-170.
- Kaye SA, Folsom AR, Sprafka JM, Prineas RJ, Wallace RB. Increased incidence of diabetes mellitus in relation to abdominal adiposity in older women. *J Clin Epidemiol* 1991; 44: 329-334.
- Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: The european prospective investigation into cancer in norfolk. *Ann Intern Med* 2004; 141: 413-420.
- King GA, Torres N, Potter C, Brooks TJ, Coleman KJ. Comparison of activity monitors to estimate energy cost of treadmill exercise. *Med Sci Sports Exerc* 2004; 36: 1244-1251.
- King H, Zimmet P, Raper LR, Balkau B. Risk factors for diabetes in three pacific populations. *Am J Epidemiol* 1984; 119: 396-409.
- King JA, Miyashita M, Wasse LK, Stensel DJ. Influence of prolonged treadmill running on appetite, energy intake and circulating concentrations of acylated ghrelin. *Appetite* 2010; 54: 492-498.
- King NA, Caudwell P, Hopkins M, Byrne NM, Colley R, Hills AP, Stubbs JR, Blundell JE. Metabolic and behavioral compensatory responses to exercise interventions: Barriers to weight loss. *Obesity (Silver Spring)* 2007; 15: 1373-1383.
- King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Individual variability following 12 weeks of supervised exercise: Identification and characterization of compensation for exercise-induced weight loss. *Int J Obes (Lond)* 2008; 32: 177-184.
- Kissebah AH, Vydellingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW. Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 1982; 54: 254-260.

- Knab AM, Lightfoot JT. Does the difference between physically active and couch potato lie in the dopamine system? *Int J Biol Sci* 2010; 6: 133-150.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346: 393-403.
- Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in pima indians: Contributions of obesity and parental diabetes. *Am J Epidemiol* 1981; 113: 144-156.
- Knuttgen HG. Strength training and aerobic exercise: Comparison and contrast. *J Strength Cond Res* 2007; 21: 973-978.
- Kodama S, Horikawa C, Fujihara K, Heianza Y, Hirasawa R, Yachi Y, Sugawara A, Tanaka S, Shimano H, Iida KT, Saito K, Sone H. Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: A meta-analysis. *Am J Epidemiol* 2012; 176: 959-969.
- Koski S. *Diabetesbarometri* 2010. 2011.
- Kotz C, Nixon J, Butterick T, Perez-Leighton C, Teske J, Billington C. Brain orexin promotes obesity resistance. *Ann N Y Acad Sci* 2012; 1264: 72-86.
- Kozey S, Lyden K, Staudenmayer J, Freedson P. Errors in MET estimates of physical activities using $3.5 \text{ ml} \times \text{kg}^{-1} \times \text{min}^{-1}$ as the baseline oxygen consumption. *J Phys Act Health* 2010; 7: 508-516.
- Krogh A, Lindhard J. A comparison between voluntary and electrically induced muscular work in man. *J Physiol* 1917; 51: 202-210.
- Krousel-Wood MA, Berger L, Jiang X, Blonde L, Myers L, Webber L. Does home-based exercise improve body mass index in patients with type 2 diabetes? results of a feasibility trial. *Diabetes Res Clin Pract* 2008; 79: 230-236.
- Ku YH, Han KA, Ahn H, Kwon H, Koo BK, Kim HC, Min KW. Resistance exercise did not alter intramuscular adipose tissue but reduced retinol-binding protein-4 concentration in individuals with type 2 diabetes mellitus. *J Int Med Res* 2010; 38: 782-791.
- Kumari M, Head J, Marmot M. Prospective study of social and other risk factors for incidence of type 2 diabetes in the whitehall II study. *Arch Intern Med* 2004; 164: 1873-1880.
- Kurumatani N, Yamaguchi B, Dejima M, Enomoto Y, Moriyama T. Aerobic capacity of forestry workers and physical demands of forestry operations. *Eur J Appl Physiol Occup Physiol* 1992; 64: 546-551.
- Kuys SS, Brauer SG, Ada L. Higher-intensity treadmill walking during rehabilitation after stroke is feasible and not detrimental to walking pattern or quality: A pilot randomized trial. *Clin Rehabil* 2011; 25: 316-326.
- Kwan M, Woo J, Kwok T. The standard oxygen consumption value equivalent to one metabolic equivalent (3.5 ml/min/kg) is not appropriate for elderly people. *Int J Food Sci Nutr* 2004; 55: 179-182.
- Laaksonen DE, Lindstrom J, Lakka TA, Eriksson JG, Niskanen L, Wikstrom K, Aunola S, Keinänen-Kiukaanniemi S, Laakso M, Valle TT, Ilanne-Parikka P, Louheranta A, Hamalainen H, Rastas M, Salminen V, Cepaitis Z, Hakumaki M, Kaikkonen H, Harkonen P, Sundvall J, Tuomilehto J, Uusitupa M, Finnish diabetes prevention study. Physical activity in the prevention of type 2 diabetes: The Finnish diabetes prevention study. *Diabetes* 2005; 54: 158-165.
- LaForgia J, Withers RT, Gore CJ. Effects of exercise intensity and duration on the excess post-exercise oxygen consumption. *J Sports Sci* 2006; 24: 1247-1264.
- Lagrange F. *Physiology of bodily exercise*. New York. D. Appleton and company. 1890: 395 p.
- Lambers S, Van Laethem C, Van Acker K, Calders P. Influence of combined exercise training on indices of obesity, diabetes and cardiovascular risk in type 2 diabetes patients. *Clin Rehabil* 2008; 22: 483-492.
- Lamonte MJ, Ainsworth BE. Quantifying energy expenditure and physical activity in the context of dose response. *Med Sci Sports Exerc* 2001; 33: S370-8; discussion S419-20.
- Lange Andersen K, Masironi R, Rutenfranz J, Seliger V, Degré S, Trygg K, Orgim M. Habitual physical activity and health. Copenhagen. World Health Organization, Regional Office for Europe. 1978: 188 p.

