STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH
175

Katja Waller

Leisure-Time Physical Activity, Weight Gain and Health

A Prospective Follow-Up in Twins

JYVÄSKYLÄN YLIOPISTO

STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH 175

Katja Waller

Leisure-Time Physical Activity, Weight Gain and Health

A Prospective Follow-Up in Twins

Esitetään Jyväskylän yliopiston liikunta- ja terveystieteiden tiedekunnan suostumuksella
julkisesti tarkastettavaksi yliopiston vanhassa juhlasalissa S212
marraskuun 4. päivänä 2011 kello 12.

Academic dissertation to be publicly discussed, by permission of
the Faculty of Sport and Health Sciences of the University of Jyväskylä,
in auditorium S212, on November 4, 2011 at 12 o'clock noon.

UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2011

Leisure-Time Physical Activity, Weight Gain and Health

A Prospective Follow-Up in Twins

STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH 175

Katja Waller

Leisure-Time Physical Activity, Weight Gain and Health

A Prospective Follow-Up in Twins

UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2011

Editors
Harri Suominen
Department of Health Sciences, University of Jyväskylä
Pekka Olsbo, Ville Korkiakangas
Publishing Unit, University Library of Jyväskylä

URN:ISBN:978-951-39-4450-6
ISBN 978-951-39-4450-6 (PDF)

ISBN 978-951-39-4449-0 (nid.)
ISSN 0356-1070

Jyväskylä University Printing House, Jyväskylä 2011

ABSTRACT

Waller, Katja
Leisure-time physical activity, weight gain and health – A prospective follow-up in twins
Jyväskylä: University of Jyväskylä, 2011, 88 p.
(Studies in Sport, Physical Education and Health
ISSN 0356-1070; 175)
ISBN 978-951-39-4449-0 (nid.)
ISBN 978-951-39-4450-6 (PDF)

The aim of this study was to find out if leisure-time physical activity (LTPA), adjusted for genetic factors and childhood environment, protects against mortality, type 2 diabetes and other chronic diseases and against increases in weight and waist circumference.

All participants were selected from the large Finnish Twin Cohort, which included 12 069 twin pairs in 1975. To investigate the occurrence of type 2 diabetes (T2D), 20 487 individuals were selected who were free of diabetes and had data on LTPA and BMI in 1975. These individuals were divided into quintiles according to their LTPA MET index. T2D risk was assessed between 1.1.1976 and 31.12.2004. For the long-term discordance analyses, 146 from 5663 healthy adult twin pairs were identified as discordant for both intensity and volume of LTPA in 1975 and 1981. Mortality analyses were carried out between 1.1.1983 and 31.12.2004. Among the 146 pairs, 95 sets of twin pairs (76 DZ, 19 MZ) were alive and participated in a follow-up telephone interview in 2005 (mean age 58.5y, range 48-78). The interview included detailed questions on the continuation of LTPA, self-measured weight and waist circumference and occurrence of chronic disease. Paired tests (McNemar's test, t-test, conditional logistic regression, Cox proportional hazard model) were used in the statistical analyses.

The paired type 2 diabetes analyses among the whole 1975 cohort showed that the BMI-adjusted hazard ratio for the active (quintiles II-V) compared to sedentary (quintile I) co-twins at follow-up was 0.54 (95% CI 0.37-0.78). Among the 146 LTPA discordant pairs, 24 co-twins (16 inactive and 8 active) had died by the end of 2004. The active co-twins had a reduced risk of all-cause mortality as social class-adjusted HR was 0.39 (95 % CI 0.18 – 0.85). This was not found among the small number of MZ pairs. Among the 95 interviewed pairs, the risk of type 2 diabetes or glucose intolerance (OR= 0.09, p=0.022) and incident elevated blood pressure (OR=0.46, p=0.039) was lower among the active co-twins. The active co-twins were more satisfied with their life at follow-up (p=0.047). In contrast, the active co-twins showed a tendency towards more sports-related injuries (OR=1.9, p=0.051). Within the subgroup of 42 pairs discordant for LTPA over 30 years, mean weight gain from 1975 through 2005 was 5.4 kg (95% CI 2.0-8.9, p=0.003) less and waist circumference 8.4 cm smaller (95% CI 4.0-12.7 cm, p<0.001) at follow-up among the active compared to inactive co-twins.

Physical activity helps in maintaining overall health by decreasing the rate of weight gain, lowering waist circumference and reducing the risk for clinical T2D. However, genetic factors may play a role in explaining some of the associations between mortality, disease occurrence and physical activity, as some of the findings were more clearer among the dizygotic than monozygotic twin pairs discordant for LTPA.

Keywords: physical activity, twins, type 2 diabetes, mortality, morbidity, weight, waist circumference, health, chronic disease, prospective follow-up

Author's address

Katja Waller, MSc
Department of Health Sciences
University of Jyväskylä, P.O. Box 35 (LL)
FI-40014 University of Jyväskylä, Finland

Supervisors

Professor Urho M. Kujala, MD, PhD
Department of Health Sciences
University of Jyväskylä, Finland

Professor Jaakko Kaprio, MD, PhD
Institute for Molecular Medicine and Hjelt Institute
Department of Public Health
University of Helsinki, Finland
&
Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare
Helsinki, Finland

Professor Taina Rantanen, PhD
Gerontology Research Centre
Department of Health Sciences
University of Jyväskylä, Finland

Reviewers

Professor Johan Eriksson, MD, DMSc
Department of General Practice and Primary Health Care, University of Helsinki, Finland
&
Helsinki University Central Hospital
Unit of General Practice, Helsinki, Finland

Professor Leo Niskanen, MD, DMSc
Department of Internal Medicine
Central Hospital Central Finland, Jyväskylä, Finland
&
Faculty of Health Sciences, School of Medicine
University of Eastern Finland, Kuopio, Finland

Opponent

Docent David Laaksonen, MD, PhD, MPH
Institute of Clinical Medicine, Internal Medicine, Kuopio University Hospital, Kuopio
&
Institute of Biomedicine, Physiology, University of Eastern Finland, Kuopio, Finland

ACKNOWLEDGEMENTS

This research has been carried out at the Department of Health Sciences, University of Jyväskylä and utilised data are drawn from the older Finnish twin cohort. I am very grateful to have had an opportunity to do this thesis on such a respected and well known cohort. The Social Insurance Institute of Finland has provided the register data and therefore I wish to thank the TwinKELA project for that data and for their support.

I wish to express my sincere gratitude to my encouraging supervisors Professor Urho Kujala, Professor Jaakko Kaprio, and Professor Taina Rantanen. I am grateful to Urho for showing me the scientific world and encouraging me to start my PhD. Thank you for all the guidance you have given me through the different stages of my work as a researcher and an assistant. You have always had time for any questions I had. Jaakko, thank you for all your guidance and help. You made me feel as if I know more than I do. Thank you for having and making time to help me and comment on my work, although I know you are very busy. I admire your knowledge in all the different fields. Taina, thank you for your support and for your valuable comments throughout the PhD process.

I sincerely thank the official reviewers of my thesis, Professor Johan Eriksson and Professor Leo Niskanen for their speedy review, valuable comments and suggestions and encouraging words. I also wish to thank Docent David Laaksonen for agreeing to be my opponent.

I wish take this opportunity to thank all of my co-authors of the original papers who are not mentioned above: Professor Markku Koskenvuo MD, PhD, Docent Karri Silventoinen, Mikko Lehtovirta MD and statistician Markku Kauppinen MSc for your valuable critics and comments. I also want to thank Michael Freeman for the language revision of my original articles and this thesis.

This work would not have happened without the financial support. This work was financially supported by the University of Jyväskylä, the Juho Vainio Foundation, the Yrjö Jahnsson Foundation and the Finnish Ministry of Education and Culture. The Finnish Twin Cohort Study is supported by the Academy of Finland Centre of Excellence in Complex Disease Genetics. I express my sincere gratitude to all these funding agencies.

I have been fortunate to have the opportunity to work as a researcher and as an assistant with skilful scientists, lecturers and other department staff. I wish to thank the staff of the entire Department of Health Sciences for a lovely and welcoming working environment. I wish to express my thanks to all of my colleagues and fellow doctoral students at the Department of Health Sciences and the Gerontology Research Centre (the bunch at the legendary coffee table) for a very enjoyable working environment. Thank you for our friendship and support; you are more than just colleagues. In particularly, I want to thank Tuija Leskinen for sharing many events and interests in research and life.

I want to thank my family, friends and Mannila "playground mums" for your support during these years. I want to thank my dear friends Reetta, Jenni,

and Iina and my sister Kaisa and your families for your friendship. I sincerely thank my mum and dad, Ulla and Ari, for your support on my different choices during my life and especially for your support on my decision to live and study in England after high school. The support and encouragement you gave me when I decided to study for a bachelor's degree in England has been very valuable as I don't think I would have got this far with my thesis without the experience and knowledge and the language skills I acquired from the years I spent in England.

During my PhD I got married and became mum to two gorgeous girls. Hilma and Saimi - thank you for being in my world. You keep me busy and remind me what the most important thing in my life is. Finally my warmest thanks go to my best friend, my husband and father of our children, Ben. I am grateful that you moved to Finland with me over 8 years ago and later on agreed to stay here (I know we were meant to stay here only two years). You put your career on hold for me and my PhD studies. Without that, this thesis would never have happened. I sincerely value your encouragement throughout this thesis. Thank you for your love and support.

Jyväskylä September 2011
Katja Waller

ORIGINAL PUBLICATIONS

The thesis is based on the following original papers, which will be referred to in the text by their Roman numbers.

I Waller K, Kujala UM, Rantanen T, Kauppinen M, Silventoinen K, Koskenvuo M, Kaprio J. 2010. Physical activity, morbidity and mortality in twins: a 24-year prospective follow-up. European Journal of Epidemiology 25(10):731-739.

II Waller K, Kujala UM, Kaprio J, Koskenvuo M, Rantanen T. 2010. Effect of physical activity on health in twins: A 30-year longitudinal study. Medicine & Science in Sports & Exercise 42(4):658-664.

III Waller K, Kaprio J, Kujala UM. 2008. Associations between long-term physical activity, waist circumference and weight gain: A 30-year longitudinal twin study. International Journal of Obesity 32:353-361.

IV Waller K, Kaprio J, Lehtovirta M, Silventoinen K, Koskenvuo M, Kujala UM. 2010. Leisure-time physical activity and type 2 diabetes during a 28 year follow-up in twins. Diabetologia 53(12):2531-2537.

Additionally, some previously unpublished results are included in the thesis.

ABBREVIATIONS

AEE	Physical activity-associated energy expenditure
BIA	Bioelectrical impedance
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence intervals
DEXA	Dual energy X-ray absorptiometry
DZ	Dizygotic
EEA	Equal environment assumption
FTO	Fat mass and obesity-associated gene
HR	Hazard ratio
ICC	Intraclass correlation coefficient
KELA	The Social Insurance Institution of Finland
LS	Life satisfaction
LTPA	Leisure-time physical activity
MET	Metabolic equivalent
MRI	Magnetic resonance imaging
MZ	Monozygotic
PA	Physical activity
OR	Odds ratio
Q	Quintile
SNP	Single nucleotide polymorphism
T2D	Type 2 diabetes
WC	Waist circumference
WHO	World Health Organization

CONTENTS

1 INTRODUCTION

Over 1.5 billion of the world's population can be considered to be overweight and of these about 500 million are obese (WHO 2011b). Both obesity and the accumulation of intra-abdominal adipose tissue are considered to be risk factors for the development of several metabolic disorders such as glucose intolerance, dyslipidaemia and hypertension (Misra & Vikram 2003, Eckel et al. 2005) as well as for mortality (Bigaard et al. 2005). Type 2 diabetes has also become a significant worldwide health problem. It has been estimated that there were over half a million people in Finland (around 10% of the population) in 2008 (Reunanen et al. 2008) and around 220 million people worldwide in 2011 (WHO 2011a) with type 2 diabetes. It has been estimated that, taking 2005 as the baseline, the worldwide figure will have doubled by 2030 (Wild et al. 2004). For example, the population prevalence of diabetes has been estimated to rise to over 11% among Australians by 2025 (Magliano et al. 2008) and to over 20% among the American Hispanic population by 2031 (Mainous et al. 2007). Main reasons for the expanding type 2 diabetes epidemic are increased excess body weight and inactivity (WHO 2011a). Also, population ageing is a well-known phenomenon in almost all countries (WHO 2010a), increasing the risk for type 2 diabetes. Other explanation for increased obesity and metabolic changes can be found in epigenetics; for example, early-life nutrition or physical activity habits may affect individuals' gene function without changes in the nucleotide sequence (Franks & Ling 2010).

Physical inactivity has been identified as the fourth leading risk factor for global mortality and the cause of approximately 6% of deaths globally (WHO 2010b). Abundant evidence from observational studies shows that active men and women have lower rates of all-cause mortality, coronary heart disease, high blood pressure, stroke, type 2 diabetes, metabolic syndrome, colon cancer, breast cancer, and depression compared to less active people (Physical Activity Guidelines Advisory Committee 2008). In order to improve health, adults should do at least 150 minutes of moderate or 75 min of vigorous aerobic physical activity per week and in addition, muscle strength training twice a week (WHO 2010b). However, most people are insufficiently active, for example

about 40% of Americans engaged in no leisure-time physical activity in 2006 (Physical Activity Guidelines Advisory Committee 2008), while in Finland in 2009, under 50% of the population met the current recommendation of 150 minutes of moderate physical activity weekly, and only just over 10% when the additional two strength training sessions weekly were included (Helakorpi et al. 2010).

Most of the studies investigating the effect of physical activity and prevention of multiple health conditions have been conducted on genetically unrelated individuals; however, genetic selection may explain some of the observed associations. Firstly, there is now evidence available that genetic selection partly explains participation in physical activity (Kaprio et al. 1981, Lauderdale et al. 1997, Kujala et al. 2002, Stubbe et al. 2006) and therefore that can favour these individuals with lower morbidity and mortality. Secondly, all diseases can be explained by genetic factors, at least to some extent. For example, moderate to high heritability has been shown for age at death from CAD (Marenberg et al. 1994, Wienke et al. 2001, Zdravkovic et al. 2002, Zdravkovic et al. 2004) as also have for BMI and waist circumference (Schousboe et al. 2003, Schousboe et al. 2004, Nelson et al. 2006, Lee et al. 2010), while heritability estimates for type 2 diabetes have been shown to vary more (Barroso 2005, Lehtovirta et al. 2010). Twin and family studies are a powerful tool for investigating the role of genetic and environmental factors in risk factor – disease relationships. Dizygotic twins (DZ) share half of their segregating genes, while monozygotic (MZ) pairs are genetically identical (Plomin et al. 2000). Both types of pairs nearly always have the same childhood environment. By studying outcomes in twin pairs discordant for an exposure, such as physical activity, the possible confounding role of genetic and early childhood experiences can be assessed (Kujala et al. 2002). In epidemiological studies, genetic selection and childhood environment may be important confounders when studying the effect of physical activity on mortality and morbidity.

The purpose of this study was to examine the sum effect of leisure-time physical activity on health. The main aim is to find out whether persistent leisure-time physical activity, adjusted for genetic factors and childhood environment, protects against premature mortality, increases in weight and waist circumference, type 2 diabetes, and other chronic diseases. Therefore for the purpose of this thesis, twin pairs who had a 6-year baseline discordance in intensity and volume (over 2 MET h/day) of leisure-time physical activity were studied prospectively over a 20-year follow-up. Among these twin pairs, the association between physical activity and all-cause mortality, anthropometrics, type 2 diabetes and other metabolic health related condition were studied. A further study among a large sample of twins was also performed to study the risk of type 2 diabetes according to baseline levels of physical activity.

2 REVIEW OF THE LITERATURE

2.1 Leisure-time physical activity

Physical activity refers to any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level (ACSM 2010). Total energy expenditure includes three components: resting metabolic rate, physical activity-associated energy expenditure (AEE) and diet-induced energy expenditure (thermogenesis) (McArdle et al. 2001). Resting metabolic rate is the main component, accounting for 60-70% of the total daily energy expenditure, while physical activity-associated energy expenditure accounts for about 20-30%, and is the most important source of variation between individuals (Vanhees et al. 2005). Activities accounting for AEE include physical activity during occupation, leisure time, sports, home and household activities, personal care and transportation (Vanhees et al. 2005). Physical inactivity or sedentariness in turn do not refer to zero activity or energy expenditure but rather to no extra voluntary activity that is required for the necessary activities of daily living or work.

Physical activity can be categorized by the mode, intensity and purpose of activity (Physical Activity Guidelines Advisory Committee 2008). The purpose of activity relates to the context in which it is performed, such as leisure-time. Activities that are not required for the necessary activities of daily living or work and that are performed at a person's own discretion are classified as leisure-time physical activities (Physical Activity Guidelines Advisory Committee 2008), and these are often considered as exercise, which is "planned, structured and repetitive activity done to improve physical fitness" (ACSM 2010). Leisure-time physical activities include sports participation, exercise conditioning or training, and recreational activities such as going for a walk, dancing, and gardening (Physical Activity Guidelines Advisory Committee 2008); in this study it also include transportation or commuting activities. Mode refers to the type of activity that is being performed (Physical Activity Guidelines Advisory Committee 2008), for example cycling, walking, skiing or weight lifting. Physical

activity intensity is often reported as MET values, in which MET refers to metabolic equivalent. One MET is the rate of energy expenditure while at rest and it is the equivalent of an oxygen uptake of 3.5 millilitres per kilogram of body weight per minute (McArdle et al. 2001). Table 1 shows how different MET intensities correspond to different physical activity categories. Frequency, duration, and total amount of physical activity performed are also terms often used when describing physical activity (Shephard 2003).

TABLE 1 MET classification by leisure-time physical activity intensity for young / middle-age subjects, modified from McArdle et al. (2001) and ACSM (2010).

Category	Maximal HR %	MET intensity	Example of activity
Rest	< 50	1-2	Sitting, arts and crafts
Light	50 – 63	2-4	Slow walking, sailing boat
Moderate	64 – 76	4-7	Brisk walking, badminton
Hard (vigorous)	77 – 94	7-10	Jogging, swimming
Maximal	> 95	>10	Running, competitive sports

HR = Heart Rate

Physical activity has many health benefits, including improvements in cardiovascular and respiratory function, decreased mortality and morbidity, reductions in coronary artery disease risk factors and many other benefits from improved psychological health to reductions in falls and injuries (ACSM 2010). Many of the health benefits are due to increases in different components of physical fitness, which are the most direct effects of physical activity (McArdle et al. 2001). The ability to complete daily tasks, perform physical activity and muscular work without too much effort and fatigue is one way of defining physical fitness (McArdle et al. 2001, Physical Activity Guidelines Advisory Committee 2008). Physical fitness and its effects are not within the scope of this thesis. Instead, this thesis focuses on the effects of physical activity.

To achieve an overall public health benefit, the current physical activity recommendations for adults is approximately 150 minutes of moderate intensity activity per week or 75 minutes of vigorous activity per week and additionally muscle-strengthening activities two or more times a week (Physical Activity Guidelines Advisory Committee 2008, WHO 2010b). There is reasonably strong evidence that participating in moderate to vigorous physical activity for more than 150 minutes per week is associated with greater health benefits for a variety of health outcomes (Physical Activity Guidelines Advisory Committee 2008).

Physical activity behaviour seems to change over the life course, especially during different transitions and life events. Physical activity behaviour has been suggested to change during important periods, just as the transition from primary to secondary school or from high school to college or university, marriage, becoming a parent, and retirement (Corder et al. 2009). However, physical activity behaviour seems to be more stable during adulthood. A few studies have demonstrated moderate correlations for the tracking of physical activity during

adulthood, the correlations varying between 0.2 to 0.4 (Kirjonen et al. 2006, Parsons et al. 2006, Morseth et al. 2011).