- LaPorte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: Problems and prospects. *Public Health Rep* 1985; 100: 131-146.
- Lavoisier AL, Laplace PSMémoire sur la chaleur. *Mémoire de l'academie des sciences*. Paris. 1780: 355-408 p.
- Lawrence RD. The effect of exercise on insulin action in diabetes. *Br Med J* 1926; 1: 648-650.
- Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *J Behav Med* 2007; 30: 77-94.
- Legg SJ, Myles WS. Maximum acceptable repetitive lifting workloads for an 8-hour work-day using psychophysical and subjective rating methods. *Ergonomics* 1981; 24: 907-916.
- Lehmann G. *Praktische arbeitsphysiologie*. Stuttgart. Georg Thieme Verlag. 1953: 355 p.
- Lehmann G. *Praktische Arbeitsphysiologie*, 2nd ed. Stuttgart: Georg Thieme Verlag, 1962: 409.
- Lehmann G, Müller EA, Spitzer H. Der calorienbedarf bei gewerblicher arbeit. *Arbeitsphysiologie* 1949; 14: 166-235.
- Lehtonen HM, Suomela JP, Tahvonen R, Vaarno J, Venojarvi M, Viikari J, Kallio H. Berry meals and risk factors associated with metabolic syndrome. *Eur J Clin Nutr* 2010; 64: 614-621.
- Leonard WR. Measuring human energy expenditure: What have we learned from the flex-heart rate method? *Am J Hum Biol* 2003; 15: 479-489.
- Leonard WR. Size counts: Evolutionary perspectives on physical activity and body size from early hominids to modern humans. *J Phys Act Health* 2010; 7 Suppl 3: S284-98.
- Levine JA. Non-exercise activity thermogenesis. *Proc Nutr Soc* 2003; 62: 667-679.
- Levine JA. Measurement of energy expenditure. *Public Health Nutr* 2005; 8: 1123-1132.
- Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science* 1999; 283: 212-214.
- Levine JA, McCrady SK, Boyne S, Smith J, Cargill K, Forrester T. Non-exercise physical activity in agricultural and urban people. *Urban Stud* 2011; 48: 2417-2427.
- Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA* 2009; 302: 179-188.
- Li S, Zhao JH, Luan J, Ekelund U, Luben RN, Khaw KT, Wareham NJ, Loos RJ. Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-norfolk prospective population study. *PLoS Med* 2010; 7: 10.1371/journal.pmed.1000332.
- Lifson N, Gordon GB, McClintock R. Measurement of total carbon dioxide production by means of D2O18. *J Appl Physiol* 1955; 7: 704-710.
- Lifson N, Gordon GB, Visscher MB, Nier AO. The fate of utilized molecular oxygen and the source of the oxygen of respiratory carbon dioxide, studied with the aid of heavy oxygen. *J Biol Chem* 1949; 180: 803-811.
- Lifson N, McClintock R. Theory of use of the turnover rates of body water for measuring energy and material balance. *J Theor Biol* 1966; 12: 46-74.
- Lightfoot JT. *Can you be born a couch potato? the genomi regulation of physical activity*. Exercise genomics. New York. Humana Press. 2011a: 45-72 p.
- Lightfoot JT. Current understanding of the genetic basis for physical activity. *J Nutr* 2011b; 141: 526-530.
- Lighton JRB. *Measuring metabolic rates: A manual for scientist*. New York. Oxford Univ. Press. 2008: 201 p.
- Lillioja S, Young AA, Culter CL, Ivy JL, Abbott WG, Zawadzki JK, Yki-Jarvinen H, Christin L, Secomb TW, Bogardus C. Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. *J Clin Invest* 1987; 80: 415-424.
- Lindhard J. Uber das minutenvolum des herzens bei rune und bai muskellarbeit. *Pflügers Arch* 1915; 161: 233-383.
- Liu S, Gao RX, Freedson PS. Computational methods for estimating energy expenditure in human physical activities. *Med Sci Sports Exerc* 2012; 44: 2138-2146.

- Livingstone MB, Strain JJ, Prentice AM, Coward WA, Nevin GB, Barker ME, Hickey RJ, McKenna PG, Whitehead RG. Potential contribution of leisure activity to the energy expenditure patterns of sedentary populations. *Br J Nutr* 1991; 65: 145-155.
- Loimaala A, Groundstroem K, Rinne M, Nenonen A, Huhtala H, Parkkari J, Vuori I. Effect of long-term endurance and strength training on metabolic control and arterial elasticity in patients with type 2 diabetes mellitus. *Am J Cardiol* 2009; 103: 972-977.
- Loimaala A, Huikuri HV, Koobi T, Rinne M, Nenonen A, Vuori I. Exercise training improves baroreflex sensitivity in type 2 diabetes. *Diabetes* 2003; 52: 1837-1842.
- Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369: 145-154.
- Loos RJ, Rankinen T, Tremblay A, Perusse L, Chagnon Y, Bouchard C. Melanocortin-4 receptor gene and physical activity in the quebec family study. *Int J Obes (Lond)* 2005; 29: 420-428.
- Louhevaara V, Sovijarvi A, Ilmarinen J, Teraslinna P. Differences in cardiorespiratory responses during and after arm crank and cycle exercise. *Acta Physiol Scand* 1990; 138: 133-143.
- Luke A, Durazo-Arvizu RA, Rotimi CN, Iams H, Schoeller DA, Adeyemo AA, Forrester TE, Wilks R, Cooper RS. Activity energy expenditure and adiposity among black adults in nigeria and the united states. *Am J Clin Nutr* 2002; 75: 1045-1050.
- Lusk G. A history of metabolism. *Endocrinology and metabolism*. New York. D. Appleton and company. 1922: 3-79 p.
- Lusk G. Animal calorimetry: Twenty-fourth paper. analysis of the oxidation of mixtures of carbohydrate and fat. *J Biol Chem* 1924; 59: 41-42.
- Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, Salonen JT. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med* 1996; 156: 1307-1314.
- Maas S, Kok ML, Westra HG, Kemper HC. The validity of the use of heart rate in estimating oxygen consumption in static and in combined static/dynamic exercise. *Ergonomics* 1989; 32: 141-148.
- Macfarlane DJ. Automated metabolic gas analysis systems: A review. *Sports Med* 2001; 31: 841-861.
- Macfarlane DJ, Lee CC, Ho EY, Chan KL, Chan D. Convergent validity of six methods to assess physical activity in daily life. *J Appl Physiol* (1985) 2006; 101: 1328-1334.
- Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S. Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1995; 1: 1155-1161.
- Malik K. Human development report 2013 - the rise of the south: Human progress in a diverse world. New York. United Nations Development Programme. 2013: 19 p.
- Malkia E. Muscular performance as a determinant of physical ability in Finnish adult population. *Turku*, 1983: 41-42.
- Mälkiä E. MET based questionnaire for the study of physical activity. Assessment of function and movement - selected papers. third nordic symposium on physiotherapy. Jyväskylä. Paino-Porras oy. 1996: 91-103 p.
- Männistö S, Laatikainen T, Vartiainen E. Suomalaisten lihavuus ennen ja nyt. tutkimuksesta tiiviisti 4. Helsinki. Terveiden ja hyvinvoinnin laitos. 2012.
- Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 1992; 268: 63-67.

- Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 1991; 338: 774-778.
- Manthou E, Gill JM, Wright A, Malkova D. Behavioral compensatory adjustments to exercise training in overweight women. *Med Sci Sports Exerc* 2010; 42: 1121-1128.
- Marcus RL, Lastayo PC, Dibble LE, Hill L, McClain DA. Increased strength and physical performance with eccentric training in women with impaired glucose tolerance: A pilot study. *J Womens Health (Larchmt)* 2009; 18: 253-260.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412-419.
- Mattocks C, Deere K, Leary S, Ness A, Tilling K, Blair SN, Riddoch C. Early life determinants of physical activity in 11 to 12 year olds: Cohort study. *Br J Sports Med* 2008; 42: 721-724.
- Mayow J. *Medico-physical works. being a translation of tractatus quinque medico-physici*. Edinburgh. The Alempric Club. 1907, original 1674: 331 p.
- McArdle WD, Katch FI, Katch VL. *Exercise physiology: Energy, nutrition and human performance*. Baltimore, ML. Lippincott Williams & Wilkins. 2007: 1068 p.
- McDonagh MJ, Davies CT. Adaptive response of mammalian skeletal muscle to exercise with high loads. *Eur J Appl Physiol Occup Physiol* 1984; 52: 139-155.
- Mclean J, Tobin G. *Animal and human calorimetry*. Cambridge. Cambridge University Press. 1987: 356 p.
- Meijer EP, Westerterp KR, Verstappen FT. Effect of exercise training on total daily physical activity in elderly humans. *Eur J Appl Physiol Occup Physiol* 1999; 80: 16-21.
- Meijer GA, Janssen GM, Westerterp KR, Verhoeven F, Saris WH, ten Hoor F. The effect of a 5-month endurance-training programme on physical activity: Evidence for a sex-difference in the metabolic response to exercise. *Eur J Appl Physiol Occup Physiol* 1991; 62: 11-17.
- Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: Are there differences between men and women? the MONICA/KORA augsburg cohort study. *Am J Clin Nutr* 2006; 84: 483-489.
- Meyer KA, Kushi LH, Jacobs DR, Jr, Folsom AR. Dietary fat and incidence of type 2 diabetes in older iowa women. *Diabetes Care* 2001; 24: 1528-1535.
- Michael ED, Jr, Hutton KE, Horvarth SM. Cardiorespiratory responses during prolonged exercise. *J Appl Physiol* 1961; 16: 997-1000.
- Michaelis AM. Clinical calorimetry: Thirty-sixth paper. A graphic method of determining certain numerical factors in metabolism. *J Biol Chem* 1924; 59: 51-58.
- Middlebrooke AR, Elston LM, Macleod KM, Mawson DM, Ball CI, Shore AC, Tooke JE. Six months of aerobic exercise does not improve microvascular function in type 2 diabetes mellitus. *Diabetologia* 2006; 49: 2263-2271.
- Mier N, Medina AA, Ory MG. Mexican americans with type 2 diabetes: Perspectives on definitions, motivators, and programs of physical activity. *Prev Chronic Dis* 2007; 4: A24.
- Misra A, Khurana L. The metabolic syndrome in south asians: Epidemiology, determinants, and prevention. *Metab Syndr Relat Disord* 2009; 7: 497-514.
- Montonen J, Knekt P, Harkanen T, Jarvinen R, Heliovaara M, Aromaa A, Reunanen A. Dietary patterns and the incidence of type 2 diabetes. *Am J Epidemiol* 2005; 161: 219-227.
- Montonen J, Knekt P, Jarvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr* 2003; 77: 622-629.
- Montoye HJ, Kemper HCG, Saris WHM, Washburn RA. *Measuring physical activity and energy expenditure*. Champaign, IL. Human Kineticss. 1996: 191 p.
- Mori M, Higuchi K, Sakurai A, Tabara Y, Miki T, Nose H. Genetic basis of inter-individual variability in the effects of exercise on the alleviation of lifestyle-related diseases. *J Physiol* 2009; 587: 5577-5584.

- Morio B, Montaurier C, Pickering G, Ritz P, Fellmann N, Coudert J, Beaufriere B, Vermorel M. Effects of 14 weeks of progressive endurance training on energy expenditure in elderly people. *Br J Nutr* 1998; 80: 511-519.
- Morris JN, Chave SP, Adam C, Sirey C, Epstein L, Sheehan DJ. Vigorous exercise in leisure-time and the incidence of coronary heart-disease. *Lancet* 1973; 1: 333-339.
- Morris JN, Heady JA. Mortality in relation to the physical activity of work: A preliminary note on experience in middle age. *Br J Ind Med* 1953; 10: 245-254.
- Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 1953; 265: 1053-7; contd.
- Mudd LM, Rafferty AP, Reeves MJ, Pivarnik JM. Physical activity recommendations: An alternative approach using energy expenditure. *Med Sci Sports Exerc* 2008; 40: 1757-1763.
- Müller EA, Franz H. Energieverbrauchsmessungen bei beruflicher arbeit mit einer verbesserten respirations-gasuhr. *Arbeitsphysiologie* 1952; 14: 499-504.
- Müller EA. The physiological basis of rest pauses in heavy work. *Q J Exp Physiol Cogn Med Sci* 1953; 38: 205-215.
- Murgatroyd PR, Shetty PS, Prentice AM. Techniques for the measurement of human energy expenditure: A practical guide. *Int J Obes Relat Metab Disord* 1993; 17: 549-568.
- Murlin JR. Normal processes of energy metabolism. *Endocrinology and metabolism*. New York. D. Appleton and Company. 1922: 515-660 p.
- Murlin JR, Burton AC. Human calorimetry. I. A semiautomatic respiration calorimeter. *J Nutr* 1935; 9: 233-260.
- Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA* 1999; 282: 1523-1529.
- Nagle FJ, Webb P, Wanta DM. Energy exchange in downhill and uphill walking: A calorimetric study. *Med Sci Sports Exerc* 1990; 22: 540-544.
- Nagy KA. CO₂ production in animals: Analysis of potential errors in the doubly labeled water method. *Am J Physiol* 1980; 238: R466-73.
- Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B, American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: Implications for care. *Diabetes Care* 2007; 30: 753-759.
- Neilson HK, Robson PJ, Friedenreich CM, Csizmadia I. Estimating activity energy expenditure: How valid are physical activity questionnaires? *Am J Clin Nutr* 2008; 87: 279-291.
- Nelson DL, Cox MM. *Lehninger principles of biochemistry*. New York. W.H. Freeman and Company. 2008: 1158 p.
- Neuparth MJ, Proenca JB, Santos-Silva A, Coimbra S. The positive effect of moderate walking exercise on chemerin levels in portuguese patients with type 2 diabetes mellitus. *J Investig Med* 2014; 62: 350-353.
- Newburgh LH, Conn JW. A new interpretation of hyperglycemia in obese middle-aged persons. *JAMA* 1939; 112: 7-11.
- Nikander R, Malkia E, Parkkari J, Heinonen A, Starck H, Ylinen J. Dose-response relationship of specific training to reduce chronic neck pain and disability. *Med Sci Sports Exerc* 2006; 38: 2068-2074.
- Nybo L, Sundstrup E, Jakobsen MD, Mohr M, Hornstrup T, Simonsen L, Bulow J, Randers MB, Nielsen JJ, Aagaard P, Krstrup P. High-intensity training versus traditional exercise interventions for promoting health. *Med Sci Sports Exerc* 2010; 42: 1951-1958.
- O'Dea K. Obesity and diabetes in "the land of milk and honey". *Diabetes Metab Rev* 1992; 8: 373-388.
- Orr JB, Leitch I. The determination of the calorie requirements of man. *Nutr Abstr Rev* 1938; 7: 509-529.
- Ovaskainen M, Valsta LM, Lauronen J. The compilation of food analysis values as a database for dietary studies – the finnish experience. *Food Chem* 1996; 57: 133-136.