2.1.1 Assessment of physical activity

Physical activity assessment is generally very challenging; however, different objective and subjective approaches are available to measure physical activity (Lagerros & Lagiou 2007). Objective, or also called observer-dependent, methods of measuring physical activity or energy expenditure include, for example, heart rate monitoring, accelerometer and doubly labelled water, and are based on biological and physiological approaches (Lagerros & Lagiou 2007). In turn, subjective or self-reported methods of measuring physical activity include physical activity records, logs and questionnaires (Lagerros & Lagiou 2007). Information obtained from self-report instruments can be converted into estimates of energy expenditure such as MET values (U.S. Department of Health and Human Services 1996). Questionnaire-based physical activity data are often used in epidemiological studies, as this method is inexpensive, easy to distribute and administer, does not require a lot of motivation or time from the study participant, and compared to many other methods, is overall a quick way of measuring physical activity in large populations (U.S. Department of Health and Human Services 1996, Lagerros & Lagiou 2007). However, the method relies on subjective interpretation of the questions and subjective perception of physical activity behaviour itself, and consequently over- or underestimation is possible (Vanhees et al. 2005).

The reliability of different physical activity questionnaires is difficult to assess as even self-reported activity questionnaires may vary from very detailed interviews on intensity, duration, frequency, and mode to a short self-filled questionnaire with a question on frequency. Some studies have compared simple self-assessed physical activity questions against different types of subjective measurements for validation purposes. The gold standard for measuring energy expenditure is direct calorimetry (Vanhees et al. 2005). As physical activity is defined as energy expenditure resulted from a body movement, direct or indirect calorimetry, including double labeled water, should be used when validating questionnaires (Vanhees et al. 2005), but as these are often impractical and expensive, other subjective measurements have been used, such as accelerometers or heart rate monitors. Studies validating physical activity questionnaires against motion sensors, such as pedometers, report correlation coefficients varying between 0.26 and 0.78 (Shephard 2003). In contrast, in a study by Philippaerts et al. (1999) three physical activity questionnaires were validated against doubly labelled water and yielded correlation coefficients of 0.57 – 0.69, indicating that questionnaires can provide valid data about physical activity and are useful in epidemiological studies. Another way of validating physical activity questionnaires is to compare them with measured fitness. Fogelholm et al. (2006) compared the short format of the International Physical Activity Questionnaire (IPAQ) against health-related fitness and found that overall fitness improved with increasing total MET min/week score, except for the high-

est MET quintile. They also found that self-reported frequency of weekly vigorous activity was associated best with increased fitness level. Surprisingly, 10% of young men who had reported very high physical activity on the IPAQ in fact had poor fitness and apparently low physical activity, indicating that young men in particular might overestimate their level of physical activity (Fogelholm et al. 2006).

2.1.2 Heritability of physical activity

Various studies have shown a moderate to strong genetic component in physical activity participation, with higher heritabilities accounting for vigorous activity (Kaprio et al. 1981, Lauderdale et al. 1997, Kujala et al. 2002, Stubbe et al. 2006). Heritability is an estimate of the genetic contributors to individual differences in different traits in a population, but it is not an estimate of a single individual (Plomin et al. 2000). A large study, which pooled data from 7 European twin registers, showed a consistent genetic influence on physical activity participation, with heritability estimates ranging between 48 and 71% (Stubbe et al. 2006). In turn, a recent study by Aaltonen et al. (2010) found slightly lower heritabilities: as genetic influences on leisure-time physical activity were moderate (44%) at baseline and declined (34%) over a 6-year follow-up among healthy adult men and women. Interestingly, another twin study found a genetic influence on changes in physical activity according to physical activity level, when using 60 minutes or 150 minutes (current recommendation) as cut-off points for physical activity (Duncan et al. 2008). Their results for lower physical activity levels (45%) were similar to those of previous studies, but the variation in physical activity for the higher levels of activity was primarily due to common and unique environmental factors. Unique environment, that is factors that are related to only one of the co-twins, contributed 72% of the variation when 150 minutes was used as the cut-off point (Duncan et al. 2008). In this connection, childhood environment has also been shown to play a modest role in adult exercise behaviour (Stubbe et al. 2006).

2.2 Genetic and environmental influences on all-cause mortality

2.2.1 Heritability of all-cause mortality

Twin (Herskind et al. 1996, Iachine et al. 1998) and adoption (Sorensen et al. 1988, Petersen et al. 2008) studies have indicated that genetics may have an important role as the underlying cause for mortality. The heritability of longevity, which is closely related to all-cause mortality, seems to vary. Herskind et al. (1996) estimated that the heritability of longevity among Danish twins is rather low; i.e. 0.2, but this has been suggested to increase after age 60 according to an analysis conducted with Nordic twin data (vB Hjelmborg et al. 2006). An adoption study showed that biological siblings have moderately increased risk (HR

1.39) for death from all causes before age 70 years if the adoptee's sibling had died by that age (Petersen et al. 2008). Longevity has also been invesigated in many family studies to demonstrate whether long-lived parents have long-lived offspring. These studies have shown that longevity seems to run in families (Gudmundsson et al. 2000, Terry et al. 2004, Westendorp et al. 2009), as siblings and offspring of nonagenarians and centenarians live longer than controls. However, this may be due to shared genes, shared environments and shared lifestyles.

Swedish and Danish twin studies have suggested that the age at death from CHD has moderate to high heritability, 0.38 – 0.58 (Marenberg et al. 1994, Wienke et al. 2001, Zdravkovic et al. 2002, Zdravkovic et al. 2004, Wienke et al. 2005). Only slight changes in heritability were observed when adjusted for known risk factors (Zdravkovic et al. 2004, Wienke et al. 2005). For example, when adjusted for smoking and BMI, heritability increased from 45% to 55% (Wienke et al. 2005). A few studies have shown that the genetic effect decreases with increasing age (Marenberg et al. 1994, Zdravkovic et al. 2002).

2.2.2 Effect of physical activity on all-cause mortality

Many observational studies have reported that leisure-time physical activity has a protective effect on all-cause mortality (Lee et al. 1995, Kujala et al. 1998, Kujala et al. 2002, Autenrieth et al. 2011) as well as on cause-specific mortality, such as coronary heart disease or cardiovascular-related death (Morris et al. 1980, Paffenbarger & Hyde 1984, Leon et al. 1987, Slattery et al. 1989, Rosengren & Wilhelmsen 1997, Erikssen et al. 1998, Carlsson et al. 2007), and cancer mortality (Rosengren & Wilhelmsen 1997, Barbaric et al. 2010, Autenrieth et al. 2011, Kenfield et al. 2011). Recently, many systematic reviews and meta-analyses have summarized the results from studies investigating the relationship between physical activity and all-cause mortality (Nocon et al. 2008, Physical Activity Guidelines Advisory Committee 2008, Lollgen et al. 2009, Woodcock et al. 2011). These reviews clearly demonstrate, on the basis of observational follow-ups, the protective effect of physical activity on all-cause mortality.

The present evidence shows an inverse non-linear dose-response relation between leisure-time physical activity and all-cause mortality. Figure 1 presents an example of the dose-response curve according to the most recent review (Woodcock et al. 2011). This dose-response curve, along with the results of the review (Woodcock et al. 2011), shows that the greatest benefits from leisure-time physical activity occur when moving from sedentary behaviour to low levels of activity; however, when activity levels are increased even further, smaller additional benefits are achieved. The underlying causes of difference in mortality between physically inactive and active subjects might reasonably be expected mainly to concern deaths related to metabolic syndrome and/or cardiovascular diseases; however, surprisingly, Woodcock et al. (2011) found a larger effect of physical activity in studies that adjusted for more cardio-metabolic variables at baseline, indicating the independent effect of physical activity on all-cause mortality from metabolic variables. However, the current evidence on

physical activity and all-cause mortality is based on longitudinal observational studies and no randomized controlled trials have been published to support the findings. This association could also be affected by genetic factors predisposing to sedentariness (Stubbe et al. 2006, Rankinen & Bouchard 2007), which also may affect the life span (Kujala 2011).

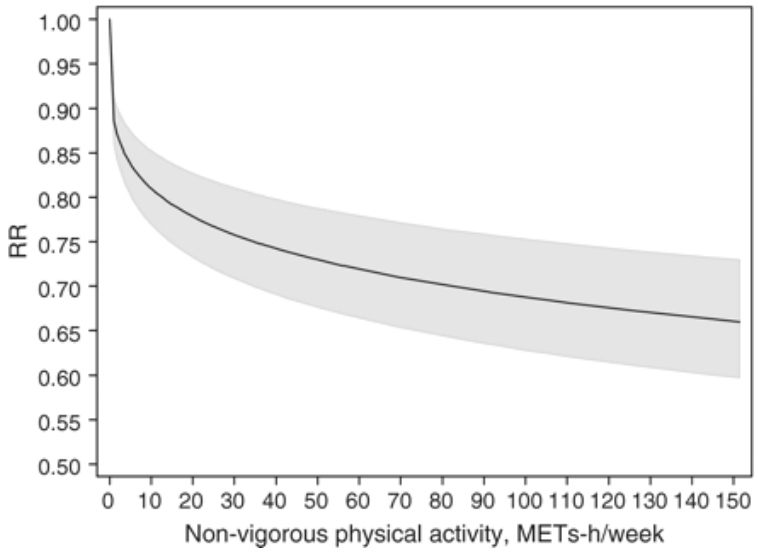

FIGURE 1 The relationship between MET-hours/week of non-vigorous physical activity and RR for all-cause mortality according to a recent review. Data were fitted with a random-effect model including a power transformation of 0.25 for MET-hours/week. Shaded area represents 95% CI (Woodcock et al. (2011), reproduced with kind permission by Oxford University Press).

2.3 Genetic and environmental influences on anthropometric characteristics

Anthropometric measurements refer to measurements of the human body for the purposes of understanding physical variation and individuals' body fat distribution. Anthropometric measurements are a set of noninvasive, quantitative techniques for measuring, recording, and analyzing specific dimensions of the body, such as height and weight, skin-fold thickness, and bodily circumference at the waist, hip, and chest (McArdle et al. 2001). However, to assess body composition and fat distribution more specifically, a wide range of assessment tools can be used, such as underwater weighing, dual energy X-ray absorptiometry (DEXA), bioelectrical impedance (BIA), computed tomography and magnetic resonance imaging (MRI) (Goodpaster et al. 2002). Underwater weighing can only be used to estimate total body fat, while DEXA and BIA can differentiate

regional body fat compartments (Hu et al. 2011). Computed tomography and MRI are the most reliable methods as they can differentiate between subcutaneous and visceral adipose tissue, and MRI can additionally quantify ectopic fat (Hu et al. 2011).

In this thesis weight, height, body mass index (BMI), and waist circumference were used to study anthropometrics. Body mass index (BMI) is a simple measure, used most often to quantify adiposity (Schousboe et al. 2003), and it is calculated as weight (kg) / height $(m)^2$ (McArdle et al. 2001). Normal or ideal BMI is classified by WHO as 18.50 - 24.99, overweight as BMI ≥ 25 and obese as BMI ≥ 30 (WHO 2006b). BMI is often used by clinicians and researchers as it is a better gender-neutral tool for assessing "normality" than body weight (McArdle et al. 2001). BMI has at most a very small correlation with height; the exact relationship depends on the study population. BMI has been shown to correlate well with the amount of body fat (Revicki & Israel 1986), but it does not show the percentage or the distribution of body fat (McArdle et al. 2001). High BMI has been shown to increase the risk for many diseases (Guh et al. 2009) and, for example, a curvilinear relationship has been found between BMI and all-cause mortality (Calle et al. 1999).

According to the WHO, waist circumference (WC) is measured at "the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest" (WHO 2008). Waist circumference is often used to estimate the amount of abdominal fat (Chan et al. 2003), as it has been found to correlate well ($r=0.82$, $p < 0.001$) with deep abdominal adipose tissue area (Despres et al. 1991). High waist circumference is associated with premature death (Pischon et al. 2008) and chronic diseases, such as diabetes (Wang et al. 2005) and myocardial infarction (Yusuf et al. 2005). These studies indicate that waist circumference could be a better predictor of morbidity and mortality than BMI. Waist-hip ratio is also another anthropometric measure that has been used to describe fat distribution (WHO 2008); however, it is not studied in this thesis.

2.3.1 Heritability of weight and waist circumference

Differences in body composition are often related to individual behaviour, but they also have a genetic component. A large twin study across eight countries confirmed that genetics, non-shared environment and gender have an important role in the variation in BMI (Schousboe et al. 2003), whereas shared environment seems to have only little influence on body weight (Plomin et al. 2000). Although, according to a recent review, common environmental factors seem to have a substantial effect on variation in BMI in mid-childhood, at adolescence the effect dissapeared (Silventoinen et al. 2010). Family and twin studies have estimated the heritability of BMI to range between 0.39 and 0.86 (Fabsitz et al. 1994, Austin et al. 1997, Maes et al. 1997, Hunt et al. 2002). A family study by Fox et al. (2005) found a heritability rate of long-term weight change of 0.24, while twin studies have estimated higher values for rate of change in BMI (Fabsitz et al. 1994, Hjelmborg et al. 2008, Ortega-Alonso et al. 2009). A review in 2009 concluded that, according to twin studies, the heritability of BMI change in

adulthood is relatively high, varying from 0.57 to 0.86 (Silventoinen & Kaprio 2009). Some studies have found that the contribution of genetic factors on weight gain and changes in BMI may increase over time (Austin et al. 1997, Goode et al. 2007, Hjelmborg et al. 2008). Heritability of waist circumference seems to have similar genetic variation as BMI and it has been found to vary between 0.48 and 0.78 (Schousboe et al. 2004, Nelson et al. 2006, Lee et al. 2010).

Some twin studies have found that physical activity modified the heritability of BMI and WC (McCaffery et al. 2009, Mustelin et al. 2009, Silventoinen et al. 2009). These studies show that high levels of physical activity decreased the additive genetic component in BMI and WC, suggesting that the effect of genes is diminished in physically active subjects. Conflicting results have been found when the interaction between physical activity and fat mass and obesity-associated gene (FTO) has been studied. The FTO gene is associated robustly with BMI and waist circumference (Frayling et al. 2007, Scuteri et al. 2007, Loos & Bouchard 2008, Vimaleswaran et al. 2009). Some recent studies have found that physical activity can attenuate the risk of obesity that is linked to variation in the FTO (Andreasen et al. 2008, Vimaleswaran et al. 2009); however, other studies with smaller number of participants did not find an interaction between FTO genotype and environment (Cornes et al. 2009) or physical activity (Hakanen et al. 2009, Liu et al. 2010). Also, in a large population-based follow-up study, Li et al. (2010) looked at the effect of physical activity on the 12 alleles that are known be associated with increased BMI. They found that obesity increased by 1.116-fold with each additional obesity-susceptibility allele, but that increase was 40% lower among active subjects than inactive subjects. Among inactive subjects, the obesity risk allele score increased weight gain in a prospective setting, while among active subjects, the obesity risk allele score decreased weight gain; overall however, the risk allele score did not predict weight gain.

2.3.2 Effect of physical activity on weight and waist circumference

Since the genetic pool changes slowly, the causes of the obesity epidemic are mainly environmental (Loos & Bouchard 2003, Lees & Booth 2004), and it has been suggested that sedentary lifestyle is at least as important as diet in the development of obesity (Hill & Melanson 1999, Jebb & Moore 1999). Many randomised controlled intervention studies have shown that physical activity is an important tool in weight loss (Shaw et al. 2006, Brown et al. 2009, Wu et al. 2009, Witham & Avenell 2010) although, reviews and meta-analyses of randomized trials seem to show that exercise alone results in only minor weight loss. However, when physical activity was accompanied with changes in diet, the results were better than those obtained by exercise or diet-induced weight loss alone. The evidence on the prevention of weight gain over time by physical activity seems to be conflicting. A recent multicenter study by Ekelund et al. (2011), involving participants from 9 European countries, found that baseline physical activity was not significantly associated with weight change among any of the

participants during a 5-year follow-up. However, that study and a few other studies have indicated that this relationship could be different according gender, age and baseline weight status. Physical activity was not associated with smaller weight gain in older overweight or obese subjects (Lee et al. 2010, Ekelund et al. 2011), whereas, high physical activity predicted lower gain in body weight in normal weight younger (≤50 years) men and women (Ekelund et al. 2011) and in normal weight middle age (≤65 years) women (Lee et al. 2010). Hankinson et al. (2010) studied young adults moving to middle age during a 20-year follow-up and found that a high physical activity level for 20 years was associated with slower weight gain when compared to the low-activity group, although more clearly in women (6.1kg difference in weight gain between high and low activity) than in men (2.6kg). Fogelholm and Kukkonen-Harjunen concluded (2000) that only large volumes of activity were associated with any amount of weight gain. Similar results have also been shown in the newer and larger follow-up studies (Hankinson et al. 2010, Lee et al. 2010).

One explanation for the possible influence of diet or physical activity habits on obesity is epigenetics. These habits (for example inactivity) might change the rate of transcription or translation of obesity-related genes and therefore increase obesity (Franks & Ling 2010). As explained by Bird 2007, in epigenetics, changes occur in gene function but these cannot be explained by changes in DNA sequence, and therefore the changes in phenotype are due to interaction between genes and the environment (Franks & Ling 2010). However, as Franks and Ling 2010 pointed out, it is still not possible to confirm whether such changes occur until after the development of obesity.

A twin study investigated the effect of physical activity on visceral and abdominal subcutaneous fat using MRI (Leskinen et al. 2009). In that study no differences were observed in weight or BMI between inactive and active co-twins, but significant results were seen in visceral and abdominal subcutaneous fat, even after controlling for genetic liability and childhood environment. Thus far, waist circumference has been a more commonly used measurement in epidemiological studies; however the evidence on reductions in waist circumference with physical activity seems to be conflicting. A review summarizing the results from some randomised controlled studies found that physical activity is an important tool in reducing waist circumference (Kay & Fiatarone Singh 2006). Some observational studies have not found any preventive effect of physical activity on increases in waist circumference (Hughes et al. 2004, Sternfeld et al. 2004, Berentzen et al. 2008) and some studies have found only small preventive effect of baseline or increased physical activity on waist circumference (Koh-Banerjee et al. 2003, Barengo et al. 2006). However, some recent large prospective follow-up studies show that high levels of physical activity are significantly and inversely associated with changes in waist circumference in both men and women, even after adjustment for baseline body weight (Hankinson et al. 2010, Ekelund et al. 2011). Similar results have also been seen among young monozygotic twins, where physical inactivity was a strong predictor of BMI-adjusted abdominal obesity (Pietilainen et al. 2008). In a study by Hankinson et al. (2010)

physical activity habits were recorded five times during a 20-year follow-up. They found that men who maintained high activity for 20 years gained 3.1 cm less in waist circumference than the low-activity group, and women who maintained high activity gained 3.8 fewer centimetres.

As the accumulating evidence on whether the rate of weight gain and increases in waist circumference are reduced by physical activity still seems to be conflicting, more long-term studies are needed; in particularly studies that control for different associated factors, such as genes and childhood environment.

2.4 Genetic and environmental influences on type 2 diabetes

Type 2 diabetes (T2D), also previously called non-insulin-dependent diabetes mellitus or adult-onset diabetes, is the most common type of diabetes, accounting for about 90% of all diabetes cases (Guyton & Hall 2000, WHO 2011a). Type 2 diabetes has become a significant worldwide health problem. In 2004, it was estimated that around 170 million people worldwide had type 2 diabetes (Wild et al. 2004), but to date worldwide figure has already increased to around 220 million people (WHO 2011a). This increase in type 2 diabetes is most likely due to the obesity epidemic, as it has been well established that obesity (Chan et al. 1994, Carey et al. 1997) and physical inactivity (Helmrich et al. 1991, Manson et al. 1991) are the main risk factors for type 2 diabetes.

Type 2 diabetes is caused primarily by a combination of increased hepatic glucose production, diminished insulin secretion and impaired insulin sensitivity (insulin resistance), leading to increased plasma insulin levels and glucose concentration (Guyton & Hall 2000, Kuzuya et al. 2002, Stumvoll et al. 2005). Obesity, especially abdominal obesity, is strongly associated with insulin resistance, as it is linked to many mechanisms in the body that lead to insulin resistance (Stumvoll et al. 2005). One such mechanism is increased circulation of free fatty acids (FFA), which ultimately leads to insulin resistance in skeletal muscle and liver (Boden & Shulman 2002). The prevention of type 2 diabetes is very important as over time type 2 diabetes is a risk for many microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischaemic heart disease, stroke and peripheral vascular disease) complications and is also associated with reduced life expectancy and diminished quality of life (WHO 2006a).