- Owens GR, Thompson FE, Scirba FC, Robertson R, Metz KF, Volmer RR. Comparison of arm and leg ergometry in patients with moderate chronic obstructive lung disease. *Thorax* 1988; 43: 911-915.
- Paffenbarger RS, Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978; 108: 161-175.
- Palmes ED, Park CR. A method of human calorimetry MDFRL project no. 55-3. Fort Knox. Medical Department, Field Research Laboratory. 1947: 12 p.
- Pan H, Guo J, Su Z. Advances in understanding the interrelations between leptin resistance and obesity. *Physiol Behav* 2014; 130: 157-169.
- Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. the da qing IGT and diabetes study. *Diabetes Care* 1997; 20: 537-544.
- Passmore R, Durnin JV. Human energy expenditure. *Physiol Rev* 1955; 35: 801-840.
- Patel KV, Dansie EJ, Turk DC. Impact of chronic musculoskeletal pain on objectively measured daily physical activity: A review of current findings. *Pain Manag* 2013; 3: 467-474.
- Pearl R. *Studies on human biology*. Baltimore: Williams and Wilkins Company, 1924: 653.
- Pedersen M, Pedersen KK, Bruunsgaard H, Krabbe KS, Thomsen C, Faerch K, Pedersen BK, Mortensen EL. Cognitive functions in middle aged individuals are related to metabolic disturbances and aerobic capacity: A cross-sectional study. *PLoS One* 2012; 7: e51132.
- Peel C, Mossberg KA. Effects of cardiovascular medications on exercise responses. *Phys Ther* 1995; 75: 387-396.
- Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* 1995; 269: 540-543.
- Peltonen M, Korpi-Hyövalti E, Oksa H, Puolijoki H, Saltevo J, Vanhala M, Saaristo T, Saarikoski L, Sundvall J, Tuomilehto J. Lihavuuden, diabeteksen ja muiden glukoosiaineenvaihdunnan häiriöiden esiintyvyys suomalaisessa aikuisväestössä dekon 2D-hanke (D2D). *Suom Lääkäril* 2006; 61: 163-170.
- Pereira MA, FitzGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM. A collection of physical activity questionnaires for health-related research. *Med Sci Sports Exerc* 1997; 29: 3-205.
- Peterson JC. The adaptive neuroplasticity hypothesis of behavioral maintenance. *Neural Plast* 2012; 2012: 516364.
- Petrofsky JS, Lind AR. Metabolic, cardiovascular, and respiratory factors in the development of fatigue in lifting tasks. *J Appl Physiol Respir Environ Exerc Physiol* 1978; 45: 64-68.
- Pettee Gabriel KK, Morrow JR, Jr, Woolsey AL. Framework for physical activity as a complex and multidimensional behavior. *J Phys Act Health* 2012; 9 Suppl 1: S11-8.
- Pettenkofer M. Ueber die respiration. *Ann Chem Pharm* 1962; 123: 1-52.
- Phelan S, Kanaya AM, Subak LL, Hogan PE, Espeland MA, Wing RR, Burgio KL, DiLillo V, Gorin AA, West DS, Brown JS, Look AHEAD Research Group. Weight loss prevents urinary incontinence in women with type 2 diabetes: Results from the look AHEAD trial. *J Urol* 2012; 187: 939-944.
- Phillips WT, Ziuraitis JR. Energy cost of the ACSM single-set resistance training protocol. *J Strength Cond Res* 2003; 17: 350-355.
- Phillips WT, Ziuraitis JR. Energy cost of single-set resistance training in older adults. *J Strength Cond Res* 2004; 18: 606-609.
- Piana N, Battistini D, Urbani L, Romani G, Fatone C, Pazzagli C, Laghezza L, Mazzeschi C, De Feo P. Multidisciplinary lifestyle intervention in the obese: Its impact on patients' perception of the disease, food and physical exercise. *Nutr Metab Cardiovasc Dis* 2013; 23: 337-343.
- Pietinen P, Hartman AM, Haapa E, Rasanen L, Haapakoski J, Palmgren J, Albanes D, Virtamo J, Huttunen JK. Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol* 1988; 128: 655-666.

- Pinnington HC, Wong P, Tay J, Green D, Dawson B. The level of accuracy and agreement in measures of FEO₂, FECO₂ and VE between the cosmed K4b2 portable, respiratory gas analysis system and a metabolic cart. *J Sci Med Sport* 2001; 4: 324-335.
- Pinto RZ, Ferreira PH, Kongsted A, Ferreira ML, Maher CG, Kent P. Self-reported moderate-to-vigorous leisure time physical activity predicts less pain and disability over 12 months in chronic and persistent low back pain. *Eur J Pain* 2014; 18: 1190-1198.
- Plasqui G, Westerterp KR. Physical activity assessment with accelerometers: An evaluation against doubly labeled water. *Obesity (Silver Spring)* 2007; 15: 2371-2379.
- Playfair L. On the food of man in relation to his useful work. Notices of the proceedings at the meetings of the members of the royal institution of great britain with abstracts of the discourses delivered at the evening meeting. London. The Royal Institution of Great Britain. 1865a: 431-433 p.
- Playfair L. On the food of man in relation to his useful work. Edinburgh. Edmonston and Douglas. 1865b: 54 p.
- Plotnikoff RC, Johnson ST, Karunamuni N, Boule NG. Physical activity related information sources predict physical activity behaviors in adults with type 2 diabetes. *J Health Commun* 2010; 15: 846-858.
- Pontzer H, Raichlen DA, Wood BM, Mabulla AZ, Racette SB, Marlowe FW. Hunter-gatherer energetics and human obesity. *PLoS One* 2012; 7: e40503.
- Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. *Annu Rev Public Health* 1987; 8: 253-287.
- Powles AC. The effect of drugs on the cardiovascular response to exercise. *Med Sci Sports Exerc* 1981; 13: 252-258.
- Priestley J. Experiments and observations on different kinds of air. London. Printed for J. Johnson, No. 72, in St. Paul's Church-Yard. 1775: 324 p.
- Priestley J. Experiments and observations on different kinds of air. vol II. London. Printed for J. Johnson, No. 72, St. Paul's Church-Yard. 1776: 399 p.
- Priestley J. Experiments and observations on different kinds of air. vol III. London. Printed for J. Johnson, No. 72, St. Paul's Church-Yard. 1777: 411 p.
- Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: A systematic review. *Int J Behav Nutr Phys Act* 2008; 5: 56-5868-5-56.
- Racette SB, Schoeller DA, Luke AH, Shay K, Hnilicka J, Kushner RF. Relative dilution spaces of 2H- and 18O-labeled water in humans. *Am J Physiol* 1994; 267: E585-90.
- Ramsay W. The life and letters of joseph black, M.D. London. Constable and Company Ltd. 1918: 148 p.
- Rangan VV, Willis LH, Slentz CA, Bateman LA, Shields AT, Houmard JA, Kraus WE. Effects of an 8-month exercise training program on off-exercise physical activity. *Med Sci Sports Exerc* 2011; 43: 1744-1751.
- Rankinen T, Sung YJ, Sarzynski MA, Rice TK, Rao DC, Bouchard C. Heritability of submaximal exercise heart rate response to exercise training is accounted for by nine SNPs. *J Appl Physiol (1985)* 2012; 112: 892-897.
- Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man. methods and results using a respiratory chamber. *J Clin Invest* 1986; 78: 1568-1578.
- Reardon FD, Leppik KE, Wegmann R, Webb P, Ducharme MB, Kenny GP. The snellen human calorimeter revisited, re-engineered and upgraded: Design and performance characteristics. *Med Biol Eng Comput* 2006; 44: 721-728.
- Regnault V, Reiset J. Recherches chimiques sur la respiration des animaux des diverses classes. *Ann Chim Phys* 1849; 26: 299-519.
- Reiff GG, Montoye HJ, Remington RD, Napier JA, Metzner HL, Epstein FH. Assessment of physical activity by questionnaire and interview. Physical activity and the heart: Proceedings of a symposium helsinki, finland. Springfield, USA. Charles C. Thomas. 1967: 336-371 p.

- Rejeski WJ, Ip EH, Bertoni AG, Bray GA, Evans G, Gregg EW, Zhang Q, Look AHEAD Research Group. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med* 2012; 366: 1209-1217.
- Rennie K, Rowsell T, Jebb SA, Holburn D, Wareham NJ. A combined heart rate and movement sensor: Proof of concept and preliminary testing study. *Eur J Clin Nutr* 2000; 54: 409-414.
- Rennie KL, Hennings SJ, Mitchell J, Wareham NJ. Estimating energy expenditure by heart-rate monitoring without individual calibration. *Med Sci Sports Exerc* 2001; 33: 939-945.
- Reunanen A. Diabetes yleistyy suomessa entistä kiivaammin, mutta diabeetikoiden ennuste paranee ja lisäsairauksien ilmaantuminen vähenee. *Diabetes Ja Lääkäri* 2006; 35: 7-10.
- Rico-Sanz J, Rankinen T, Rice T, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C. Quantitative trait loci for maximal exercise capacity phenotypes and their responses to training in the HERITAGE family study. *Physiol Genomics* 2004; 16: 256-260.
- Roberts CK, Little JP, Thyfault JP. Modification of insulin sensitivity and glycemic control by activity and exercise. *Med Sci Sports Exerc* 2013; 45: 1868-1877.
- Rodahl K, Vokac Z. The work physiology of fishing. *Psychother Psychosom* 1979; 32: 52-59.
- Rose MH, Lokkegaard A, Sonne-Holm S, Jensen BR. Improved clinical status, quality of life, and walking capacity in parkinson's disease after body weight-supported high-intensity locomotor training. *Arch Phys Med Rehabil* 2013; 94: 687-692.
- Rothney MP, Neumann M, Beziat A, Chen KY. An artificial neural network model of energy expenditure using nonintegrated acceleration signals. *J Appl Physiol* 2007; 103: 1419-1427.
- Rowland TW. The biological basis of physical activity. *Med Sci Sports Exerc* 1998; 30: 392-399.
- Rubio-Martin E, Soriguer F, Gutierrez-Repiso C, Garrido-Sanchez L, de Adana MS, Garcia-Fuentes E, Morcillo S, Esteve I, Chaves FJ, Rojo-Martinez G. C-reactive protein and incidence of type 2 diabetes in the pizarra study. *Eur J Clin Invest* 2013; 43: 159-167.
- Rubner M. Ueber den einfluss der körpergrösse auf stoff- und kraftwechsel. *Zeitschrift Für Biologie* 1883; 40: 536-562.
- Rubner M. Calorimetrische untersuchungen II. *Zeitschrift Für Biologie* 1885; 42: 337-410.
- Rubner M. Die quelle der thierischen wärme. *Zeitschrift Fur Biologie* 1894; 30: 73-142.
- Rutenfranz J. Energy expenditure constrained by sex and age. *Ergonomics* 1985; 28: 115-118.
- Salbe AD, Nicolson M, Ravussin E. Total energy expenditure and the level of physical activity correlate with plasma leptin concentrations in five-year-old children. *J Clin Invest* 1997; 99: 592-595.
- Sallis JF, Haskell WL, Wood PD, Fortmann SP, Rogers T, Blair SN, Paffenbarger RS, Jr. Physical activity assessment methodology in the five-city project. *Am J Epidemiol* 1985; 121: 91-106.
- Salminen R, Aunola S, Malkia E, Vuori I. Computerized breath-by-breath analysis of respiratory variables during exercise. *Med Prog Technol* 1982; 9: 27-32.
- Salonen JT, Puska P, Tuomilehto J, Homan K. Relation of blood pressure, serum lipids, and smoking to the risk of cerebral stroke. A longitudinal study in eastern finland. *Stroke* 1982; 13: 327-333.
- Saltin B. Aerobic and anaerobic work capacity after dehydration. *J Appl Physiol* 1964; 19: 1114-1118.
- Saremi A, Shavandi N, Parastesh M, Daneshmand H. Twelve-week aerobic training decreases chemerin level and improves cardiometabolic risk factors in overweight and obese men. *Asian J Sports Med* 2010; 1: 151-158.
- Sato KK, Hayashi T, Harita N, Yoneda T, Nakamura Y, Endo G, Kambe H. Combined measurement of fasting plasma glucose and A1C is effective for the prediction of type 2 diabetes: The kansai healthcare study. *Diabetes Care* 2009; 32: 644-646.
- Sawada SS, Lee IM, Muto T, Matuszaki K, Blair SN. Cardiorespiratory fitness and the incidence of type 2 diabetes: Prospective study of japanese men. *Diabetes Care* 2003; 26: 2918-2922.
- Sawada SS, Lee IM, Naito H, Noguchi J, Tsukamoto K, Muto T, Higaki Y, Tanaka H, Blair SN. Long-term trends in cardiorespiratory fitness and the incidence of type 2 diabetes. *Diabetes Care* 2010a; 33: 1353-1357.