2.4.1 Heritability of type 2 diabetes

Type 2 diabetes has been shown to be an environmental and lifestyle associated disease, but it also has a genetic component (Barroso 2005, Malecki & Klupa 2005). A study by Meigs et al. (2000) found that diabetes risk was 3.5-fold higher for persons with one diabetic parent and 6-fold higher for those with two diabetic parents compared with offspring without parental diabetes. According to a review article by Barrosso (2005), several twin studies have shown that concordance rates among MZ twins vary widely between 0.2 and 0.9 while

in DZ twins the range is smaller, varying between 0.10 and 0.43. Higher concordance values indicate genetic involvement in the aetiology of type 2 diabetes. However, the interpretation of concordance rates is dependent on the prevalence of type 2 diabetes in the study population, and the nature of the study (cross-sectional vs prospective). The best studies are prospective and have a large population-based sample, as in the studies by Kaprio et al. (1992) and Lehtovirta et al. (2010). These studies found that MZ twins are more concordant for type 2 diabetes than DZ twins as the proband-wise concordance for MZ pairs is 0.34–0.41 compared with 0.16–0.19 in DZ twins (Kaprio et al. 1992, Lehtovirta et al. 2010), with heritability estimates in excess of 70%.

Although as shown earlier, type 2 diabetes has high heritability, it is only during the past few years that progress in genome-wide association studies (GWASs) has resulted in the discovery of approximately 20 gene variants associated with T2D (De Silva & Frayling 2010). It is well known that increased BMI and waist circumference are associated with increased risk for type 2 diabetes (Vazquez et al. 2007), and it is reasonable to assume, therefore, that these conditions have some similar genetic background. Some studies, for example, have found that the FTO gene, which has been shown to be linked to obesity, also predisposes to type 2 diabetes (Frayling et al. 2007, Andreasen et al. 2008). Li et al. (2011) showed a similar trend with some other obesity-linked SNPs. However, in all of these studies the association seemed to be mediated by the effect of increased fat mass, as the association disappears when adjusting for BMI. Lehtovirta et al. (2010) also showed in twin data that shared genetics only partly explains the association between diabetes risk and obesity. Consistent with this, most of the new genes identified are specific to BMI (Speliotes et al. 2010) and specific to type 2 diabetes (Voight et al. 2010). Vimaleswaran and Loos (2010) concluded that altogether 19 loci for common obesity have been identified and 18 for common type 2 diabetes, but that the combined contribution of these loci to the variation in obesity and diabetes risk seems to be small.

2.4.2 Effect of physical activity on preventing type 2 diabetes

Although genetic elements are clearly involved in the pathogenesis of type 2 diabetes, lifestyle and overeating seem to be the triggers for developing the condition (Stumvoll et al. 2005). Many randomized controlled studies have shown that type 2 diabetes is preventable by changing lifestyles among high-risk individuals (Pan et al. 1997, Tuomilehto et al. 2001, Knowler et al. 2002, Ramachandran et al. 2006). These lifestyle interventions included changes in both diet and physical activity and they aimed for weight reduction. Uusitupa et al. (2011) summarised the results from both randomized trials and implementation studies and showed that the prevention of type 2 diabetes with lifestyle changes is possible also in a "real life" setting, as reduction in body weight with lifestyle changes of 5% resulted in a 60-70% reduction in diabetes risk. They also concluded that the preventive effect was sustained for many years after the intervention had finished (Uusitupa et al. 2011). However, randomized controlled

trials are often conducted on subjects with high risk for the studied condition and therefore the results might not be generalisable to the general population.

Many prospective follow-up studies (Hu et al. 1999, Folsom et al. 2000, Hu et al. 2003, Demakakos et al. 2010) and one randomized controlled trial (Pan et al. 1997, Tuomilehto et al. 2001) have shown that physical activity has an independent role in the prevention and treatment of type 2 diabetes. The only randomized controlled study that included a physical activity group without other lifestyle modifications was randomized by clinic rather than by subject (Pan et al. 1997). Laaksonen et al. (2005) carried out post hoc analyses from the Finnish Diabetes Prevention study on the role of LTPA in prevention of diabetes. According to this originally randomized controlled trial, the subjects who increased their LTPA most were 63–65% less likely to develop diabetes. Recently, many reviews have summarized the results from observational studies and these reveal that both moderate and vigorous physical activity can prevent type 2 diabetes (Jeon et al. 2007, Gill & Cooper 2008, Physical Activity Guidelines Advisory Committee 2008). A meta-analysis of 10 prospective cohort studies concluded that moderate intensity physical activity decreased the risk of type 2 diabetes as BMI-unadjusted RR was 0.69 (95% CI 0.58–0.83) and BMI-adjusted RR was 0.83 (0.76–0.90) (Jeon et al. 2007). The follow-up periods in these studies were between 4 and 17 years. The Physical Activity Guidelines Advisory Committee (2008) in America summarized the results on the associations between physical activity and prevention of type 2 diabetes in 2008. According to their report, the dose-response relationship for type 2 diabetes prevention varied from any amount of activity to as high as vigorous exercise. However, they concluded that 150 minutes per week or 30 minutes of moderate intensity exercise preferably daily appears to be sufficient to prevent type 2 diabetes. There is also evidence that even low intensity activity only once a week might be associated with reduced type 2 diabetes risk especially in older adults (Demakakos et al. 2010).

A recent review by Qin et al. (2010) studied the evidence of both obesity and physical inactivity and their interaction on type 2 diabetes risk. They found a positive interaction between these two variables and that obesity was a stronger independent risk factor than physical inactivity for type 2 diabetes. Interestingly, they also found that the joint effect of obesity and physical inactivity was larger than the sum of the individual effects, meaning that the risk for type 2 diabetes in individuals who are both obese and physically inactive is greater than would be expected if the effect of obesity and physical inactivity are summed (Qin et al. 2010).

2.5 Genetic and environmental influences on other health-related measurements

2.5.1 Heritability of other health-related measurements

Different medical conditions are a result of genetic and environmental factors in different proportions. A genetic component may play an indirect role in accounting for the relationship between physical activity and chronic disease as well as directly explaining the studied variable. A review by Casas et al. (2006) clearly demonstrated that coronary artery disease (CAD) has a genetic component and that different risk factors for CAD have high heritabilities; for example LDL and HDL heritabilities range between 0.5 and 0.6. Significant genetic influences on cholesterol levels, smoking and hypertension have been repeatedly reported (Batra et al. 2003, Kupper et al. 2005, Casas et al. 2006). These heritability estimates are population and time-specific, depending on the gene pool and the environmental factors present in the population. Thus, it is good to remember that even high heritability does not mean that the trait is genetically determined and unchangeable. As stated earlier, twin studies have shown that age at death from CAD has a strong genetic component, particularly early onset of CAD (Marenberg et al. 1994). Heritability of blood pressure varies between 30% and 70% (Fagard et al. 1995, Evans et al. 2003, Hernelahti et al. 2004). The genetic contribution to the variance in liability to asthma has been found to be high among Finnish twins, with heritability of around 70% in adolescence (Laitinen et al. 1998), but lower in adulthood (Nieminen et al. 1991). A meta-analysis showed that the heritability of major depression is likely to be within the range 31–42% (Sullivan et al. 2000).

Different musculoskeletal conditions and injuries have varying genetic components. For example, in twin and family studies the heritability of osteoarthritis has been estimated from to be 44-50% or more, varying slightly according to the different site of the body (Spector et al. 1996, Spector & MacGregor 2004). Low back pain has been shown to have a heritability between 30% and 52% (MacGregor et al. 2004, Battie et al. 2007, Nyman et al. 2010). Some studies have suggested that sport-related injuries, such as tendon and ligament injuries might also have a genetic component (September et al. 2007).

2.5.2 Effect of physical activity on other health conditions

Observational follow-up studies have provided substantial evidence among adults that, in addition to the effects already mentioned, physical activity plays an important role in the prevention of several chronic diseases, such as cardiovascular disease (CVD), stroke, coronary heart disease (CHD), hypertension, metabolic syndrome, and colon and breast cancer (Kesäniemi et al. 2001, Warburton et al. 2006, Physical Activity Guidelines Advisory Committee 2008). There is strong evidence that physical activity improves cardiorespiratory and muscular fitness, prevents falls and reduces depression, and moderate evidence

that physical activity lowers hip fracture risk, increases bone density and sleep quality and lowers risk for some other types of cancers (Physical Activity Guidelines Advisory Committee 2008). The effects of exercise participation or leisure-time physical activity on psychological health have been investigated in many studies. A study by Stubbe et al. (2007) found that exercise participation was associated with higher levels of life satisfaction and happiness, but this was not seen in twin pairs.

Although physical activity has many positive outcomes for health, the most severe adverse effect of physical activity or exercise training is the risk of sudden coronary death or other acute coronary events. These are mainly seen in vigorous activity and in older persons with latent or diagnosed atherosclerotic artery disease and who have not exercised regularly (Corrado et al. 2006). The more common adverse effects of leisure physical activity are an increased rate of musculoskeletal injuries (Hootman et al. 2002). For example, it is well documented that endurance training, and especially running, can lead to overload injuries of muscle, tendon, and bone (Cosca & Navazio 2007). However, the evidence on whether running causes hip or knee osteoarthritis remains still conflicting as some studies have found that running can increase the risk of osteoarthritis of these sites and others have found no such association (Cymet & Sinkov 2006). Hootman et al. (2002) studied an American adult population with variety of activity level at baseline and found that 25% of all participants reported at least one musculoskeletal injury. Injuries were most likely among the younger and more active subjects and the knee was the most frequently reported site of injury (Hootman et al. 2002). Another study by the same researchers observed a dose-response relationship between increasing leisure-time physical activity level and increasing incidence of self-reported injuries related to sport or leisure-time activities (Carlson et al. 2006).

2.6 Twin study designs

Twin studies are a useful way of studying the net effect of genes and environment, especially for complex disorders and behavioural traits (Plomin et al. 2000, Boomsma et al. 2002). Twins can be either monozygotic (MZ), known as identical twins, or dizygotic (DZ) known as fraternal twins. MZ twins have the same genomic sequence, but may already differ in their epigenome, while DZ twins are as alike as full siblings genetically (but experience the same pregnancy and are of the same age). Twin data can be used to estimate genetic and environmental contributions to individual differences in phenotypic traits, and the estimates are based on variances and covariances in MZ and DZ pairs (Derks et al. 2006). The classical twin study design is based on three assumptions for twins reared together. The first refers to the additive and dominant genetic effects that show a correlation of 1 for both in MZ twin pairs and 0.5 for additive and 0.25 for dominant effects in DZ twin pairs and are derived from basic principles in quantitative genetics, assuming random mating and absence

of gene-environment interactions (Thomas 2002). The second and third assumptions relate to the environment. The second is the equal environment assumption (EEA), in which the estimation of genetic and environmental effects is based on the assumption that environmental influences are shared to the same extent by both types of twins reared in the same family; early childhood environment is an example of EEA. In the third, the nonshared environmental effects do not correlate in MZ and DZ twin pairs, and hence are called unique environmental effects (Plomin et al. 2000, Derks et al. 2006). According to these assumptions if MZ pairs are more alike in a set phenotype, for example in weight or a disease like schizophrenia, than DZ pairs, then it can be assumed that genetic factors are important for the trait. However, if both types of twin pairs are similar, environmental attributes can be found. Using the above correlations, heritability estimates of different traits can be calculated, but these refer to the genetic contribution to individual differences on the population level and not to a single individual (Plomin et al. 2000). Heritability also only refers to a particular trait in a studied population at a certain time. Even if a genetic influence is found for a complex trait, like type 2 diabetes, environmental factors are not unimportant (Plomin et al. 2000) and might serve as trigger for developing the condition (Stumvoll et al. 2005).

Another important assumption relates to generalisability. It is assumed in twin studies that the co-twins themselves do not differ from the singletons and that the studied traits in twins do not differ from those in singletons (Plomin et al. 2000). In general, twins are considered to be similar to the other people in the same birth cohort in the same nation and no clear evidence has been found that deviations in the assumptions impair the ability to interpret or generalise from twin studies (Kyvik 2000), although it is known that twins are often born three to four weeks premature (Plomin et al. 2000) and weigh about 600 - 1000 g less than singletons at birth (Kyvik 2000, Loos et al. 2005), with DZ twins weighing slightly less than MZ twins at birth (Loos et al. 2005). Some twin studies have shown that twins have same prevalence of several diseases and the same mortality as the general population (Kyvik 2000). However, it has been hypothesised that low birth weight might be a cause of some diseases. De Silva and Frayling (2010) point out that many epidemiological studies have found an association between reduced birth weight and the development of type 2 diabetes. Nevertheless, De Silva and Frayling (2010) go on to state that the cause of the association between reduced foetal growth and adverse metabolic traits in later life is not known, both environmental and genetic causes being possible. According to a recent meta-analysis, birth weight is also associated with leisure-time physical activity, with both low and high birth weights being associated with lower probability of undertaking LTPA (Andersen et al. 2009). Overall, this low birth weight is related to the concept of the developmental origins of health and disease. According to the current literature, the phenotype and and/or epigenetic state of offsprings is affected by uterus conditions, such as maternal nutrition and stress, maternal size, parity and maternal age (Gluck-

man et al. 2011) and therefore to some extent the future health status might be coded in humans in the very early stages of life.

The co-twin control study is one type of twin study design (Gesell 1942). Studies of this type are very effective for studying different traits and different environmental risk factors, if the studied trait is heritable (Duffy 2000). In particular, MZ pairs are ideal for carrying out case-control studies as they are identical in their genetic background and also, usually, in their childhood environment (Boomsma et al. 2002), and thus these confounding factors are automatically controlled for. In an experimental co-twin control study one member of a MZ pair undergoes a particular treatment, for example receives a vitamin C supplement, and is then compared to the untreated control co-twin (Gesell 1942, Duffy 2000, Boomsma et al. 2002). In twins, observational co-twin control studies are longitudinal studies of a cohort of twin pairs discordant for the assumed disease exposure risk factor and then followed for a period of time to record the occurrence of disease (Duffy 2000, Kujala et al. 2002). Studies with twin pairs discordant for health behaviour, such as physical activity, are called co-twin control studies.

The evidence on the effects of physical activity on different health conditions is currently based on randomized controlled intervention studies and observational follow-up studies. However, the existing intervention studies have often had small sample size and short follow-ups, while the larger observational studies might have had unclear cause-and-effect evaluation due to confounding factors and genetic selection bias (Kujala 2011). In this thesis, to be able to tackle the issue of genetic selection bias in an observational study, the effects of physical activity on different health outcomes are studied among twin pairs.

3 AIMS OF THE STUDY

The purpose of this study was to examine the sum effect of leisure-time physical activity on health. The main aim was to find out whether persistent leisure physical activity, adjusted for genes and childhood environment, protects against chronic disease, metabolic syndrome related conditions or mortality. In detail, the specific aims were:

To examine whether baseline leisure-time physical activity is associated with

1. decreased all-caused mortality (study I)
2. decreased type 2 diabetes risk (studies I, II and IV)
3. slower weight gain and smaller waist circumference (study III)
4. fewer chronic diseases, less use of medication and lower frequency of other related measurements, such as dyspnea and hospital use (studies I and II)

4 PARTICIPANTS AND METHODS

This thesis is based on a prospective follow-up design and most of the analyses have been carried out as a co-twin control design. All the baseline study materials are based on the older Finnish Twin Cohort, which is a questionnaire based study conducted initially in 1975 and 1981 (Kaprio & Koskenvuo 2002). Either the 1975 (study IV) or both the 1975 and 1981 (studies I, II and III) studies were used as the baseline for all of the analyses presented in this thesis. For one study (IV), the participants were followed for 28 years from 1975 to study the development of type 2 diabetes. In the other three studies (I, II, III), the participants were comprehensively selected from the 1975 and 1981 baseline cohorts to be followed for 24 years. These three studies use co-twin control design. Figure 2 shows all the studies and how they are linked to the baseline cohort in 1975.

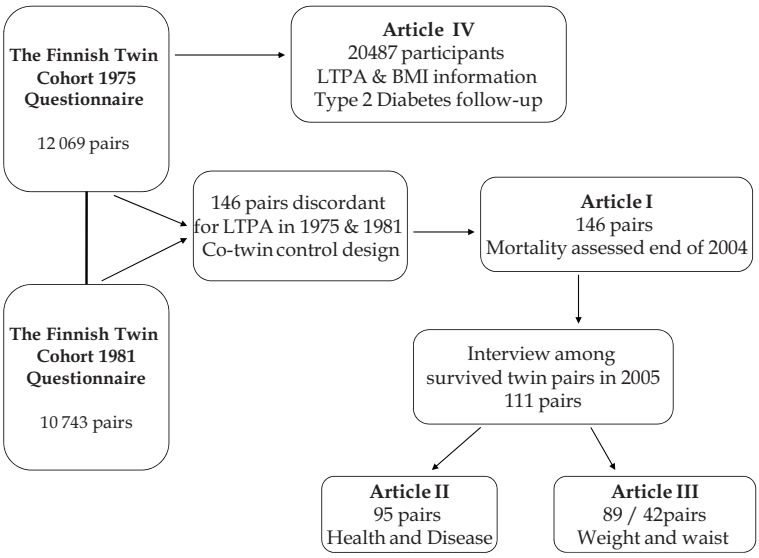

FIGURE 2 Datasets and participants in each study (for more details see figure 3).

4.1 Subjects

The Finnish Twin Cohort consists of virtually all the same-sex twin pairs born in Finland before 1958 and with both co-twins alive in 1967 (Kaprio & Koskenvuo 2002). These twin pairs were identified from the Central Population Registry of Finland in 1974. Between August and October 1975, a baseline questionnaire was sent out to twin pairs with both members alive. The total number of twin pairs with was 12 069 at the beginning of the prospective follow-up. A second set of similar questionnaires was sent out to all twin pairs in 1981 (Kaprio & Koskenvuo 2002). Among those for whom addresses were known (93.5 percent of subjects) in 1975, the response rate for twin pairs was 87.6 percent. The corresponding response rate among those responding in 1975 and alive in 1981 was 90.7 percent. Determination of zygosity was based on an accurate and validated questionnaire method (Sarna et al. 1978).

For the co-twin control studies (I, II, III), the initial inclusion criteria were employment (including women working at home and students) in 1981 and complete data on leisure-time physical activity, required for the MET index calculations (see explanation below), gathered by postal surveys at baseline in 1975 and 1981. The subjects were between 24 to 60 years of age on January 1, 1982 and comprised 17 968 individuals (Kujala et al. 2002). All pairs in which at least one of the twins did not respond to both questionnaires, had died or had a chronic disease, except hypertension, by the end of 1982 were excluded (Kujala et al. 2002). The healthy cohort comprised 5 663 same-sex twin pairs (3 551 dizygotic, 1 772 monozygotic and 340 pairs with unknown zygosity) (Kujala et al. 2002). Among these 5 663 twin pairs, 146 pairs were discordant for leisure-time physical activity for both participation in vigorous activity and volume (calculated by intensity x duration x frequency) of activity in both 1975 and 1981 (Figure 3). These 146 discordant pairs were included in the mortality assessment at the end of 2004. The mean age of the subjects was 38.1 years at the beginning of the follow-up (1.1.1983). The final study cohort for the mortality assessment (146 pairs) consisted of 65 male and 81 female pairs, of which 29 were monozygotic, 116 dizygotic and one of uncertain zygosity.

After the mortality assessment, a telephone interview follow-up study was carried out in 2005 among the surviving twin pairs. To be included in the interview, it was required that both co-twins were known to be living in Finland and spoke Finnish as their native language, which resulted in the exclusion of 12 pairs. The interview study sample at the 2005 follow-up comprised 111 twin pairs, as only those pairs were included in which both twins were still alive. An attempt was made to contact all 222 subjects. Of these, 203 subjects (95 complete pairs, 54 female and 41 male) took part in the interview, as one co-twin died during the interview period and 18 did not participate (Figure 3). The mean age of the subjects was 58 years (range 47 to 79) at interview. Those 203 subjects consisted of 89 twin pairs (40 male, 49 female, 72 DZ, 17 MZ pairs) who had completed all the physical activity questions in the telephone interview in 2005.

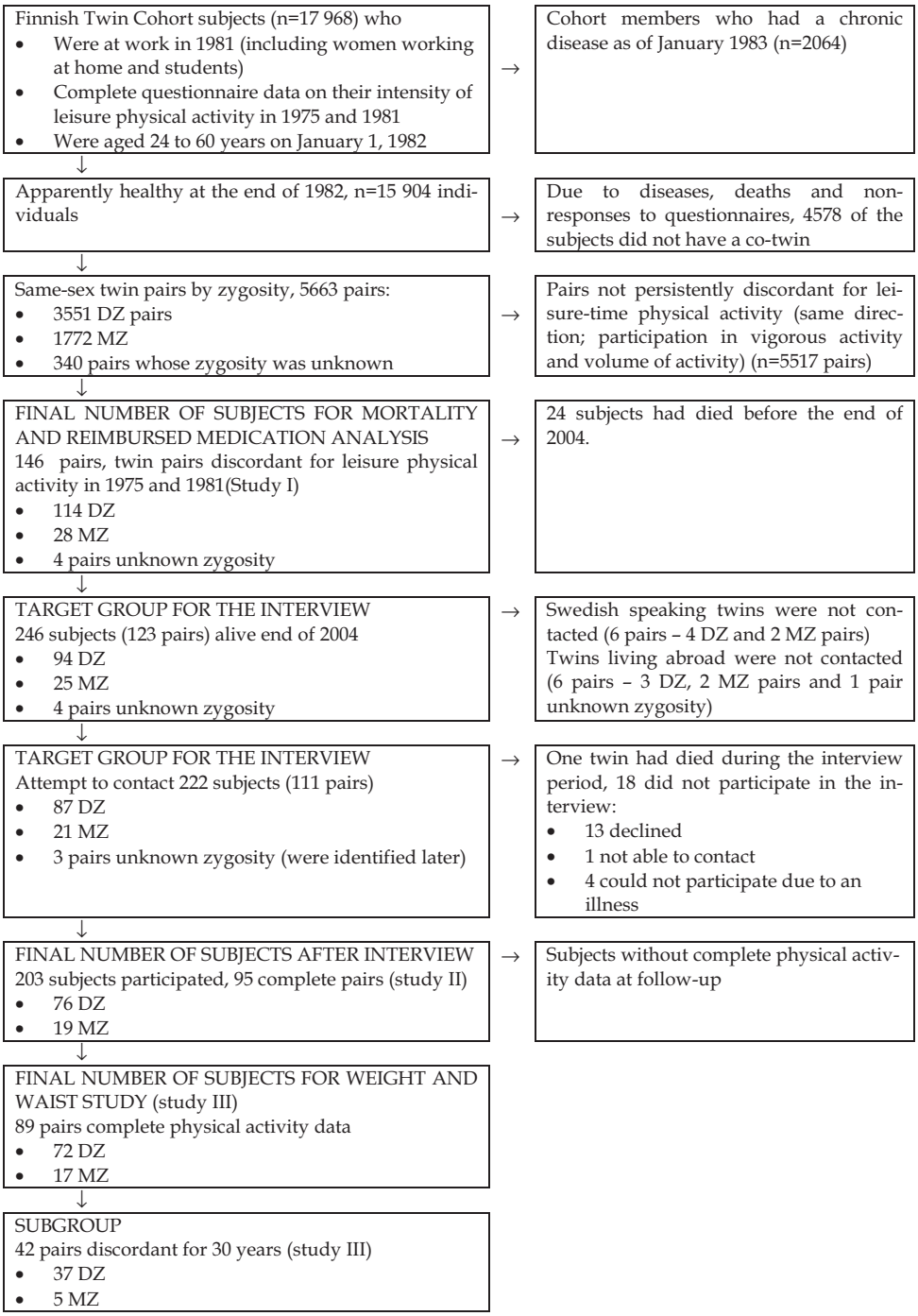

FIGURE 3 Subject selection for the telephone interview (studies I, II, III). Right column shows excluded participants.

To study type 2 diabetes further in a large sample, the baseline cohort of 1975 was followed until end of 2004 for type 2 diabetes incidence. For the diabetes study (study IV), all subjects with diagnosed diabetes at baseline, those of undefined zygosity and those who had moved abroad before 1976 were excluded. The cohort consisted of 23 585 individuals for whom self-reported baseline data were available on education, social and occupational class, alcohol consumption, physical activity and BMI (Lehtovirta et al. 2010). To be included in the final study sample, comprehensive physical activity information for the MET index calculations (see explanation below) was required. Therefore, the final cohort included 20 487 individuals, of whom 9 842 were male and 10 645 female, and 6 399 MZ and 14 088 DZ twin individuals. The cohort consisted of 8182 complete sets of twin pairs (2 627 MZ pairs and 5 555 DZ pairs). To remove the confounding factors due to disease, a subgroup of 13 291 presumably healthy individuals was also studied. Subjects with chronic diseases (such as angina pectoris, MI, stroke, diabetes, CVD, COPD and malignant cancer) affecting weight and ability to engage in leisure-time physical activity prior to 1982 had been identified by a questionnaire in 1981 and by medical records as described in detail elsewhere (Kujala et al. 1998). Type 2 diabetes (Glumer et al. 2003) and some other diseases can remain subclinical and undiagnosed for some time after the first onset of symptoms. Therefore a six-year period was set in order to ensure that any undiagnosed cases in 1975 would have been diagnosed by 1981. Thus, a true cohort of subjects free of clinical co-morbidities was obtained.

4.2 Assessment of baseline predictors

The subjects were mailed similar questionnaires in 1975 and 1981. These questionnaires included questions on weight, height, physical activity, occupation, alcohol use, smoking and physician-diagnosed diseases. Physical activity habits elicited by identical questions in 1975 and 1981 were used as the baseline predictor in the present study.

4.2.1 Leisure-time physical activity

Assessment of vigorous physical activity was based on the following question:

Is your physical activity during leisure-time about as strenuous on average as:
1) walking
2) alternately walking and jogging
3) jogging
4) running

Those who chose 2, 3 or 4 were classified as engaging in vigorous activity. Assessment of volume of activity (MET index) was based on a series of structured questions on leisure-time physical activity (mean duration, monthly frequency

and mean intensity of sessions) and activity during work journeys. Leisure-time physical activity was explained in the questionnaire as "activity which does not occur at work or on the way to work" (Kaprio et al. 1978). The following questions were used for the MET index calculation:

How long does the physical activity last at one session on average:
a) less than 15 minutes (class midpoint 7.5)
b) 15 min – less than 30 min (22.5)
c) 30 min – less than 1 hour (45)
d) 1 hour – less than 2 hours (90)
e) over two hours (120)

Presently how many times per month do you engage in physical activity during your leisure time:
a) less than once a month (class midpoint 0.5)
b) 1-2 times per month (1.5)
c) 3-5 times per month (4)
d) 6-10 times per month (8)
e) 11-19 times per month (15)
f) more than 20 times per month (20)

For the intensity of a session the same question was used as for vigorous activity, but following MET values were included for the alternatives:
a) walking (corresponding to 4 MET)
b) alternately walking and jogging (6 MET)
c) jogging (10 MET)
d) running (13 MET)

The following question was asked about physical activity during journeys to and from work:

How much of your daily journey to work is spent in walking, cycling, running and/or cross-country skiing?
a) less than 15 min (class midpoint 7)
b) 15 min – less than an half an hour (22)
c) half an hour to less than an hour (45)
d) hour or more (75)
e) I am presently not at work (0)

The MET index was calculated by assigning a multiple of resting metabolic rate (MET value as indicated above) and by calculating the product of activity, i.e. intensity x duration x frequency (Kujala et al. 1998). Physical activity during work journeys was calculated with a similar formula. A MET value of 4 and frequency of 5 times per week were used for the work journey calculations. The MET index was expressed as the sum-score of leisure MET hours/day. One

MET hour/day corresponds to approximately 30 minutes of slow walking every other day.

For the mortality follow-up study (study I) and the telephone interview study (studies II and III), twin pairs were comprehensively selected from the entire Finnish Twin Cohort on the basis of leisure-time physical activity discordance. All twin pairs from the entire cohort were selected who were LTPA discordant for both participation in vigorous activity and volume of activity (MET index) in 1975 and 1981. For this comprehensive selection of discordant twin pairs (146 pairs) a 2 MET hours/day borderline was set for the volume of activity (about 30 minutes of slow walking per day). Those subjects whose volume of activity was ≥2 MET hours/day and participated in vigorous activity were classified as physically active compared to their inactive co-twins whose level of activity was < 2 MET hours/day and did not participate in vigorous activity.

For the type 2 diabetes analyses (study IV), the MET index established was divided into quintiles. The same quintiles were used as in an earlier study on mortality (Kujala et al. 1998):

Quintile I: < 0.59 MET hours/day,
Quintile II: 0.59 to < 1.30,
Quintile III: 1.30 to < 2.50,
Quintile IV: 2.50 to < 4.50
Quintile V: > 4.50.

For further analyzes the index was dichotomised as sedentary <0.59 MET hours/day (Quintile 1) and active >0.59 MET hours/day (combined Quintiles II-V) subjects.

At follow-up, physical activity was assessed in the telephone interview; for details, see chapter 4.3.1.

4.2.2 Covariates

For the analyses, self-reported BMI, smoking status, use of alcohol, work-related physical activity, age and sex at baseline in 1975 or 1981, depending on the study, and social class in 1975 were used as covariates. Baseline weight and height were used to calculate BMI. Smoking status was coded into four categories (never smoked, former smoker, occasional smoker, and current (daily) smoker) determined from responses to detailed questions on smoking history (Kaprio & Koskenvuo 2002). Pack-years of smoking was used to describe the lifelong dose of smoking, which was calculated as smoking 1 pack per day for a year (Kujala et al. 1998). Alcohol use was a dichotomous index of binge drinking and defined by whether the subject had drunk at least five drinks on a single occasion, at least monthly (Kaprio et al. 1987). Social class was a categorical variable with six categories (for categories see subject characteristics table), and the classification was based on job title according to the Central Statistical Office of Finland (Central Statistical Office of Finland 1972). Work-related physical activity was used as a categorical variable with a four-point ordinal scale (Kujala et al. 2002).

4.3 Follow-up assessments

For the follow-up outcomes, register information (type 2 diabetes, mortality and some other conditions) and telephone interview data were used. The participants were informed about the purposes of the overall cohort study when given the baseline questionnaire in 1975. By responding to the questionnaire, participants also gave their informed consent for future register follow-ups. The record linkages were approved by the appropriate authorities responsible for the registers and the Ethics Committee of the Department of Public Health, University of Helsinki.

To participate in the telephone interview, the subjects were first sent an invitation letter, which was followed by a telephone interview in 2005. Subjects provided an informed consent to participate in the study and the ethics committee of the University of Jyväskylä approved the study. All outcome assessments (including interview and data entry) were carried out blinded to baseline status. Two experienced and trained interviewers interviewed at random one co-twin from each pair. The interview included questions on weight, height, waist circumference, physical activity habits, and occurrence of chronic diseases. The mean duration of the interviews was 50 minutes.

4.3.1 Physical activity level

The telephone interview included questions on current and past physical activity. Physical activity level was assessed by two sets of questions. The first, a shorter retrospective assessment (years 1980, 1985, 1990, 1995, 2000 and 2005) of participation in vigorous physical activity and physical activity volume (including calculation of the MET index), used the same questions as in 1975 and 1981. To increase recall, subjects were asked to state their marital and work status for each year before the retrospective physical activity questions (Winters-Hart et al. 2004). The mean MET index for all six measurements between 1980 and 2005 was calculated. The intraclass correlation coefficient (ICC) between the questionnaire-based leisure-time physical activity MET index in 1981 and the interview-based retrospective MET index in 1980 was 0.56 ($p<0.001$).

The second, a detailed assessment of leisure-time physical activity volume over the previous 12 months (12-month MET index), was done using a modified version of the Kuopio Ischemic Heart Disease Risk Factor Study Questionnaire (Lakka & Salonen 1997). The assessment included questions on leisure-time physical activities (termed conditioning activities in earlier publications (Lakka & Salonen 1992)), physical activities during journeys to and from work as well as daily activities such as gardening and berry picking. Each activity included a question on monthly frequency, mean duration and mean intensity of sessions. The ICC between the shorter 2005 MET index and the detailed 12-month physical activity MET index was 0.68 ($p<0.001$) for leisure-time physical activity and 0.93 ($p<0.001$) for work journey.

4.3.2 Mortality

The mortality follow-up began on January 1, 1983, which allowed for a lag of 1 year from the second physical activity assessment. The follow-up continued until December 31, 2004.[1] For mortality assessment, dates of death were available from the Population Register Centre of Finland.

4.3.3 Anthropometric measurements

In the interview, subjects were asked about their current height, weight and waist circumference. Previous studies have validated self-reported height and weight against measured values (Schousboe et al. 2003, Silventoinen et al. 2003). Change in weight was calculated by subtracting weight in 1975 or 1981 from weight in 2005. Body mass index (BMI, kg/m^2) was calculated from self-reported values. In another study of Finnish twins the correlation between self-reported and measured BMI was very high (Mustelin et al. 2009).

Subjects were sent a tape measure prior to the interview to measure waist circumference. They were asked to measure their waist circumference in the standing position according to an instruction clarified with a picture. The measurement was to be done at the narrowest part of the waist; if this could not be found, they were instructed to measure midway between the iliac crest and the lowest rib. In a separate validation study, a healthcare professional measured the subjects waist circumference blinded to the subjects' (N=24) measurements, and the ICC between these was 0.97 ($p<0.001$).

4.3.4 Type 2 diabetes

Type 2 diabetes was assessed in three different studies. Reimbursed medication data were analysed for the entire 1975 cohort (study IV) and for 146 pairs (study I), and type 2 diabetes and prediabetes (study II) were inquired about in the telephone interview in 2005. The data collection for study I is explained later in chapter 4.3.5.

For study IV, the follow-up period for type 2 diabetes was from January 1, 1976 to December 31, 2004. Type 2 diabetes information for 1976 – 1996 was collected from death certificates, the National Hospital Discharge Register and the Reimbursed Medication Register of the Social Insurance Institution by linking this information to the personal ID assigned to all residents of Finland (Lehtovirta et al. 2010). The Social Insurance Institution of Finland (KELA) is the agency responsible for the provision of basic social security. KELA reimburses whole or part of the cost of essential medications to patients who are certified by a physician as having a diagnosed severe chronic disease, while reimbursement for diabetes-related medications is 100% (The Social Insurance Institution of Finland 2010). Although the register is not sensitive to cases of mild diseases,

[1] Note: paper I shows the results from the updated mortality data until the end of 2006.

it has very high validity and the possibility of false positive cases is unlikely (Kujala et al. 2003). The relevant medical records for 1976 - 1996 were reviewed and cases classified as type 2 diabetes, type 1 diabetes, gestational diabetes, secondary diabetes or other diagnoses, as described elsewhere (Kaprio et al. 1992, Lehtovirta et al. 2010). The date of onset of disease symptoms was determined and used in the analyses. The diabetes information for 1996 – 2004 was collected solely from the Reimbursed Medication Register and, given the age of the subjects, presumed to be type 2 diabetes (Lehtovirta et al. 2010). For this period, the date of being granted the right to reimbursed medication was used in the analysis as the date of disease onset. Cases of gestational diabetes were not included as medication for this type of diabetes is not eligible for reimbursement and therefore these cases were not included in the register (The Social Insurance Institution of Finland 2010).

For study II, glucose intolerance (including type 2 diabetes) was assessed in the telephone interview in 2005 with a question: Has your doctor told you that you have diabetes? If subject answered 1) yes, type 2 diabetes or 2) no, but I have been told that I have elevated blood glucose (meaning either impaired glucose tolerance or impaired fasting glycaemia), they were classified as having diabetes or prediabetes.

4.3.5 Type 2 diabetes, hypertension and CHD among 146 pairs

To investigate type 2 diabetes, hypertension and coronary heart disease (CHD) among 146 twin pairs discordant for physical activity, reimbursed medication information was analysed. The reimbursed medication follow-up began on January 1, 1983, which allowed for a lag of one year from the second physical activity assessment, and the follow-up continued until December 31, 2004. Reimbursed medication information for all 146 pairs was obtained from the Social Insurance Institution of Finland, as explained above. The date of being granted the right to reimbursed medication was used in the analysis.

4.3.6 Other health-related variables assessed by telephone interview

The follow-up interview included a four-question dyspnea scale on whether the subject became breathless during walking and daily tasks (Rose & Blackburn 1968). This was used as a categorical variable with 5 categories (0-4), where subject scored 0 if no "yes" answers were given, and 4 if all questions were answered "yes", indicating that person gets breathless very easily. The interview included a four-question scale for life satisfaction (LS) with sum scores ranging between 4 and 20, with an increasing score indicating a decrease in life satisfaction (Koivumaa-Honkanen et al. 2002, Koivumaa-Honkanen et al. 2005). The life satisfaction scale has been found to correlate well ($r>0.6$) with the 21-item Beck Depression Inventory (Koivumaa-Honkanen et al. 2002).

Physician-diagnosed diseases were elicited as follows: for example "Has your doctor told you that you have coronary artery disease?" or "Has your doc-

tor told you that you have asthma?" and "If yes, at what age were you diagnosed with that particular disease?" Other chronic conditions requested were cardiac insufficiency, myocardial infarction, stroke, intermittent claudication, pulmonary emphysema, chronic bronchitis, COPD, gastric ulcer, depression. Similar questions were asked about presence of rheumatoid arthritis, osteoarthritis (knee, hip or other), sports-related injuries (achilles tendon inflammation, other tendon inflammation, achilles tendon rapture, other tendon rapture, meniscus injury, knee ligament injury, ankle ligament injury), sciatica, and tension neck. For blood pressure, a question with four alternatives was used: these were a) yes I have hypertension and I have medication for it, b) hypertension, but no medication, c) no hypertension, but occasionally high blood pressure, d) normal blood pressure. Other physician-diagnosed diseases were assessed with an open question: "Have you got any other physician-diagnosed diseases?" If the answer yes, they were asked "what disease/ diseases did you have and at what age was it diagnosed?"

Hospital stay was investigated with the question "How many days have you spent in a hospital during the last 3 years?" The subjects were given the instruction to include nights, as outpatient visits were not included. Medication use was investigated with the question "Do you have any physician prescribed medications? If yes, what and what is the dose?"

4.4 Statistical Methods

4.4.1 Descriptive statistics

All statistical analyses were performed by using SPSS (SPSS 12.0 and 14.0) and Stata (8.0 and 9.0) statistical software packages. In all the studies the level of significance was set at $p<0.05$ and all the p-values reported are two-sided.

To compare differences between inactive and active co-twins in the outcome measurements obtained by the telephone interview, paired samples t-test and McNemar's test were used. All of these statistical analyses were based on pairwise tests. When studying the data on the occurrence of different diseases and health-related variables obtained by the telephone interview, most of the analyses were conducted for 95 twin pairs. The weight and waist circumference (study III) analyses were first conducted for 89 pairs (Figure 3), who had answered all the physical activity questions at the follow-up. Secondly, the analyses were carried out for 42 pairs who had remained consistently discordant for physical activity over the thirty-year follow-up and for 47 pairs who had not been consistently discordant (discordance not in the same direction at one or more time points). The main results are also reported by gender and zygosity.