- Sawada SS, Lee IM, Naito H, Tsukamoto K, Muto T, Blair SN. Muscular and performance fitness and the incidence of type 2 diabetes: Prospective study of Japanese men. *J Phys Act Health* 2010b; 7: 627-632.
- Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care* 2001; 24: 1397-1402.
- Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H. Body mass index history and risk of type 2 diabetes: Results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. *Am J Clin Nutr* 2006; 84: 427-433.
- Schiffer T, Knicker A, Dannohl R, Struder HK. Energy cost and pole forces during Nordic walking under different surface conditions. *Med Sci Sports Exerc* 2009; 41: 663-668.
- Schiffer T, Knicker A, Montanarella M, Struder HK. Mechanical and physiological effects of varying pole weights during Nordic walking compared to walking. *Eur J Appl Physiol* 2011; 111: 1121-1126.
- Schneider PL, Crouter SE, Lukajic O, Bassett DR, Jr. Accuracy and reliability of 10 pedometers for measuring steps over a 400-m walk. *Med Sci Sports Exerc* 2003; 35: 1779-1784.
- Schoeller DA. Measurement of energy expenditure in free-living humans by using doubly labeled water. *J Nutr* 1988; 118: 1278-1289.
- Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. *J Appl Physiol* 1982; 53: 955-959.
- Schubert MM, Desbrow B, Sabapathy S, Leveritt M. Acute exercise and subsequent energy intake. A meta-analysis. *Appetite* 2013; 63: 92-104.
- Schulz S, Westerterp KR, Bruck K. Comparison of energy expenditure by the doubly labeled water technique with energy intake, heart rate, and activity recording in man. *Am J Clin Nutr* 1989; 49: 1146-1154.
- Schulze MB, Hoffmann K, Manson JE, Willett WC, Meigs JB, Weikert C, Heidemann C, Colditz GA, Hu FB. Dietary pattern, inflammation, and incidence of type 2 diabetes in women. *Am J Clin Nutr* 2005; 82: 675-84; quiz 714-5.
- Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr* 2004; 80: 348-356.
- Schulze MB, Schulz M, Heidemann C, Schienkiewitz A, Hoffmann K, Boeing H. Carbohydrate intake and incidence of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. *Br J Nutr* 2008; 99: 1107-1116.
- Scientific Advisory Committee on Nutrition. Dietary reference values for energy. London. TSO. 2012: 225 p.
- Scott CB. Quantifying the immediate recovery energy expenditure of resistance training. *J Strength Cond Res* 2011; 25: 1159-1163.
- Sedentary Behaviour Research N. Letter to the editor: Standardized use of the terms "sedentary" and "sedentary behaviours". *Appl Physiol Nutr Metab* 2012; 37: 540-542.
- Shapiro S, Weinblatt E, Frank CW, Sager RV. The H.I.P. study of incidence and prognosis of coronary heart disease; preliminary findings on incidence of myocardial infarction and angina. *J Chronic Dis* 1965; 18: 527-558.
- Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med* 2003; 37: 197-206; discussion 206.
- Shephard RJ, Aoyagi Y. Measurement of human energy expenditure, with particular reference to field studies: An historical perspective. *Eur J Appl Physiol* 2012; 112: 2785-2815.
- Shephard RJ, Bouhlef E, Vandewalle H, Monod H. Muscle mass as a factor limiting physical work. *J Appl Physiol* 1988; 64: 1472-1479.
- Shetty PS, Henry CJ, Black AE, Prentice AM. Energy requirements of adults: An update on basal metabolic rates (BMRs) and physical activity levels (PALs). *Eur J Clin Nutr* 1996; 50 Suppl 1: S11-23.
- Sieverdes JC, Sui X, Lee DC, Church TS, McClain A, Hand GA, Blair SN. Physical activity, cardiorespiratory fitness and the incidence of type 2 diabetes in a prospective study of men. *Br J Sports Med* 2010; 44: 238-244.

- Sigal RJ, Kenny GP, Boule NG, Wells GA, Prud'homme D, Fortier M, Reid RD, Tulloch H, Coyle D, Phillips P, Jennings A, Jaffey J. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: A randomized trial. *Ann Intern Med* 2007; 147: 357-369.
- Simonson DC, DeFronzo RA. Indirect calorimetry: Methodological and interpretative problems. *Am J Physiol* 1990; 258: E399-412.
- Singh J, Prentice AM, Diaz E, Coward WA, Ashford J, Sawyer M, Whitehead RG. Energy expenditure of gambian women during peak agricultural activity measured by the doubly-labelled water method. *Br J Nutr* 1989; 62: 315-329.
- Singleton WT. Introduction to ergonomics. Geneva: World Health Organization, 1972: 145.
- Sjögren T. Effectiveness of a workplace physical exercise intervention on the functioning, work ability, and subjective well-being of office workers - a controlled randomised controlled cross-over trial with a one-year follow-up. *Studies in Sport, Physical Education and Health* 2006; 118: 1-99.
- Skowron MA, Stodolska M, Shinew KJ. Determinants of leisure-time physical activity participation among latina women. *Leisure Sci* 2008; 30: 429-447.
- Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* 2007; 92: 1023-1033.
- Smith E. Health and disease as influenced by the daily, seasonal, and other cyclical changes in the human system, 1861: 409.
- Smolander J, Ajoviita M, Juuti T, Nummela A, Rusko H. Estimating oxygen consumption from heart rate and heart rate variability without individual calibration. *Clin Physiol Funct Imaging* 2011; 31: 266-271.
- Snellen JW, Chang KS, Smith W. Technical description and performance characteristics of a human whole-body calorimeter. *Med Biol Eng Comput* 1983; 21: 9-20.
- Snodgrass JJ. Human energetics. *Human biology: An evolutionary and biocultural perspective*. Hoboken, New Jersey. John Wiley & Sons, Inc. 2012: 325-384 p.
- Snodgrass JJ, Leonard WR, Tarskaia LA, Schoeller DA. Total energy expenditure in the yakut (sakha) of siberia as measured by the doubly labeled water method. *Am J Clin Nutr* 2006; 84: 798-806.
- Sobngwi E, Mbanya JC, Unwin NC, Kengne AP, Fezeu L, Minkoulou EM, Aspray TJ, Alberti KG. Physical activity and its relationship with obesity, hypertension and diabetes in urban and rural cameroon. *Int J Obes Relat Metab Disord* 2002; 26: 1009-1016.
- Soysal M, Kara B, Arda MN. Assessment of physical activity in patients with chronic low back or neck pain. *Turk Neurosurg* 2013; 23: 75-80.
- Speakman JR. The history and theory of the doubly labeled water technique. *Am J Clin Nutr* 1998; 68: 932S-938S.
- Spinnler G, Jequier E, Favre R, Dolivo M, Vannotti A. Human calorimeter with a new type of gradient layer. *J Appl Physiol* 1973; 35: 158-165.
- Spitzer H, Hettinger T. Tafeln für den kalorieumsatz bei körperlicher arbeit. Darmstadt. REFA. 1964: 100 p.
- Spitzer H, Hettinger T, Kaminsky G. Tafeln für den energieumsatz bei körperlicher arbeit, 6. vollständig überarbeitete auflage. Berlin. Beuth Verlag GmbH. 1982: 160 p.
- Spranger J, Kroke A, Mohlig M, Hoffmann K, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Inflammatory cytokines and the risk to develop type 2 diabetes: Results of the prospective population-based european prospective investigation into cancer and nutrition (EPIC)-potdam study. *Diabetes* 2003; 52: 812-817.
- Spurr GB, Prentice AM, Murgatroyd PR, Goldberg GR, Reina JC, Christman NT. Energy expenditure from minute-by-minute heart-rate recording: Comparison with indirect calorimetry. *Am J Clin Nutr* 1988; 48: 552-559.
- Staudenmayer J, Pober D, Crouter S, Bassett D, Freedson P. An artificial neural network to estimate physical activity energy expenditure and identify physical activity type from an accelerometer. *J Appl Physiol* 2009; 107: 1300-1307.