4.4.2 Multivariate analyses

In order to study mortality and some metabolic-related conditions in more detail, multivariate analyses were used. Conditional logistic regression was used to determine odds ratios (OR) for likelihood of weight gain, obesity and different chronic diseases. The Cox proportional hazard model was used to calculate hazard ratios (HR) with their 95% confidence intervals (CI) for mortality, type 2 diabetes (studies II and IV), hypertension and CHD. The follow-up ended on December 31, 2004 or at emigration or death and for the disease analyses at the time when reimbursed medication status was granted. Both individual and pairwise analyses were used. In the individual level analyses, lack of statistical independence between co-twins was taken into account by computing robust variance estimators for cluster-corrected data (Williams 2000) to yield correct standard errors and p-values.

First, for the mortality analysis, hazard ratios (HR) were calculated for 146 physical activity discordant twin pairs. After that the model was adjusted for social class, smoking status and alcohol use at baseline by adding one covariate at the time into the model. Similar analyses were carried out for reimbursed medications for 146 pairs. All of these analyses were then carried out separately for MZ and DZ pairs. Three co-twins were excluded from all of the analyses, as they had emigrated before the follow-up start date, and 10 co-twins were excluded from the hypertension analyses, as these subjects had been granted hypertension reimbursed medication before the follow-up start date. Inactive co-twins were used as the reference group in all of the analyses.

The hazard ratios for the incidence of type 2 diabetes (study IV) were estimated by the MET quintiles for the whole 1975 cohort. The inactive category (Quintile I: <0.59 MET hours/day) was used as the reference group. First, the regression model was run as an individual analysis and second, the analyses were done as pairwise analyses, in which the data were stratified by pair, and thus the risk estimates were within-pair estimates. For the individual analysis the regression model was adjusted for age and sex, and additionally for BMI. The pairwise analyses were controlled for by the study design for age and sex (co-twin control -design); however, the models were also adjusted for BMI and were run separately for MZ and DZ pairs, if the numbers permitted. The basic individual analysis was additionally adjusted for work-related physical activity, social class, use of alcohol and smoking.

5 RESULTS

5.1 Baseline subject characteristics

In 1975, the mean leisure-time MET index for the 146 twin pairs was 4.59 MET hours/day for the active and 0.71 MET hours/day for the inactive co-twins (Figure 4). In 1981 the MET indices were slightly higher for both active and inactive co-twins. The mean difference in the MET index between inactive and active co-twins was 3.88 MET hours/day in 1975 (paired t-test, $p<0.001$) and 4.96 MET hours/day in 1981 ($p<0.001$). Similar results were seen for male, female, monozygotic and dizygotic pairs and also for the subgroups of 95 (study III, Figure 4) and 89 (study I) pairs.

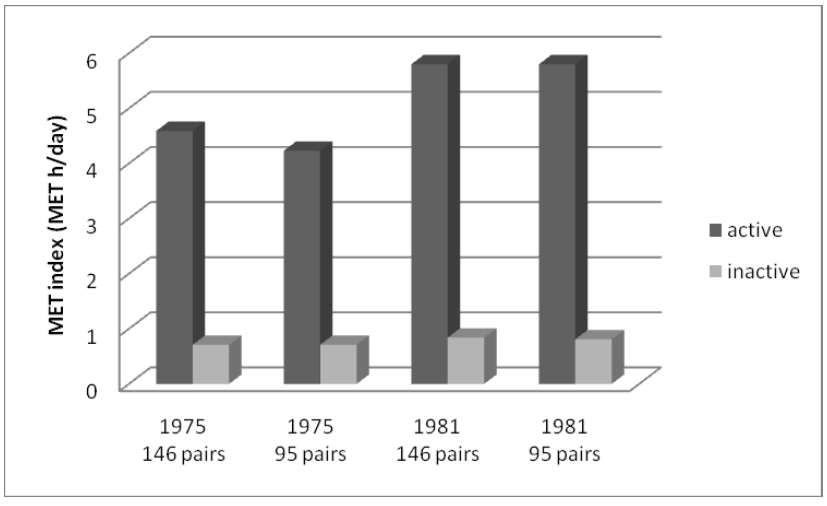

FIGURE 4 Mean leisure-time MET indices for 146, and subgroup of 95, twin pairs. Pairs are discordant for both intensity and volume of physical activity in 1975 and 1981.

Table 2 summarises the baseline characteristics for the 146 pairs and 95 pairs in 1975. Among the 146 and 95 pairs, differences between inactive and active co-twins were seen in smoking habits in both 1975 and 1981, as the inactive twins smoked more. The active co-twins reported greater life satisfaction among both groups at baseline in 1975, but not in 1981. Among the 146 pairs, the inactive co-twins had physically heavier work in 1975 and 1981, but this was not observed among the 95 pairs. No differences in weight or BMI were seen in 1975, but in 1981 the inactive co-twins had higher BMI than their active co-twins among both the 146 pairs (23.8 vs. 23.0, p=0.004) and 95 pairs (23.3 vs. 22.6, p=0.043). No other differences were seen between the inactive and active co-twins at baseline.

TABLE 2 Baseline characteristics in 1975 for 146 twin pairs (study I) and 95 pairs (study II, 89 pairs for study III). [a]

	146 pairs in 1975			95 pairs in 1975		
Characteristics	Inactive	Active	P value	Inactive	Active	P value
Age, years	30.1±8.1	30.1±8.1		28.5 ± 6.9	28.5 ± 6.9	
Height, cm	168.5 ± 8.5	169.5± 8.5	0.024	168,9 ± 8.4	169.3 ± 8.3	0.47
Weight, kg	64.6 ± 12.4	64.9 ± 10.9	0.73	63.2 ± 12.1	63.7 ± 10.2	0.65
BMI (kg/m^2)	22.6 ± 3.1	22.5 ± 2.5	0.53	22.0 ± 2.8	22.1 ± 2.3	0.76
Ever regular smoker	83 (56.8%)	67(45.9%)	0.027	51 (53.7%)	43 (45.3%)	0.22
Pack years smoked	4.2 ± 6.2	2.6 ± 4.9	<0.001	3.1 ± 4.8	1.9 ± 3.4	0.008
Alcohol, grams/day	8.1 ± 13.4	9.0 ± 15.4	0.49	7.2 ± 14.4	7.6 ± 11.8	0.73
Binge drinking	31(21.2%)	34 (23.3%)	0.59	17 (17.9%)	21 (22.1%)	0.36
Diagnosed hypertension [b]	16 (11%)	9 (6.2%)	0.19	7 (7.4%)	5 (5.3%)	0.75
Life satisfaction [c]	8.8 ± 2.7	8.0 ± 2.5	0.004	8.8 ± 2.5	8.0 ± 2.7	0.026
Work-related PA			0.019			0.19
Sedentary	47 (32.4%)	57 (39.3%)		28 (29.8%)	33 (34.7%)	
Standing/walking	26 (17.9%)	32 (22.1%)		14 (14.9%)	20 (21.1%)	
Light manual labour	61 (42.1%)	52 (35.9%)		46 (48.9%)	39 (41.1%)	
Heavy manual labour	11 (7.6%)	4 (2.8%)		6 (6.4%)	3 (3.2%)	
Social class						0.26
White-collar worker	11 (7.5%)	13 (8,9%)		6 (6.3%)	8 (8.4%)	
Clerical worker	48 (32.9%)	51 (34.9%)		28 (29.5%)	25 (26.3%)	
Skilled worker	48 (32.9%)	52 (35.6%)		33 (34.7%)	39 (41.1%)	
Unskilled worker	11 (7.5%)	11 (7.5%)		7 (7.4%)	8 (8.4%)	
Farmer	19 (13.0%)	3 (2.1%)		14 (14.7%)	2 (2.1%)	
Other [d]	9 (6.2%)	16 (11.0%)		7 (7.4%)	13 (13.7%)	

[a] Values are means ±SD or N (%).

[b] According to questionnaire answer or medication information in 1975.

[c] The life satisfaction index was a four-question scale with sum score ranging from 4-20, with an increasing score indicating a decrease in life satisfaction.

[d] Students, army recruits, retired, unknown

The baseline subject characteristics for the diabetes study (study IV) show that the sedentary subjects in quintile I were the oldest, had the highest BMI, and smoked the most, whereas alcohol consumption was higher among the active subjects. Inactive subjects had heavy physical work more often compared to active subjects.

5.2 Mortality

24 co-twins died during the follow-up (1.1.1983 – 31.12.2004).[2] Altogether 16 inactive (14 DZ and 2 MZ) and 8 active (6 DZ and 2 MZ) co-twins died. Among the 24 individuals who died during the follow-up, both co-twins in 3 pairs died, including 2 active and 1 inactive co-twin who died before their co-twins. Figure 5 shows the survival curves for inactive and active co-twins. In the individual based analyses, the active co-twins had decreased risk of death when compared with their inactive co-twins (age and sex adjusted HR=0.48, 95% CI 0.22 – 1.04). After additionally adjusting for social class, the HR was 0.39 (95% CI 0.18 – 0.85). When adjusted for work-related physical activity instead of social class, the HR was 0.38 (95% CI 0.17 - 0.86). The tendency for lower hazard ratios persisted after the further adjustments for alcohol and smoking habits. The hazard ratios persisted when the analyses were done for DZ pairs only: age- and sex-adjusted HR was 0.40 (95% CI 0.17 – 0.98) and social class-adjusted HR was 0.31 (95% CI 0.13 – 0.77). When analysing the MZ pairs, no differences were seen between the inactive and active co-twins.

Pairwise analyses showed lower but non-significant hazard ratios among all pairs: unadjusted HR was 0.54 (95% CI 0.22 – 1.35), social class-adjusted HR was 0.27 (95% CI 0.07 – 1.13) and work-related PA-adjusted HR was 0.43 (95% CI 0.12 – 1.54). Pairwise analyses among the DZ pairs showed again lower hazard ratios: as unadjusted HR was 0.42 (0.15 – 1.18) and social class-adjusted HR was 0.17 (0.02 – 1.28). The actual causes of death among the 16 inactive co-twins who died by the end of 2004 were 7 cancers, 3 myocardial infarctions, 2 suicides, 1 cerebrovascular disease, 1 disease of respiratory system, 1 alcohol-related disease and 1 accidental fall. The causes of death for 8 active co-twins were 3 myocardial infarctions, 2 cancers, 1 alcohol related disease, 1 traumatic injury and 1 water-transport-related drowning.

[2] Note: paper I shows the results from the updated mortality data until the end of 2006.

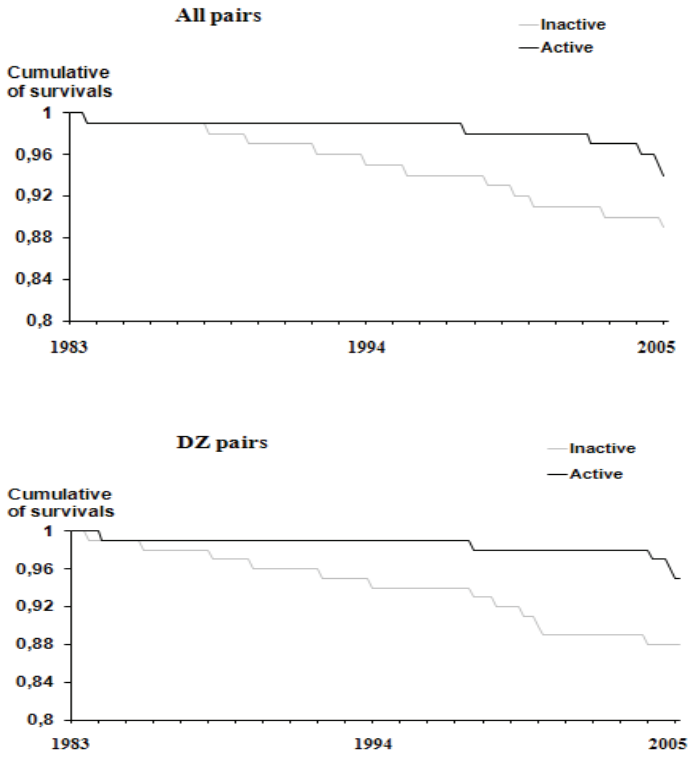

FIGURE 5 Survival curves for mortality in twin pairs discordant for leisure-time physical activity. Upper panel for all and lower panel for DZ pairs.

5.3 Physical activity

Among the 89 interviewed twin pairs who had answered all the physical activity questions, 42 pairs (5 monozygotic, 4 female and 1 male, and 37 dizygotic, 17 female and 20 male) were consistently discordant for physical activity at all the 5-year time points (years 1980, 1985, 1990, 1995, 2000 and 2005) across the 30-year period (Figure 6). 47 pairs (12 monozygotic, 7 female and 5 male, and 35 dizygotic, 21 female and 14 male) were not consistently discordant. Dizygotic twin pairs seemed to remain discordant for longer and the discordances appear greater when compared with those of the monozygotic pairs. The mean MET index (Table 3) from 1980 through 2005 was significantly higher in the active than inactive co-twins in all 89 twin pairs (mean MET difference 4.3 MET h/day, $p < 0.001$) as well as in the 42 consistently discordant pairs and 47 not consistently discordant pairs. Among 47 pairs, as seen in Figure 6C, the inactive co-twins increased and active co-twins decreased their, amount of activity during the follow-up.

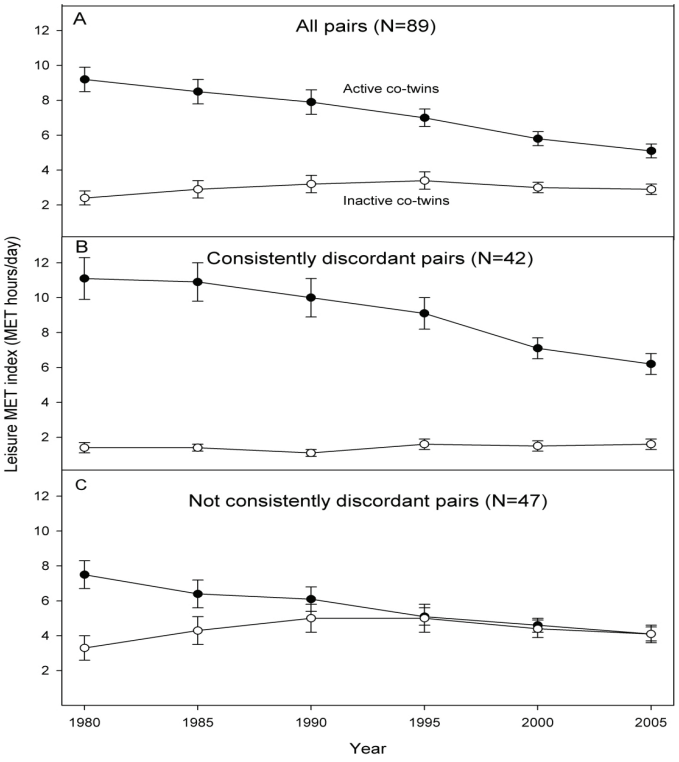

FIGURE 6 Leisure-time MET indices (mean±SE) in inactive and active members of the twin pairs from 1980 through 2005. Figures A and B show a significant difference ($p<0.001$) between inactive and active co-twins at each measurement, in C a difference is significant only in 1980 ($p<0.001$) and 1985 ($p<0.05$).

TABLE 3 Mean MET indices in 1980 – 2005 (MET hours/day) for all pairs, consistently discordant pairs and not consistently discordant pairs.[a,b]

	Inactive	**Active**	**Mean difference (95% CI)**	**T-test, P value**
All 89 pairs	3.0 ± 3.1	7.2 ± 4.4	4.27 (3.16 to 5.38)	< 0.001
Consistently discordant, 42 pairs	1.4 ± 1.2	9.1 ± 4.9	7.65 (6.20 to 9.10)	< 0.001
Not consistently discordant, 47 pairs	4.4 ± 3.6	5.6 ± 3.2	1.25 (0.15 to 2.34)	0.03

[a] Plus-minus values are means ±SD.
[b] Mean MET index 1980-2005 calculated from the shorter retrospective LTPA assessment.

5.4 Anthropometric measurements

An increase in weight over time was seen in both inactive and active co-twins (Table 4, Figure 7) in all subgroups. Among all 89 pairs, the active members gained 2.8 kg less weight during the 30-year follow-up than their inactive co-

twins (p=0.01). Trends for weight gain were similar for DZ (difference 2.1 kg, p=0.07), MZ (6.0 kg, p=0.06) and male (5.2 kg, p=0.002) pairs, but not for female pairs (0.90, p=0.55). Among the 42 consistently discordant twin pairs, the active co-twins gained significantly less weight (5.4 kg, 95% confidence interval 1.95 to 8.87 kg, p=0.003) during the 30-year follow-up when compared with their inactive co-twins, with similar trends in the DZ (4.4 kg, p=0.02), MZ (12.6 kg, p=0.11), male (6.6 kg, p=0.01) and female (4.2 kg, p=0.11) pairs. However, the results for the 47 not consistently discordant pairs did not show any differences between inactive and active co-twins in 2005.

TABLE 4 Anthropometric measurements for 1975, 1981 and 2005 for all 89 pairs, 42 pairs consistently discordant for LTPA and 47 not consistently discordant for LTPA.[a]

Variable	Inactive	Active	Mean difference (95% CI)	Paired T-test, P value
All 89 pairs				
Height 75 (cm)	169.3 ± 8.5	169.5 ± 8.5	0.24	0.67
Weight 75 (kg)	63.5 ± 12.5	63.9 ± 10.5	0.39	0.72
Weight 81 (kg)	67.1 ± 13.7	65.2 ± 10.7	-1.99	0.10
Weight 05 (kg)	74.7 ± 15.1	72.3 ± 11.7	-2.43	0.09
Change in weight 1975 - 1981 (kg)	3.6 ± 4.7	1.3 ± 3.8	- 2.38	<0.001
Change in weight 1981 - 2005 (kg)	7.6 ± 7.3	7.1 ± 5.9	- 0.44	0.64
Change in weight 1975 - 2005 (kg)	11.2 ± 9.0	8.4 ± 7.1	-2.82	0.01
BMI 75 (kg/m^2)	22.0 ± 2.9	22.2 ± 2.3	0.14	0.66
BMI 81 (kg/m^2)	23.3 ± 3.4	22.6 ± 2.4	-0.73	0.05
BMI 05 (kg/m^2)	25.9 ± 3.9	25.1 ± 3.0	-0.80	0.08
Waist circumference (cm)	90.7 ± 12.1	86.7 ± 10.2	-4.05	0.003
Consistently discordant pairs (42 pairs)				
Height 75 (cm)	169.7 ± 8.5	169.3 ± 8.5	-0.39	0.67
Weight 75 (kg)	65.9 ± 12.9	64.4 ± 10.1	-1.50	0.38
Weight 81 (kg)	69.9 ± 14.6	65.0 ± 9.7	-4.86	0.02
Weight 05 (kg)	78.9 ± 15.4	72.0 ± 11.8	-6.91	0.002
Change in weight 1975 - 1981 (kg)	4.0 ± 5.4	0.6 ± 4.2	-3.36	0.002
Change in weight 1981 - 2005 (kg)	9.0 ± 8.5	7.0 ± 6.6	-2.05	0.17
Change in weight 1975 - 2005 (kg)	13.0 ± 10.1	7.6 ± 7.8	-5.41	0.003
BMI 75 (kg/m^2)	22.7 ± 2.9	22.4 ± 2.2	-0.30	0.53
BMI 81 (kg/m^2)	24.2 ± 3.6	22.6 ± 2.2	-1.57	0.01
BMI 05 (kg/m^2)	27.1 ± 4.0	25.1 ± 3.4	-2.05	0.006
Waist circumference (cm)	94.2 ± 12.4	85.8 ± 10.2	-8.37	<0.001
Not consistently discordant pairs (47 pairs)				
Height 75 (cm)	168.9 ± 8.6	169.7 ± 8.6	0.79	0.25
Weight 75 (kg)	61.4 ± 11.8	63.5 ± 10.9	2.09	0.13
Weight 81 (kg)	64.7 ± 12.4	65.3 ± 11.67	0.57	0.68
Weight 05 (kg)	71.0 ± 13.9	72.6 ± 11.6	1.58	0.35
Change in weight 1975 - 1981 (kg)	3.3 ± 3.9	1.8 ± 3.5	-1.51	0.02
Change in weight 1981 - 2005 (kg)	6.3 ± 5.8	7.3 ± 5.4	1.00	0.40
Change in weight 1975 - 2005 (kg)	9.6 ± 7.6	9.1 ± 6.5	-0.51	0.70
BMI 75 (kg/m^2)	21.4 ± 2.8	21.9 ± 2.3	0.53	0.23
BMI 81 (kg/m^2)	22.6 ± 3.1	22.6 ± 2.6	0.01	0.99
BMI 05 (kg/m^2)	24.8 ± 3.5	25.1 ± 2.7	0.32	0.56
Waist circumference (cm)	87.7 ± 11.1	87.4 ± 10.2	-0.28	0.84

[a] Plus-minus values are means ±SD. CI denotes confidence interval.

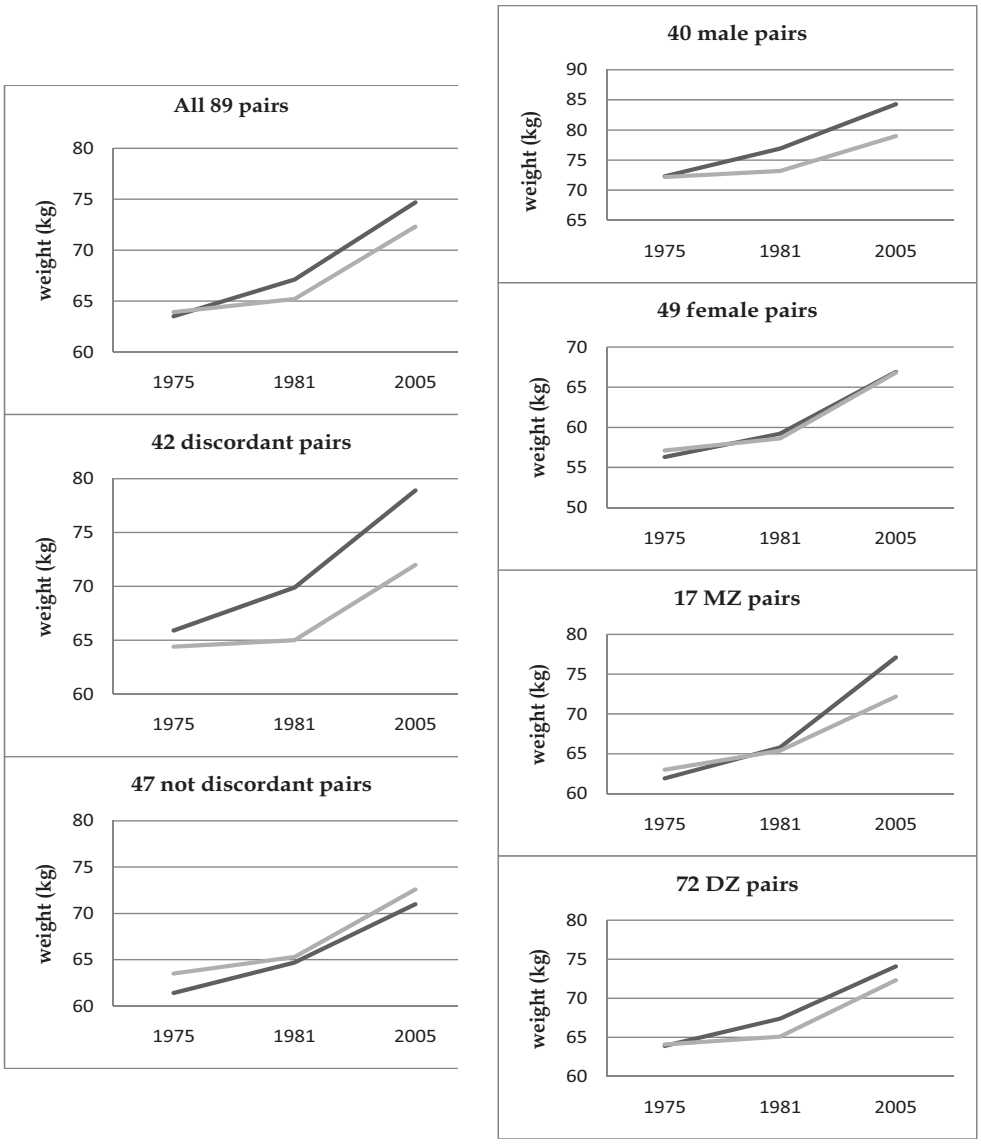

FIGURE 7 Weight change from 1975 through 2005 for inactive (dark line) and active (light grey) for all 89 pairs, 42 consistently discordant pairs, 47 not consistently discordant pairs and for 40 male, 49 female, 17 MZ and 72 DZ pairs.

Inactive co-twins had a higher risk for major weight gain (≥15 kg) during the follow-up (OR 2.18, 95% CI 1.07 - 4.45, p=0.03), but this was mainly seen in men (OR 7.5, 95% CI 1.72 - 32.8, p=0.007) as no significant difference was observed in women. Inactive co-twins also had an increased but statistically non-significant risk for obesity (BMI ≥30) in 2005 (OR 2.75, 95% CI 0.88 - 8.64, p=0.08) compared

to their active co-twins. Among the 42 consistently discordant pairs, the inactive co-twins had an even higher risk for major weight gain (OR 4.33, 95% CI 1.24 - 15.21, p=0.02) and obesity in 2005 (OR 4.5, 95% CI 0.97 - 20.8, p=0.054) than their active co-twins. Among all 89 pairs, active co-twins were more likely to maintain their weight (max 2 kg increase between 1975 and 2005) during the follow-up (OR 0.38, 95% CI 0.15 - 0.96, p=0.04) compared to their inactive co-twins. Altogether, 23 active (meanMET for 30 -years 8.9 MET h/day) and 13 inactive (3.4 MET h/day) co-twins maintained their weight. Weight maintenance was even more clearly seen among the 42 consistently discordant pairs, as OR was 0.1 (95% CI 0.013 - 0.78, p=0.028). However, no pairwise difference was seen in weight gain or weight maintenance among the 47 not consistently discordant pairs.

Among all 89 pairs, waist circumference was 4.1 cm smaller (1.42 to 6.67, p=0.003) in the active than inactive co-twins at follow-up. Again, the trends were similar for DZ (difference 3.6 cm, p=0.009), MZ (5.9 cm, p=0.16), male (5.3 cm, p=0.006) and female (3.0 cm, p=0.12) pairs. Among the 42 consistently discordant twin pairs, waist circumference was 8.4 cm smaller (p<0.001) among the active co-twins (Figure 8) with similar trends in DZ (7.8 cm, p<0.001), MZ (12.6 cm, p=0.32), male (9.8 cm) and female (7.1 cm) pairs. However, no pairwise difference was seen in waist circumference among the not consistently discordant pairs.

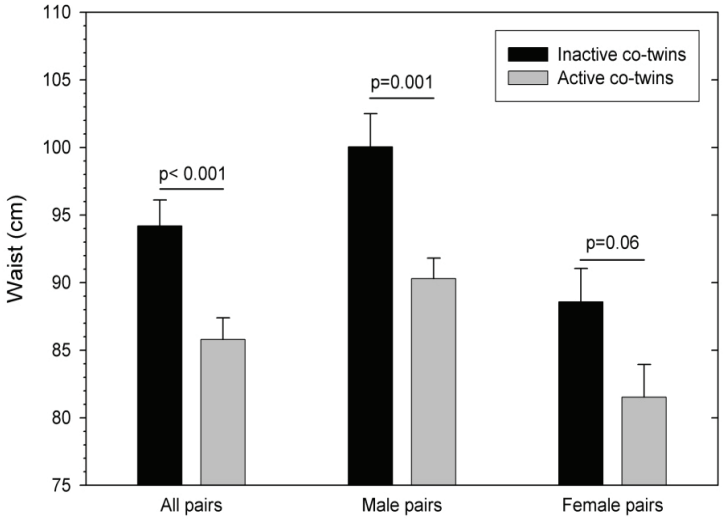

FIGURE 8 Waist circumference (mean±SE) difference for 42 consistently discordant pairs, for 21 consistently discordant male pairs, and for 21 consistently discordant female pairs.

5.5 Type 2 diabetes

In study I, the type 2 diabetes reimbursed medication analysis among the 146 pairs showed that 8 inactive and 6 active co-twins had started medication for diabetes (8 inactive and 3 active DZ co-twins) during the follow-up period. No statistically significant difference in the risk for type 2 diabetes was observed in the multivariate analysis among all subjects (HR 0.72, 95% CI 0.24 – 2.14), but among the dizygotic pairs the active co-twins had decreased risk, with a hazard ratio of 0.34 (95% CI 0.09 – 1.34), although this was not statistically significant.

The results of the telephone interview study (study II) among 95 pairs showed that the active co-twins had a decreased risk for the combined type 2 diabetes variable (including type 2 diabetes and prediabetes), with an odds ratio of 0.09 (95% CI 0.01 – 0.70). The results were similar for the DZ pairs (OR=0.1, 95 % CI 0.01 – 0.78), but no difference was seen among the MZ pairs (OR=1). Although, statistically non-significant, the active twins showed a lower prevalence of type 2 diabetes: 7 inactive and 3 active co-twins had type 2 diabetes (OR 0.2, 95% CI 0.02 – 1.71).

When type 2 diabetes was studied further in the whole cohort (study IV), a total of 535 000 person-years were accumulated during the follow-up period from 1976 to 2004. During this period, 1 082 new type 2 diabetes cases occurred among the 20 487 subjects. The hazard ratios between the different MET quintiles for all, men, women and baseline healthy individuals are presented in table 5 and the same graphically in Figure 9a. The individual analyses among all the participants showed that the subjects in physical activity quintiles III – V had significantly lower age- and sex-adjusted hazard ratios during the follow-up compared to the sedentary individuals in quintile I. Analysis of healthy subjects with no known medical constraints on physical activity (n = 13 291 individuals) also showed similar hazard ratios. After adjusting the model among all individuals for work-related physical activity, social class, smoking and alcohol use (all separately in the model), the hazard ratios remained similar. When the model was adjusted for BMI (Table 5, Figure 9b), the differences were no longer significant. There was no difference between individuals in risk by zygosity.

TABLE 5 Risk for type 2 diabetes during 1976-2004 for individual analyses according to leisure-time physical activity (MET quintiles)[a] in 1975. Sedentary (< 0.59 met h/day) individuals are reference group.

	HR (95% CI) + age and sex adj.	P value	HR (95% CI) + age, sex and BMI75 adj.	P value
All individuals				
MET Quintile II	0.91 (0.76 – 1.10)	0.32	0.99 (0.81 – 1.21)	0.90
MET Quintile III	0.73 (0.60 – 0.89)	0.001	0.88 (0.72 – 1.08)	0.23
MET Quintile IV	0.78 (0.65 – 0.94)	0.010	0.97 (0.80 – 1.19)	0.80
MET Quintile V	0.74 (0.61 – 0.90)	0.002	0.95 (0.77 – 1.17)	0.61
Men				
MET Quintile II	1.16 (0.89 – 1.51)	0.28	1.27 (0.94 – 1.72)	0.12
MET Quintile III	0.86 (0.66 – 1.14)	0.29	1.02 (0.75 – 1.38)	0.91
MET Quintile IV	0.95 (0.72 – 1.24)	0.68	1.17 (0.86 – 1.58)	0.32
MET Quintile V	0.83 (0.63 – 1.09)	0.19	1.07 (0.78 – 1.46)	0.67
Women				
MET Quintile II	0.73 (0.56 – 0.96)	0.022	0.79 (0.59 – 1.05)	0.098
MET Quintile III	0.66 (0.50 – 0.86)	0.003	0.82 (0.62 – 1.08)	0.15
MET Quintile IV	0.68 (0.53 – 0.89)	0.004	0.86 (0.65 – 1.13)	0.28
MET Quintile V	0.71 (0.53 – 0.94)	0.017	0.91 (0.68 – 1.21)	0.51
Healthy in 1981				
MET Quintile II	0.84 (0.62 – 1.12)	0.24	0.83 (0.61 – 1.13)	0.24
MET Quintile III	0.66 (0.49 – 0.89)	0.007	0.78 (0.57 – 1.06)	0.12
MET Quintile IV	0.77 (0.57 – 1.02)	0.07	0.92 (0.68 – 1.24)	0.59
MET Quintile V	0.68 (0.50 – 0.93)	0.015	0.88 (0.64 – 1.21)	0.43

[a] For cut-off points of MET quintiles see method section or Figure 9

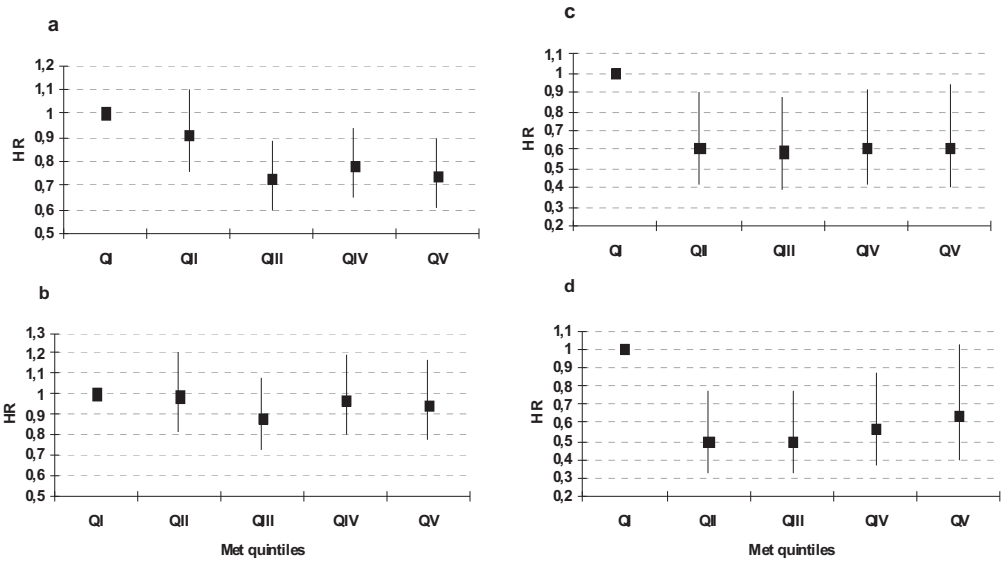

FIGURE 9 Hazard ratios and 95% confident intervals for different MET quintiles for all subjects: a) individual analyses, b) individual analyses adjusted for age, sex and BMI, c) pairwise analyses and d) pairwise analyses adjusted for BMI. Quintile I: < 0.59 MET hours per day, Quintile II: 0.59 to < 1.30, Quintile III: 1.30 to < 2.50, Quintile IV: 2.50 to < 4.50 and Quintile V: > 4.50.

The pairwise analysis showed (Table 6, Figure 9c and d) that the subjects in physical activity quintiles II to V were significantly less likely to have type 2 diabetes (QII: HR 0.61, 95% CI 0.41–0.90; QIII: 0.59, 0.39–0.87; QIV: 0.61 0.41–0.91; QV: 0.61, 0.40–0.94) during the follow-up than their co-twins in the sedentary quintile. This analysis takes into account all pairs discordant for physical activity across all the quintiles. The hazard ratios were reduced even further when the model was adjusted for BMI, except that for marginally not significant quintile V. Similar results were found for both zygosities, with the MZ twins showing the lowest hazard ratios. Although numerically the lowest, the hazard ratios for the MZ pairs were not all statistically significant as the MZ twins also had the lowest number of informative discordant pairs. Again, the results of the subgroup analysis of the healthy subjects with no known constraints on physical activity showed similar hazard ratios. The BMI-adjusted hazard ratios for type 2 diabetes remained statistically significant in all quintiles.

TABLE 6 Risk for type 2 diabetes during 1976-2004 for pairwise analyses according to LTPA (MET quintiles)[a] in 1975. Inactive (< 0.59 MET h/day) co-twins are reference group.

	Hazard ratios (95% CI)	P Value	Hazard ratios (95% CI) adjusted for baseline BMI	P Value
All pairs				
MET Quintile II	0.61 (0.41 – 0.90)	0.012	0.50 (0.32 – 0.78)	0.002
MET Quintile III	0.59 (0.39 – 0.87)	0.008	0.50 (0.32 – 0.78)	0.002
MET Quintile IV	0.61 (0.41 – 0.91)	0.014	0.57 (0.37 – 0.88)	0.012
MET Quintile V	0.61 (0.40 – 0.94)	0.025	0.64 (0.40 – 1.02)	0.06
Monozygotic				
MET Quintile II	0.33 (0.13 – 0.87)	0.025	0.32 (0.12 – 0.88)	0.027
MET Quintile III	0.56 (0.23 – 1.35)	0.20	0.49 (0.19 – 1.25)	0.13
MET Quintile IV	0.67 (0.29 – 1.56)	0.35	0.63 (0.26 – 1.56)	0.32
MET Quintile V	0.44 (0.18 – 1.04)	0.06	0.49 (0.20 – 1.22)	0.13
Dizygotic				
MET Quintile II	0.69 (0.45 – 1.06)	0.09	0.56 (0.34 – 0.92)	0.023
MET Quintile III	0.59 (0.38 – 0.92)	0.02	0.50 (0.30 – 0.83)	0.008
MET Quintile IV	0.59 (0.38 – 0.93)	0.023	0.56 (0.33 – 0.93)	0.024
MET Quintile V	0.67 (0.41 – 1.12)	0.13	0.70 (0.40 – 1.23)	0.21
Healthy in 1981				
MET Quintile II	0.47 (0.22 – 1.02)	0.055	0.37 (0.16 – 0.86)	0.021
MET Quintile III	0.35 (0.16 – 0.76)	0.008	0.34 (0.15 – 0.81)	0.014
MET Quintile IV	0.45 (0.21 – 0.96)	0.038	0.41 (0.17 – 0.949	0.035
MET Quintile V	0.26 (0.11 – 0.61)	0.002	0.32 (0.13 – 0.80)	0.015

a For cut-off points of MET quintiles see method section or figure 9

Of all the twin pairs, 1 919 pairs were discordant for physical activity when sedentariness (quintile I <0.59 MET h/d) was compared with any activity category (combined quintiles II-V) and 809 pairs were discordant for type 2 diabetes. Of these, 146 pairs were discordant for both baseline physical activity and fol-

low-up type 2 diabetes. Of these 146 pairs, among 85 pairs the sedentary co-twin at baseline was diagnosed with diabetes during the follow-up, while the active co-twin remained healthy, and among 61 pairs the converse was true. Among the MZ pairs the corresponding numbers were 21 and 10.

Further pairwise analyses showed that the BMI-adjusted hazard ratio (0.54; 95% CI 0.37-0.78) was lower in the members of the twin pairs who were physically active (combined quintiles II-V: >0.59 MET h/d) compared to their inactive (quintile I: <0.59 MET h/d) co-twins (Figure 10). The survival curves are shown in Figure 11. The results of the BMI-adjusted pairwise analyses were significant for all the analysed subgroups; i.e. men (HR 0.49; 95% CI 0.27 – 0.87), women (HR 0.59; 95% CI 0.36 – 0.96), DZ (HR 0.56; 95% CI 0.37 – 0.86) and healthy (HR 0.36; 95% CI 0.17 – 0.76), except the MZ pairs were marginally non-significant. However, the MZ pairs showed a similar or even lower hazard ratio (HR 0.49; 95% CI 0.23 – 1.04) than the other groups.