- Stefanov T, Bluher M, Vekova A, Bonova I, Tzvetkov S, Kurktschiev D, Temelkova-Kurktschiev T. Circulating chemerin decreases in response to a combined strength and endurance training. *Endocrine* 2013.
- St-Onge M, Mignault D, Allison DB, Rabasa-Lhoret R. Evaluation of a portable device to measure daily energy expenditure in free-living adults. *Am J Clin Nutr* 2007; 85: 742-749.
- Strath SJ, Swartz AM, Bassett DR, Jr, O'Brien WL, King GA, Ainsworth BE. Evaluation of heart rate as a method for assessing moderate intensity physical activity. *Med Sci Sports Exerc* 2000; 32: S465-70.
- Stubbe JH, Boomsma DI, De Geus EJ. Sports participation during adolescence: A shift from environmental to genetic factors. *Med Sci Sports Exerc* 2005; 37: 563-570.
- Sui X, Hooker SP, Lee IM, Church TS, Colabianchi N, Lee CD, Blair SN. A prospective study of cardiorespiratory fitness and risk of type 2 diabetes in women. *Diabetes Care* 2008; 31: 550-555.
- Sukhatme P,V. On the trend of obesity in advanced countries. *Diabetes – preceedings of the sixth congress of the international diabetes federation. Amsterdam. Expecta Medica Foundation. 1969: 704-714 p.*
- Sund R, Koski S. FinDM II. diabeteksen ja sen lisäsairauksien esiintyvyyden ja ilmaantuvuuden rekisteriperusteinen mittaaminen -tekninen raportti. 2009.
- Swartz AM, Strath SJ, Bassett DR, Jr, O'Brien WL, King GA, Ainsworth BE. Estimation of energy expenditure using CSA accelerometers at hip and wrist sites. *Med Sci Sports Exerc* 2000; 32: S450-6.
- Taheri S. The link between short sleep duration and obesity: We should recommend more sleep to prevent obesity. *Arch Dis Child* 2006; 91: 881-884.
- Tammelin T, Ekelund U, Remes J, Näyhä S. Physical activity and sedentary behaviors among finnish youth. *Med Sci Sports Exerc* 2007; 39: 1067-1074.
- Tanner CJ, Barakat HA, Dohm GL, Pories WJ, MacDonald KG, Cunningham PR, Swanson MS, Houmard JA. Muscle fiber type is associated with obesity and weight loss. *Am J Physiol Endocrinol Metab* 2002; 282: E1191-6.
- Taylor CM, MacLeod G. *Rose's laboratory handbook for dietetics.* New York. The MacMillan Company. 1949: 358 p.
- Taylor HL, Jacobs DR, Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978; 31: 741-755.
- Taylor R, Ram P, Zimmet P, Raper LR, Ringrose H. Physical activity and prevalence of diabetes in melanesian and indian men in fiji. *Diabetologia* 1984; 27: 578-582.
- Teske JA, Billington CJ, Kotz CM. Neuropeptidergic mediators of spontaneous physical activity and non-exercise activity thermogenesis. *Neuroendocrinology* 2008; 87: 71-90.
- Tipton CM. Susruta of india, an unrecognized contributor to the history of exercise physiology. *J Appl Physiol* (1985) 2008; 104: 1553-1556.
- Tremblay MS, Esliger DW, Tremblay A, Colley R. Incidental movement, lifestyle-embedded activity and sleep: New frontiers in physical activity assessment. *Can J Public Health* 2007; 98 Suppl 2: S208-17.
- Tremblay MS, Leblanc AG, Janssen I, Kho ME, Hicks A, Murumets K, Colley RC, Duggan M. Canadian sedentary behaviour guidelines for children and youth. *Appl Physiol Nutr Metab* 2011a; 36: 59-64; 65-71.
- Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, Goldfield G, Connor Gorber S. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. *Int J Behav Nutr Phys Act* 2011b; 8: 98-5868-8-98.
- Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the united states measured by accelerometer. *Med Sci Sports Exerc* 2008; 40: 181-188.
- Troiano RP, McClain JJ, Brychta RJ, Chen KY. Evolution of accelerometer methods for physical activity research. *Br J Sports Med* 2014; 48: 1019-1023.
- Trost SG, Wong WK, Pfeiffer KA, Zheng Y. Artificial neural networks to predict activity type and energy expenditure in youth. *Med Sci Sports Exerc* 2012; 44: 1801-1809.

- Tsao TS, Li J, Chang KS, Stenbit AE, Galuska D, Anderson JE, Zierath JR, McCarter RJ, Charron MJ. Metabolic adaptations in skeletal muscle overexpressing GLUT4: Effects on muscle and physical activity. *FASEB J* 2001; 15: 958-969.
- Tudor-Locke C, Bell RC, Myers AM, Harris SB, Ecclestone NA, Lauzon N, Rodger NW. Controlled outcome evaluation of the first step program: A daily physical activity intervention for individuals with type II diabetes. *Int J Obes Relat Metab Disord* 2004; 28: 113-119.
- Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343-1350.
- Turner JE, Markovitch D, Betts JA, Thompson D. Nonprescribed physical activity energy expenditure is maintained with structured exercise and implicates a compensatory increase in energy intake. *Am J Clin Nutr* 2010; 92: 1009-1016.
- Turner MJ, Kleeberger SR, Lightfoot JT. Influence of genetic background on daily running-wheel activity differs with aging. *Physiol Genomics* 2005; 22: 76-85.
- U.S. Departments of Health and Human Services. 2008 physical activity guidelines for americans. www.health.gov/paguidelines (accessed 19 March 2013). Washington. U.S. Departments of Health and Human Services. 2008: 61 p.
- UKK Institute. Physical activity pie. http://www.ukkinstituutti.fi/en/products/physical_activity_pie (accessed 6 November 2013). Tampere. UKK Institute. 2010.
- Vague J. La différenciation sexuelle facteur déterminant des formes de l'obésité. *Presse Med* 1947; 55: 339-340.
- Vague J. The degree of masculine differentiation of obesities: A factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr* 1956; 4: 20-34.
- Van Etten LM, Westerterp KR, Verstappen FT, Boon BJ, Saris WH. Effect of an 18-wk weight-training program on energy expenditure and physical activity. *J Appl Physiol* 1997; 82: 298-304.
- Van Remoortel H, Giavedoni S, Raste Y, Burtin C, Louvaris Z, Gimeno-Santos E, Langer D, Glendenning A, Hopkinson NS, Vogiatzis I, Peterson BT, Wilson F, Mann B, Rabinovich R, Puhon MA, Troosters T, PROactive consortium. Validity of activity monitors in health and chronic disease: A systematic review. *Int J Behav Nutr Phys Act* 2012; 9: 84-5868-9-84.
- van Rooijen AJ, Rheeder P, Eales CJ, Becker PJ. Effect of exercise versus relaxation on haemoglobin A1C in black females with type 2 diabetes mellitus. *QJM* 2004; 97: 343-351.
- Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. *Am J Physiol Regul Integr Comp Physiol* 2003; 285: R271-3.
- Vogel JA, Hansen JE, Harris CW. Cardiovascular responses in man during exhaustive work at sea level and high altitude. *J Appl Physiol* 1967; 23: 531-539.
- Vokac Z, Bell H, Bautz-Holter E, Rodahl K. Oxygen uptake/heart rate relationship in leg and arm exercise, sitting and standing. *J Appl Physiol* 1975; 39: 54-59.
- Walsberg GE, Hoffman TC. Direct calorimetry reveals large errors in respirometric estimates of energy expenditure. *J Exp Biol* 2005; 208: 1035-1043.
- Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 2005; 81: 555-563.
- Wankhade UD, Good DJ. Melanocortin 4 receptor is a transcriptional target of nescient helix-loop-helix-2. *Mol Cell Endocrinol* 2011; 341: 39-47.
- Wannamethee SG, Shaper AG. Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. *Diabetes Care* 1999; 22: 1266-1272.
- Warms C. Physical activity measurement in persons with chronic and disabling conditions: Methods, strategies, and issues. *Fam Community Health* 2006; 29: 78S-88S.