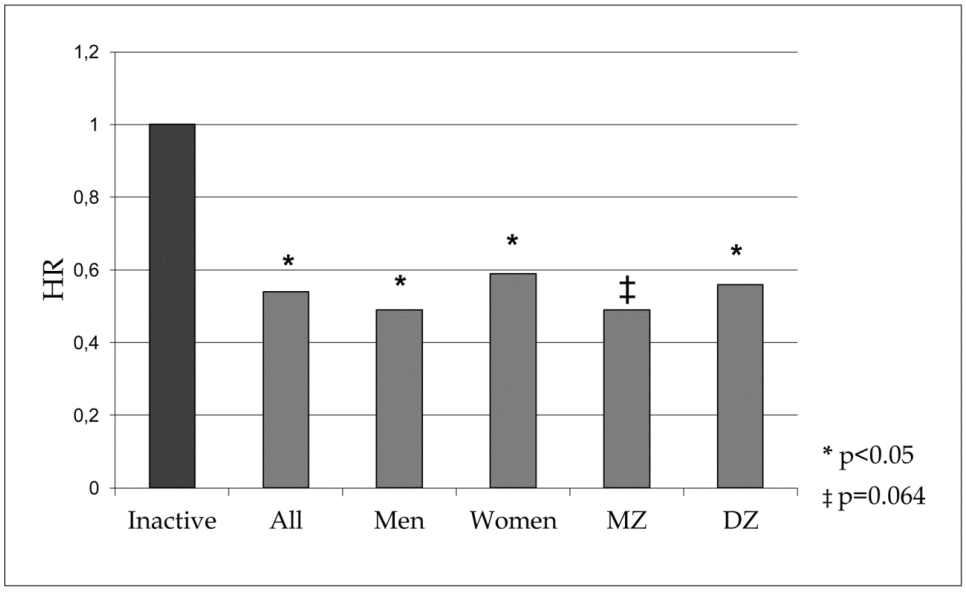

FIGURE 10 Hazard ratios from pairwise analyses for active (> 0.59 MET h/day) twins as compared to inactive (≤ 0.59 MET h/day) twins for all, male, female, MZ and DZ pairs.

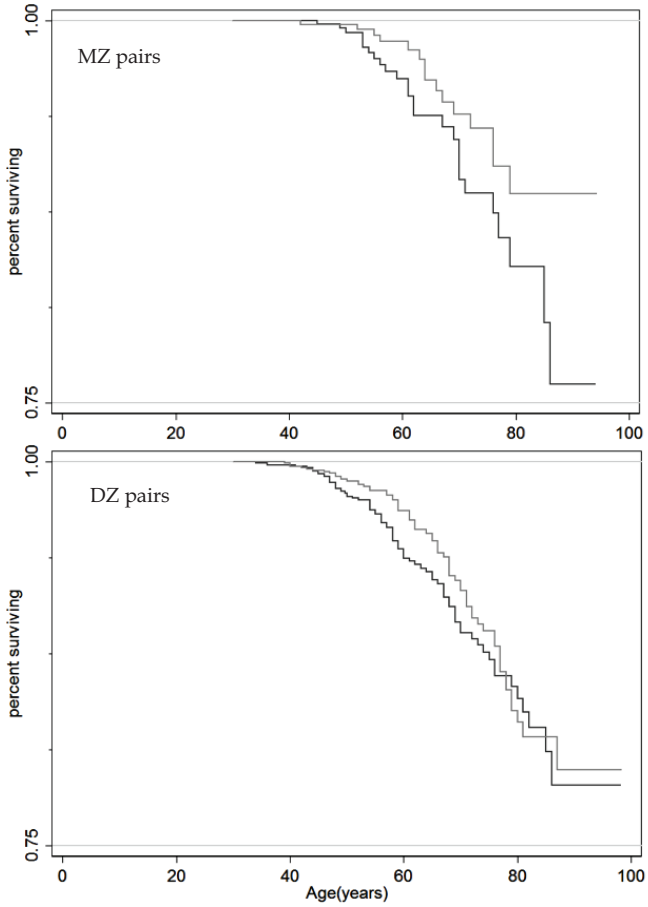

FIGURE 11 Kaplan-Meier survival curves for type 2 diabetes incidence for inactive (black) and active (gray) co-twins. Upper panel for MZ and lower panel for DZ pairs.

5.6 Other conditions and health-related measurements

The reimbursed medication analyses showed that among the 146 pairs, 23 inactive and 20 active co-twins (19 inactive and 14 active DZ co-twins) had at least one of the studied reimbursed medications (diabetes, hypertension and CHD). Among the individual medication groups, 18 inactive and 12 active co-twins (16 inactive and 8 active DZ co-twins) had medication for hypertension and 7 physically inactive and 6 active co-twins (5 inactive and 5 active DZ co-twins) had medication for coronary heart disease. The reimbursed medication analyses showed non-significant but slightly decreased hazard ratios for the active vs. inactive co-twins. Among the DZ pairs, the active co-twins had lower risk for hypertension medication during the follow-up compared to their active co-

twins (HR=0.46, 95% CI 0.21 – 0.996): when adjusted for work-related physical activity HR was 0.45 (95% CI 0.21 - 0.98). No differences were seen within MZ pairs.

The results for physician-diagnosed diseases between inactive and active co-twins among 95 pairs are shown in Table 7. Among the monozygotic twin pairs the active co-twins had a reduced risk for having at least 2 chronic diseases, (with the exception of hypertension): 1 active MZ and 7 inactive MZ co-twins had 2 or more chronic diseases (OR=0.14, p=0.031), although the difference was not significant when MZ and DZ pairs were taken together (OR=0.54, p=0.19). No differences were seen in the cumulative incidence of diagnosed hypertension between inactive and active co-twins when studying new cases of hypertension since 1975. Overall, the active co-twins had a decreased risk for elevated blood pressure (OR=0.46, p=0.039; DZ OR=0.44, 95% CI 0.19 – 1.02; MZ OR=0.5, 95% CI 0.09 – 2.73). Although statistically non-significant, the active twins showed a lower prevalence of any pulmonary disease and of other physician-diagnosed diseases. No differences between inactive and active co-twins were seen in stroke, intermittent claudication, cardiac failure, COPD, chronic bronchitis and gastric ulcer (results not shown).

Some differences were observed in selected musculoskeletal problems between inactive and active co-twins (Table 7). The active co-twins had a marginally non-significant increased risk for at least one sports-related injury (OR=1.9, p=0.051) compared to their inactive co-twins, the finding being more salient in DZ pairs (OR=2.2, 95% CI 1.07 - 4.45) than MZ pairs (OR=1, 95% CI 0.25 – 4.0). For individual sports-related injuries the active co-twins again had a statistically non-significant increased risk for getting an ankle ligament injury (OR=1.8, p=0.14; DZ OR=2.17, 95% CI 0.82 – 5.70; MZ OR=1.3, 95% CI 0.34 – 4.66). Non-significant differences were seen in other than knee or hip osteoarthritis and sciatica between inactive and active co-twins, but other conditions did not differ (results not shown for knee ligament injury, tension neck and hip and knee osteoarthritis).

Active co-twins had tendency for fewer self-reported physician described medications than their inactive co-twins as shown in Table 6. Active co-twins had a non-significantly decreased risk for 2 or more physician-prescribed medication than their inactive co-twins (OR 0.54, 95% CI 0.28 – 1.06) and for psychiatric medications (OR 0.22, 95% CI 0.05 – 1.03). No other differences were seen in self-reported medication use between inactive and active co-twins.

Among 95 twin pairs, the inactive co-twins had a tendency towards dyspnea at follow-up when compared with their active co-twins (p=0.067), more so in DZ (p=0.10) than in MZ pairs (p=1.00). The active co-twins remained more satisfied with their life at the end of the follow-up: mean life satisfaction (LS) was 6.5 for active and 7.1 for the inactive co-twins (paired t-test p=0.047) among 95 pairs. Rather similar results were obtained for dizygotic (6.4 vs. 6.9, p=0.12) and monozygotic (6.8 vs. 7.9, p=0.24) pairs. Out of 95 pairs, 23 inactive and 13 active co-twins had been hospitalised within the last 3 years prior to the interview for a total of 171 and 95 nights, respectively. On average, the inactive co-

twins spent 1.8 nights and the active co-twins 1 night (paired t-test p=0.16) in hospital during that period. The active co-twins had a non-significant decreased risk for having been hospitalised (OR=0.47, p=0.065); this risk was rather similar for both DZ pairs (OR=0.54, 95% CI 0.22 - 1.35) and MZ pairs (OR=0.33, 95% CI 0.07 – 1.65).

TABLE 7 Other chronic diseases measured either as self-reported diseases or medication use in 2005 (95 pairs). Inactive co-twins serve as reference group.

Disease	**Inactive N (%)**	**Active N (%)**	**OR (95 % CI)**
Cardiovascular disease [a]	5 (5.3%)	7 (7.4%)	1.67 (0.40 – 6.97)
CHD including MI	4 (4.2%)	5 (5.3%)	1.5 (0.25 – 8.98)
Reported BP medication in 2005 [b]	18 (21.4%)	19 (22.6%)	1.09 (0.48 – 2.47)
Elevated BP or BP medication in 2005 [b]	43 (51.2%)	31 (36.9%)	0.46 (0.22 – 0.96)
Pulmonary disease [a]	8 (8.4%)	3 (3.2%)	0.33 (0.09 – 1.23)
Asthma	7 (7.4%)	2 (2.1%)	0.29 (0.06 – 1.38)
Depression	9 (9.5%)	9 (9.5%)	1
Rheumatoid arthritis	1 (1.1%)	4 (4.2%)	4 (0.45 – 35.79)
Osteoarthritis, at least one: hip, knee or other	22 (23.2%)	25 (26.3%)	1.21 (0.6 – 2.46)
Any other osteoarthritis [c]	10 (10.5%)	17 (17.9%)	2.17 (0.82 – 5.70)
Sciatica	29 (30.5%)	22 (23.2%)	0.68 (0.35 - 1.31)
Injuries typical for athletes (acute or stress)	29 (30.5%)	42 (44.2%)	1.87 (0.98 – 3.49)
Acute injuries	24 (25.3%)	31 (32.6%)	1.44 (0.76 – 2.72
Tendon rupture (achilles or other)	6 (6.3%)	5 (5.3%)	0.8 (0.22 – 2.98)
Knee or ankle injury, at least one	20 (21.1%)	30 (31.6%)	1.77 (0.90 – 3.48)
Knee meniscus	5 (5.3%)	8 (8.4%)	1.75 (0.51 – 5.98)
Ankle ligament	13 (13.7%)	21 (22.1%)	1.8 (0.83 – 3.90)
Stress injury/ Tendonitis (achilles or other)	10 (10.5%)	17 (17.9%)	1.88 (0.8 – 4.42)
Achilles tendon inflammation	4 (4.2%)	6 (6.3%)	1.5 (0.42 - 5.321)
Other tendon inflammation	7 (7.4%)	12 (12.6%)	1.83 (0.68 - 4.96)
Other physician diagnosed chronic disease [d]	30 (31.6%)	21 (22.1%)	0.57 (0.28 – 1.16)
Self-reported medication use			
At least one medication	57 (60%)	52 (54.7%)	0.80 (0.44 – 1.44)
At least two medications	43 (45.3%)	32 (33.7%)	0.54 (0.28 – 1.06)
At least one med other than BP med	53 (55.8%)	43 (45.3%)	0.60 (0.32 – 1.14)
Cholesterol medication	15 (15.8%)	15 (15.8%)	1
BP medication	24 (25.3%)	24 (25.3%)	1
Respiratory medication (mainly asthma)	9 (9.5%)	5 (5.3%)	0.50 (0.15 – 1.66)
Female hormonal medication	15 (15.8%)	11 (11.6%)	0.60 (0.22 – 1.65)
Psychiatric medication	9 (9.5%)	2 (2.1%)	0.22 (0.05 – 1.03)
Neurological medication	4 (4.2%)	2 (2.1%)	0.50 (0.09 – 2.73)
Metabolic and endocrine medication	22 (23.2%)	21 (22.1%)	0.84 (0.40 – 2.08)

[a] Includes different diseases

[b] New cases since 1975. If a person had reported hypertension on the questionnaire or was found to have medication for hypertension in 1975 they were excluded from the analyses; 84 pairs were included in the analyses.

[c] Other osteoarthritis includes osteoarthritis in the hand (15 individuals), shoulder (6), neck (6), back (4), toes (3) and wrists (1).

[d] Includes diseases such as cancer (8 individuals - breast cancer 4), different allergies (7), osteoporosis (5), thyroid gland problem (5), eye problems (5 - glaucoma 3), migraine (3).

6 DISCUSSION

The present study investigated the protective effect of baseline leisure-time physical activity on weight gain and health decline, controlled for genes and childhood environment, in twins over a more than 20-year follow-up. Specifically, the aim was to find out whether persistent leisure-time physical activity protects against increases in weight, chronic diseases, metabolic syndrome-related conditions or mortality, using a co-twin control design.

In these twins, baseline leisure-time physical activity was associated with reduced risk of mortality, type 2 diabetes, elevated or high blood pressure and major weight gain. The co-twins consistently active for thirty years had smaller waist circumference, reduced weight gain and were more likely to have maintained their baseline weight at follow-up compared to their inactive co-twins. The active co-twins also had better life satisfaction and a tendency towards lower risk for asthma, sciatica, other physician-diagnosed diseases and lower medication use, especially psychiatric medications. However, the active co-twins had a tendency towards sustaining more injuries that are typical for athletes. Some of the results were more clearly seen among DZ pairs than MZ pairs, showing that genetics might explain some of the association. However, decreased risk for type 2 diabetes was significantly reduced among the larger cohort of active MZ co-twins, indicating the independent effect of physical activity, which was also independent of baseline BMI.

One mechanism accounting for some of the differences between the inactive and active co-twins could be epigenetics, as physical activity or inactivity might cause a different rate of transcription or translation of genes, which could then lead to changes in clinical phenotype (Franks & Ling 2010). For example, a study by Leskinen et al. (2010) found that among a smaller group twin pairs discordant for leisure-time physical activity for 30 -years, the active co-twins had up-regulated gene expression in the muscle tissue samples for the central pathways related to energy metabolism, including oxidative phosphorylation, lipid metabolism and supportive metabolic pathways.

6.1 Mortality

Premature all-cause mortality assessment showed that the inactive co-twins were more likely to die earlier than their active co-twins when childhood family environment was controlled for. This finding is in accordance with earlier studies, where physical activity has been associated with reduced all-cause or coronary heart disease mortality (Morris et al. 1980, Paffenbarger & Hyde 1984, Leon et al. 1987, Lee et al. 1995, Kujala et al. 1998, Carlsson et al. 2007). A study similar to the present study, which partially included the same study population, was conducted by Kujala et al. in 2002: however, the present study concentrated on a smaller, but more discordant group of twins over a longer follow-up period. The main difference between the studies was a stricter determination of leisure-time physical activity between discordant pairs, where both intensity and volume of leisure-time physical activity were taken into account for 6 - years at baseline. The difference in discordance in leisure-time physical activity in the present study was clearer than in the previous study. New cases of death had also occurred since the previous study. Both analyses showed an association between high physical activity and reduced mortality in DZ twin pairs but not MZ pairs (Kujala et al. 2002), although the present study used survival analyses methods (hazard ratios) for pairwise analyses which were not used in the previous study. Recently, many systematic reviews and meta-analyses have also confirmed the existence of the relationship between physical activity and reduced all-cause mortality (Nocon et al. 2008, Physical Activity Guidelines Advisory Committee 2008, Lollgen et al. 2009, Woodcock et al. 2011); however, the present study indicates that there is a possible genetic pleiotropy underlying physical activity and mortality (Kujala 2011). A Swedish twin study by Carlsson et al. (2007) found a difference in mortality among activity-discordant MZ pairs, but their study had limitations as they did not exclude subjects with chronic diseases at baseline (Carlsson et al. 2007, Rankinen & Bouchard 2007). Although we had only a small number of MZ pairs, the study shows that it is important to investigate the genes which are associated with both physical activity and the underlying causes of diseases.

Some slightly older review studies have estimated that high levels of physical activity are needed and energy expenditure of at least 1000 kcal/week is likely to decrease mortality rates (Lee & Skerrett 2001, Oguma et al. 2002). A recent review by Woodcock et al. (2011) does not totally concur with this, as the review showed that the greatest benefits from physical activity occur when moving from sedentary behaviour to low levels of activity, but that when activity levels are increased further only small additional benefits are achieved. Although both earlier reviews (Lee & Skerrett 2001, Oguma et al. 2002) acknowledged that a lower volume of physical activity could also have beneficial effects on all-cause mortality, this was only a speculation. The present study is more in line with the older reviews and findings in a favour of a higher activity level, as the active co-twins exercised for at least 2 MET hours/day in 1975 and 1981 (on

average 4.59 MET hours/day in 1975 and 5.80 MET hours/day in 1981) and the intensity of activity was vigorous in both baseline years. This indicates that the activity level of these co-twins was relatively high during this 6-year period.

As seen in this study, physical activity continued for 30 years for a subgroup of 42 active co-twins. This indicates that adulthood physical activity habits are often maintained for long time, and thus it is possible that the long continuation of physical activity habits partly explains the difference in mortality. Incipient disease can reduce the ability to exercise and thus attenuate within-pair differences in physical activity over time. However, according to this study it is not possible to confirm that physical activity is the major reason for this mortality difference as no such difference was found for the MZ pairs, and therefore the possibility of genetic selection towards premature mortality remains. On the other hand, the number of MZ pairs was very small.

The mortality difference could also be partly due to differences in disease incidence between inactive and active co-twins during the follow-up. The use of type 2 diabetes, hypertension, and coronary heart disease medication was studied among the same cohort as mortality. In particular, the use of hypertension medication was higher among the inactive co-twins. It is known that physical inactivity is a risk factor for hypertension (Paffenbarger & Lee 1997, Barengo et al. 2005) and that increased blood pressure is a predictor of mortality (Selmer 1992, Lewington et al. 2002). Among the 16 inactive co-twins who died by the end of 2004, the causes of death were cancer (7), myocardial infarction (3), suicide (2), cerebrovascular disease (1), disease of respiratory system (1), alcohol-related disease (1) and accidental fall (1). Therefore, the increased prevalence of T2D and high blood pressure alone do not explain the increased mortality of the physically inactive co-twins. However, a number of these causes of death are associated with a physically inactive lifestyle, such as some cancers (Physical Activity Guidelines Advisory Committee 2008), CVD (Morris et al. 1980, Paffenbarger & Hyde 1984, Physical Activity Guidelines Advisory Committee 2008), pulmonary disease (Kujala et al. 1996), alcohol-related problems (Korhonen et al. 2009) and accidental falls (Physical Activity Guidelines Advisory Committee 2008).

6.2 Anthropometric characteristics

This thesis shows that physical activity during adulthood is associated with decreased weight gain and with smaller waist circumference in twin pairs consistently discordant for leisure-time physical activity habits over 30 years. The trends were similar for both monozygotic and dizygotic twin pairs, and therefore the findings were most likely due to physical activity and not primarily influenced by genes or childhood environment. In this study, the subjects gained weight regardless of their baseline physical activity status. Similar weight gain trends have been observed in other longitudinal studies (Hankinson et al. 2010, Lee et al. 2010, Ekelund et al. 2011). In the present study, the ac-

tive co-twins gained less weight during the follow-up when compared with the inactive co-twins, especially those consistently active 30 years. This was not seen in the large study by Eckelund et al. (2011), where no difference was observed in annual weight change between inactive and active subjects. However, many other studies have found that physical activity slows down weight gain (Haapanen et al. 1997b, Droyvold et al. 2004, Hankinson et al. 2010, Lee et al. 2010), although these studies had shorter follow-ups, were based on analyses of unrelated individuals and the reduction in weight gain often depended on sex, age or baseline BMI. Hankinson et al. (2010) found that a high level of physical activity was associated with slower weight gain in women but less so in men. Interestingly, this was the opposite in the present study as a difference in weight gain was seen in men but not in women. In the present study, the active co-twins were more likely to maintain their weight (≤ 2 kg increase during 30 years) compared to the inactive co-twins. A study by Lee et al. (2010) found that women who successfully maintained normal weight (fewer than 2.3 kg weight gain over 13 years) averaged approximately 60 minutes a day of moderate-intensity activity throughout, which resembles that seen among subjects who maintained their weight in the present study, where the mean MET index for active weight maintainers for 30 years was 8.9 MET h/day. Hill and Wyatt (2005) proposed that physical activity is important for weight maintenance because of its impact on energy expenditure and effects on body composition through enhancing fat-free mass and increasing total fat oxidation.