- Washburn RA, Montoye HJ. The assessment of physical activity by questionnaire. *Am J Epidemiol* 1986; 123: 563-576.
- Webb P. The measurement of energy exchange in man: An analysis. *Am J Clin Nutr* 1980; 33: 1299-1310.
- Webb P. Daily activity and body temperature. *Eur J Appl Physiol Occup Physiol* 1993; 66: 174-177.
- Webb P. The physiology of heat regulation. *Am J Physiol* 1995; 268: R838-50.
- Webb P, Annis JF, Troutman SJ, Jr. Human calorimetry with a water-cooled garment. *J Appl Physiol* 1972; 32: 412-418.
- Webb P, Troutman SJ, Jr, Annis JF. Automatic cooling in water cooled space suits. *Aerosp Med* 1970; 41: 269-277.
- Webster JD, Welsh G, Pacy P, Garrow JS. Description of a human direct calorimeter, with a note on the energy cost of clerical work. *Br J Nutr* 1986; 55: 1-6.
- Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN. The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 1999; 130: 89-96.
- Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol* 1949; 109: 1-9.
- Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; 112: 1796-1808.
- Welk GJ, McClain J, Ainsworth BE. Protocols for evaluating equivalency of accelerometry-based activity monitors. *Med Sci Sports Exerc* 2012; 44: S39-49.
- Welk GJ, McClain JJ, Eisenmann JC, Wickel EE. Field validation of the MTI actigraph and BodyMedia armband monitor using the IDEEA monitor. *Obesity (Silver Spring)* 2007; 15: 918-928.
- Wentworth JM, Naselli G, Brown WA, Doyle L, Phipson B, Smyth GK, Wabitsch M, O'Brien PE, Harrison LC. Pro-inflammatory CD11c+CD206+ adipose tissue macrophages are associated with insulin resistance in human obesity. *Diabetes* 2010; 59: 1648-1656.
- Westerterp KR, Speakman JR. Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals. *Int J Obes (Lond)* 2008; 32: 1256-1263.
- Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; 94: 311-321.
- WHO Collaborating Centre for Drug Statistics Methodology. International language for drug utilization research, ATC/DDD. <http://www.whocc.no/> (accessed 2014). Oslo. WHO Collaborating Centre for Drug Statistics Methodology. 13 May 2014.
- Williams HB, Riche JA, Lusk G. Animal calorimetry: Second paper. metabolism of the dog following the ingestion of meat in large quantity. *J Biol Chem* 1912; 12: 349-376.
- Williamson DA, Rejeski J, Lang W, Van Dorsten B, Fabricatore AN, Toledo K, Look AHEAD Research Group. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. *Arch Intern Med* 2009; 169: 163-171.
- Wilmore JH, Davis JA, Norton AC. An automated system for assessing metabolic and respiratory function during exercise. *J Appl Physiol* 1976; 40: 619-624.
- Winslow C-A, Herrington LP, Gagge AP. A new method of partitioned calorimetry. *Am J Physiol* 1936; 116: 641-655.
- Wisse W, Rookhuizen MB, de Kruif MD, van Rossum J, Jordans I, ten Cate H, van Loon LJ, Meesters EW. Prescription of physical activity is not sufficient to change sedentary behavior and improve glycemic control in type 2 diabetes patients. *Diabetes Res Clin Pract* 2010; 88: e10-3.
- World Health Organization. Global health risks : Mortality and burden of disease attributable to selected major risks. Geneva. World Health Organization. 2009.
- World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization, 2010: 3-58.

- Wyndham CH, Strydom NB, Williams CG, von R.M. A physiological basis for the 'optimum' level of energy expenditure. *Nature* 1962: 195: 1210-1212.
- Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006: 29: 657-661.
- Yates T, Davies M, Gorely T, Bull F, Khunti K. Effectiveness of a pragmatic education program designed to promote walking activity in individuals with impaired glucose tolerance: A randomized controlled trial. *Diabetes Care* 2009: 32: 1404-1410.
- Yates T, Davies MJ, Gorely T, Talbot D, Bull F, Sattar N, Khunti K. The effect of increased ambulatory activity on markers of chronic low-grade inflammation: Evidence from the PREPARE programme randomized controlled trial. *Diabet Med* 2010: 27: 1256-1263.
- Yudkin PL, Stratton IM. How to deal with regression to the mean in intervention studies. *Lancet* 1996: 347: 241-243.
- Zhang WS. Construction, calibration and testing of a decimeter size heat-flow calorimeter. *Thermochim Acta* 2010: 499: 128-132.
- Zhang K, Pi-Sunyer FX, Boozer CN. Improving energy expenditure estimation for physical activity. *Med Sci Sports Exerc* 2004: 36: 883-889.
- Zhang K, Werner P, Sun M, Pi-Sunyer FX, Boozer CN. Measurement of human daily physical activity. *Obes Res* 2003: 11: 33-40.
- Zimberg IZ, Damaso A, Del Re M, Carneiro AM, de Sa Souza H, de Lira FS, Tufik S, de Mello MT. Short sleep duration and obesity: Mechanisms and future perspectives. *Cell Biochem Funct* 2012: 30: 524-529.
- Zimmet P. Epidemiology of diabetes and its macrovascular manifestations in pacific populations: The medical effects of social progress. *Diabetes Care* 1979: 2: 144-153.
- Zimmet P, Faaiuso S, Ainuu J, Whitehouse S, Milne B, DeBoer W. The prevalence of diabetes in the rural and urban polynesian population of western samoa. *Diabetes* 1981: 30: 45-51.
- Zuntz N, Loewy A, Müller F, Caspari W. Höhenklima und bergwanderungen in ihren wrkung auf den menschen. ergebnisse experimenteller forschungen im hochgebirge und laboratorium. Leipzig. Deutsches Verlaugs Bong & Co. 1906: 510 p.
- Zuntz N, Schumburg WAEF. Studien zu einer physiologie des marches. Berlin. A. Hirchwald. 1901: 361 p.

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