Weight may increase once participation in physical activity is reduced, indicating the need to adjust the diet during periods of inactivity. This increase in weight was seen in the not consistently discordant pairs, whereas weight was significantly different between the inactive and active co-twins in 1981, although no longer in 2005. However, it is noteworthy that the weight increase from 1975 to 2005 tended to be lower in both of the not consistently discordant twin pair members (means 9.1 and 9.6 kg) than in the inactive members of the consistently discordant pairs (13.0 kg). Thus, on the basis of the non-paired analyses, and also in accordance with Schmitz et al. (2000), periodical participation in physical activity also seems to slow down long-term weight gain. The results of the truly prospective design (activity discordance 1975 – 1981 and weight gain 1981 - 2005), however, showed similar weight gain for both inactive and active co-twins ($p=0.64$) among all 89 pairs. This could be explained by converging amounts of physical activity, as most of the active co-twins reduced their amount of activity while the inactive co-twins slightly increased it or it remained the same. Although the prospective design did not show a difference in weight gain between inactive and active co-twins, the final cross-sectional design showed a significant difference in major weight gain (≥15 kg), weight maintenance (≤2 kg) and waist circumference at follow-up. This could partly be explained by reverse causality as a decrease in weight might lead to increased participation in physical activity or vice versa (Pietilainen et al. 2008). In our study even a small increase in exercise habits in the passive co-twins seemed to slow down weight gain, although persistent activity was more beneficial. The

correlation between pairwise differences in mean MET and in weight gain was significant (r=-0.28, p=0.008), reinforcing the dose-response relationship between long-term physical activity and a slow rate of weight gain.

As expected, in the present study waist circumference was clearly lower in the active compared with inactive co-twins at follow-up. This has also been found in other studies (Sternfeld et al. 2004, Ekelund et al. 2011). It has been shown that while increasing physical activity over time may not always reduce body weight, it often induces changes in body composition and body fat distribution, such as reductions in abdominal fat (Ross et al. 2004, Leskinen et al. 2009, Ekelund et al. 2011). A review in 2006 (Kay & Fiatarone Singh 2006) concluded that physical activity seems to have a beneficial influence on reductions in abdominal and visceral fat in overweight and obese subjects when using imaging techniques, although such changes were not necessarily observed in waist circumference. This indicates that the difference in fat in abdominal area might have been even larger in this study had more sensitive measurements been used. A ten-centimetre difference in waist circumference has high clinical significance, as this measurement has a strict association with other manifestations metabolic syndrome (Eckel et al. 2005). An increase in waist circumference of about ten centimetres has been shown to increase the risk of at least one other CVD risk factor (OR) by 4.6-fold in men and by 2.6-fold in women (Han et al. 1995) and type 2 diabetes (RR) by 5.0-fold in men (Wang et al. 2005). A twin study by Rönnemaa et al. (1997) found that among middle-aged identical twins discordant for obesity, only those who differed most in visceral fat level exhibited major alterations in insulin sensitivity and glucose tolerance.

The same genes may predict lower weight gain as well as make it easier for some individuals to exercise more. However, it was observed that whit continuous activity discordance, the trend was same for both zygosities in all our outcome measurements, although the number of monozygotic pairs did not permit strong inference. As the trend was the same in both monozygotic and dizygotic pairs and the difference in outcome was relatively high also whitin the monozygotic pairs (12.6 kg in weight gain and 12.6 cm in waist circumference), it is likely that the association is also present in genetically controlled conditions. The significant difference in the dizygotic pairs indicates that the association between physical activity and the outcome variables are not due to childhood environmental effects.

6.3 Type 2 diabetes

The reduced risk of type 2 diabetes was seen in several different analyses. The findings from the telephone interview data showed that in DZ, but not in MZ pairs, the active co-twins were more likely to have either type 2 diabetes or prediabetes (elevated blood glucose) compared to inactive co-twins (study II), suggesting a possible gene-physical activity interaction, such as documented for the FTO gene (Andreasen et al. 2008) for physical activity in BMI and glucose

metabolism parameters. In the 28-year prospective follow-up study (study IV) the association between leisure-time physical activity and reduced risk for type 2 diabetes was even more evident, as now the difference was observed in the pairwise analyses among both MZ and DZ pairs, and therefore genetic predisposition and childhood home environment were controlled for. It can therefore be assumed that physical activity independently protects against or at least slows down the development of type 2 diabetes, as many unmeasured confounding factors (both genetic and environmental) are controlled for by the co-twin control design. These findings are consistent with those of earlier population-based studies (Hu et al. 1999, Folsom et al. 2000, Hu et al. 2003, Jeon et al. 2007, Gill & Cooper 2008, Demakakos et al. 2010). However, this study had a longer follow-up time and was able to investigate the issue in genetically controlled subjects. No other similar longitudinal study on twins have been reported.

Because obesity is the major independent predictor of type 2 diabetes, the analyses should be adjusted for BMI. In many previous studies, adjustment for BMI has markedly attenuated the association between physical activity and risk for diabetes (Gill & Cooper 2008). In the present study adjustment for BMI was done in the whole cohort study. Baseline BMI adjustment removed the association in the individual analyses; however, the hazard ratios persisted at a similar level in pairwise analyses even after the BMI adjustments. This might be explained by the similar body mass indices of both individuals in each pair despite their difference in the amount of physical activity. However, use of BMI as a covariate may be problematic as it seems to be a concomitant variable. It can modify the physical activity – type 2 diabetes interaction in two ways. High BMI may lead to inactivity and then to type 2 diabetes or other way around: inactivity may lead to higher BMI and then to type 2 diabetes. It is also problematic as both high muscle mass and high fat mass contribute to high BMI. Also, high BMI does not indicate the place of fat mass in the body. This was shown in the present study among a smaller cohort, where despite the lack of statistically significant differences in BMI between the physically active and inactive members of twin pairs, physical activity reduced waist circumference. Another twin-study has shown similarly that leisure-time physical activity did not reduce BMI but reduced high-risk body fat (ectopic fat stores, liver fat and visceral fat) while maintaining skeletal muscle mass and function (Leskinen et al. 2009), leading to lowered type 2 diabetes risk independent of BMI. It is also possible that the results from the BMI-adjusted analyses are over–adjusted as physical activity may reduce type 2 diabetes by also independently reducing BMI.

Physical activity is an important modulator in diabetes risk for two main reasons, first, by preventing and reducing obesity (Gill & Cooper 2008) and, second, by independently delaying the initiation and progression of the dysregulation of glucose metabolism which ultimately leads to type 2 diabetes (LaMonte et al. 2005). Physical activity or exercise training has been proven to influence many mechanisms that enhance glucose tolerance and the insulin sen-

sitivity of skeletal muscles (Tresierras & Balady 2009) and therefore prevent type 2 diabetes. More specifically, physical activity or exercise training has been shown to reduce visceral fat (Leskinen et al. 2009), improve skeletal muscle insulin sensitivity (Zierath 2002, Wang et al. 2009) and increase the oxidative capacity of skeletal muscle, all factors which correlate with insulin sensitivity (Bruce et al. 2004), and also leads to increased/modified fat oxidation, most likely preventing lipid-mediated insulin resistance (Slentz et al. 2009).

The evidence to date on the dose-response relationship regarding the amount of physical activity needed to prevent type 2 diabetes remains conflicting (Physical Activity Guidelines Advisory Committee 2008). In this study any amount of physical activity seemed to reduce the risk for type 2 diabetes, as shown by the pairwise analyses. As little physical activity as 0.6 – 1.3 MET hours/day (4.2 – 9.1 MET hours/week) produced significant results compared to sedentariness, including among MZ pairs. 4 – 9 MET hours/week is equivalent to one to two hours of moderate intensity exercise weekly, which is less than the generally advised 150 minutes of moderate intensity exercise per week (Physical Activity Guidelines Advisory Committee 2008). Some evidence is now also available that even low intensity activity only once a week might be associated with reduced type 2 diabetes risk, especially in older adults (Demakakos et al. 2010). The hazard ratios in the pairwise analyses were similar across all the physical activity quintiles (II – V), indicating that total inactivity in particular is a predictor of future type 2 diabetes. Gill and Cooper (2008) also summarized that all levels of activity above a sedentary baseline appear to be beneficial in type 2 diabetes prevention. It has also been shown that sedentary a lifestyle, such as TV watching, is associated with a significantly increased risk of type 2 diabetes (Hu et al. 2003). However, in the present study it is possible that, during such a long follow-up, individuals who at baseline reported the highest amount of exercise reduced their exercise levels during follow-up, which may explain the flattening of the dose-response curve. The dose-response relation between physical activity and the occurrence of type 2 diabetes, and particularly the role of the intensity of activity, still remain unclear.

6.4 Other conditions

In the present longitudinal follow-up study on twins discordant for physical activity, the active co-twins reported less breathlessness than their inactive co-twins during the performance of specific daily tasks. This would be expected as the most direct effect of physical training is an increase in fitness, which is also known to reduce disease risk (Lakka et al. 1994, Blair et al. 2001). In the present study the active co-twins also had decreased risk for elevated blood pressure or hypertension. This was seen in two separate analyses, self-reports and reimbursed medication analyses among all and DZ pairs. The active co-twins reported greater life satisfaction at follow-up. They had been hospitalised less often and for shorter times compared to their inactive co-twins. The active co-

twins also showed a tendency towards fewer chronic diseases and less self-reported medication use, especially psychiatric medications. In contrast, the active co-twins showed a tendency towards having more sports-related injuries at follow-up than their inactive co-twins. As more inactive than active co-twins had before the follow-up, it would be expected that these results would be further emphasised if the whole cohort had remained alive.

In line with these results it has been well documented in previous studies and reviews that physical activity is effective in the primary and secondary prevention of several chronic diseases, such as cardiovascular disease, diabetes, cancer, hypertension, obesity, depression and osteoporosis (Warburton et al. 2006, Brown et al. 2007, Physical Activity Guidelines Advisory Committee 2008). Although, in this study, no difference was found in self-reported and physician-diagnosed depression between the inactive and active co-twins, the active co-twins reported greater life satisfaction and less physician-described psychiatric medications at the follow-up. This could be explained by the effect of physical activity on increased life satisfaction, and therefore possibly to a lower need for antidepressant. However, a review by Rejeski and Mihalko (2001) reported lack of consistency in the results of previous studies on physical activity and life satisfaction in older adults, with only some studies reporting positive effects. Lower use of psychiatric medication is supported by a recent meta-analysis which indicated that clinically depressed patients who had been randomised into the exercise treatment group had significant alleviation of depressive symptoms than those receiving the control treatment (Rethorst et al. 2009).

The active co-twins seemed to have more musculoskeletal problems and sports related injuries, as 30.5% of the inactive and 44.2 % of the active subjects reported having had at least one sports-related injury during the follow-up. Hootman et al. (2002) studied adults who participated in various levels of recreational physical activity and found that 25% of subjects had sustained a musculoskeletal injury within the 12 months preceding the survey and that sports participants had the highest risk for injuries. In the present study, the risk of a sport-related injury was 1.87 among the active compared to inactive co-twins. A similar risk has been reported in another study, while an active person had 1.53-fold (95% CI, 1.19–1.98) greater change of reporting a sport- or leisure-time activity-related injury than an inactive person (Carlson et al. 2006). Although, in this thesis, the active co-twins had slightly more injuries, the true number of injuries could have been even higher as only injuries that had been diagnosed by a physician were included in our study. It is very likely that only the more severe sports-related/musculoskeletal injuries were reported to a physician and therefore less severe injuries were excluded from our study.

6.5 Study strengths and limitations

The main strengths of this study were a very long follow-up period and a twin study design. Most of the analyses used a co-twin control design which is very

effective for studying different traits and different environmental risk factors, especially if the studied trait is heritable (Duffy 2000). As the twin sister or brother is used as the control, the genetic factors and childhood environment can be reliably controlled for. This study used twin pairs comprehensively selected from the large Finnish Twin Cohort, which included all the same-sex twin pairs born in Finland before 1958 (mean age at 1975 baseline among 146 pairs was 30 years) and with both co-twins alive in 1967 (Kaprio & Koskenvuo 2002). However, it has been discussed whether the results obtained from twin studies are generalisable. In general, twins are considered to be similar to other people in the same birth cohort in the same nation, and no clear evidence has been found that deviations in the assumptions impair the ability to interpret or generalise from twin studies (Kyvik 2000). However, as De Silva and Frayling (2010) pointed out, many epidemiological studies have found an association between reduced birth weight and the development of type 2 diabetes. Also it has been discussed that the prenatal nutritional limitation, causing reductions in fetal growth, might lead to increased risk for disease later life (Gluckman et al. 2011). In particular, metabolic compromises are possible due to mismatch between reduced fetal nutrition and a nutritionally rich postnatal world (Gluckman et al. 2011). This might be true among twins as they might have less food in the uterus compared to singletons. Therefore, it means that the twins in this study might have had slightly increased risk for type 2 diabetes compared to the non-twin population, as was seen among elderly twins in a study by Poulsen et al. (2008). However, this was a relatively small and selected sample and included only elderly twins. Despite a slightly lower birth weight in MZ twins, MZ twins weigh a little less in adolescence and either weigh less or do not differ from DZ twins in adulthood, and show no difference from MZ and DZ twins in T2D risk (Lehtovirta et al. 2010). Another Danish twin study also showed in an age-dependent model that low birth weight was associated with increased insulin sensitivity (Monrad et al. 2009). However, if this is the case, it should not change the T2D estimates according to physical activity, as all the subjects in this study were twins and therefore type 2 diabetes risk might have been elevated in all of the subjects.

An additional strength of most of the analyses (studies I, II, III) was the 6-year baseline assessment period during which physical activity discordance was assessed twice, indicating a true and long-term difference in this particular health habit during adulthood before the follow-up period began. A further strength of the diabetes study (study IV) was a large sample size. The sample included a very large proportion of all the same-sex twin pairs born in Finland before 1958 and therefore can be expected to be a good representation of the Finnish general population of that generation. Another important strength of the study was the use of reliable registers (hospital discharge, death registers and information on reimbursed medication) for identifying mortality dates and specific chronic diseases (type 2 diabetes, hypertension and CHD), which provided data on outcomes on all subjects. In particular, the number of false posi-

tive type 2 diabetes cases in the data is very low if non-existent (Kujala et al. 2003).

One study limitation that relates to all the analyses was the use of self-report physical activity and BMI data at baseline. However, these types of physical activity questions have commonly been used in epidemiological studies. In a study by Kujala et al. (1998), the same physical activity questions predicted morbidity and mortality in a fashion consistent with other studies using somewhat different measures providing external validation to the questions. The correlation between self-reported and measured BMI is very high (Mustelin et al. 2009). Retrospective physical activity data collection presents some limitations; however, we observed moderate correlations between the different physical activity assessments in the study. These types of data collection methods are also commonly used in epidemiological physical activity research (Lagerros & Lagiou 2007). It would have been difficult to measure total energy expenditure for thirty years to validate the retrospective physical activity assessment. One of the limitations of the study is the lack of comprehensive data on dietary habits at baseline or during follow-up, but it would have been impossible to collect reliable dietary data for such a long period with current data collection methods.

To maximize the participation rate and minimize selection bias, a telephone interview-based study was conducted, with the result that the information was self-reported rather than based on data gathered from laboratory tests, medical registers or subjects' formal medical notes. Weight, height and waist circumference were all measured by the participants. Although self-measurements are a limitation, as stated earlier, self-reports and measured values have a high correlation and have been shown to be valid and clinically relevant. Although the medical information was also self-reported, studies have shown that agreement between self-reported medical history and medical records is generally good, especially with respect to well-known chronic diseases (Haapanen et al. 1997a, Okura et al. 2004). Recall bias due to subjects not remembering all their diseases is an issue in twin studies if recall between active and inactive co-twins differ; active subjects may have a better memory for injuries and musculoskeletal disorders as these would have affected an important part of their life more than in the case of inactive subjects, thus biasing the risk estimates upwards. However, subjects with severe dementia and subjects who had died did not participate.

Despite the fact that we started with a large population-based twin cohort, the number of twin pairs discordant for physical activity was relatively small (146 pairs). Small sample size is a limitation, especially when studying diseases and mortality as outcomes. The mortality rate was low as only 8.2% of the original sample had died; likewise the number of outcomes was small for medications and self-reported diseases. The reason for finding a low number of twin pairs discordant for disease could either be due to diseases occurring in both co-twins for genetic reasons or to having a relatively young (mean age of subjects was 30.1 years in 1975 among 146 pairs) and healthy (exclusion of subjects with

any disease but hypertension) study cohort at baseline. Also, one co-twins in each pair was relatively active, indicating the existence of a healthy lifestyle for at least half of the subjects, while the other half were genetically closely related. Due to the low numbers of incidences it was not possible to adjust the interview-based disease analyses with known covariates; only the reimbursed medication analyses for hypertension were adjusted for work-related physical activity among the 146 pairs. The study design adjusts for gender, age and shared familial factors, and it is known that twins show similar health habits more often than do unrelated subjects. The mortality analyses were adjusted separately for social class and work-related physical activity and additionally for smoking and alcohol; neither adjustments changed the hazard ratios (results not shown).

The optimal study design for this type of analysis (co-twin control design) would have been to use a large sample of activity-discordant MZ pairs. However, even in this initially large twin cohort there were not sufficient numbers of discordant MZ pairs. Although the selection procedure was comprehensive and all the pairs that fulfilled the criteria were included in the study, the number of such MZ pairs was very small. Therefore, for the main analyses, the MZ pairs were pooled together with the DZ pairs. From among the baseline cohort of 5663 (31% MZ and 63% DZ) healthy twin pairs, a sub-sample of 146 (20% MZ and 80% DZ) pairs were selected for the follow-up study. The reduced number of MZ pairs in our sample is probably due to the earlier findings that MZ pairs consistently discordant for common traits are rare (Lauderdale et al. 1997, Kujala et al. 1998), as was also the case in this study, where only 5 MZ pairs out of 42 pairs were consistently discordant for physical activity for 30 years. In addition, the high heritability of persistent physical activity (Stubbe et al. 2006) makes it difficult to find MZ twin pairs discordant for both physical activity and mortality or chronic diseases. The number of MZ pairs, the relatively small overall sample size and the small number of outcome events among the MZ twin pairs in all the analyses do not allow conclusions to be drawn separately for MZ pairs. Even the large diabetes study (study IV), with over 20 000 individuals had a relatively low number of MZ pairs discordant for activity and diabetes. This is an unfortunate limitation, and therefore the effect of genetic predisposition cannot be excluded in the mortality and chronic diseases analyses, except for type 2 diabetes. The significant difference in the DZ pairs suggests that the association between physical activity and the outcome variables is not due to childhood environmental effects. As it was only assumed that the childhood environment was the same for both co-twins, it is therefore possible that some differences in non-shared environmental effects outside the home are present.

The diabetes study (study IV) also has a few other limitations. Baseline undiagnosed cases of type 2 diabetes or prediabetes cases were not excluded from the data as no clinical tests were done for the subjects at the baseline. To remove the confounding factors due to disease, a subgroup of 13 291, presumably healthy, individuals in 1981 was analysed. For these individuals the follow-up started from January 1982. This long delay between the baseline in 1975 and

start of the diabetes follow-up in 1982 would most likely have eliminated all the prediabetes cases that would have been present in 1975. As stated earlier, the reimbursed medication register is very reliable, but it, too, has the limitation that diagnoses of type 2 diabetes tend to be delayed, which in turn means a delay in granting the right to reimbursed medication. However, this would only bias the results if the delay differed by physical activity category, which is unlikely. Biochemical assessment of all subjects for follow-up status would have been ideal. In practice repeated measures of glucose metabolism from all subjects would not have been possible, as this may also lead to participation bias based on the presence of diabetes or related symptoms. Another limitation in our study relates to the use of baseline BMI as a covariate. This does not control for possible changes in BMI over time which are highly likely during such a long follow-up. More detailed measures of body composition in 1975 would have been desirable but were not available. However, BMI, waist circumference, and waist/hip ratio, are all similarly associated with incident diabetes (Vazquez et al. 2007) and therefore the use of, for example, waist circumference over BMI would not have been necessary.

6.6 Future directions

The present study supports the existing literature, clearly showing that leisure-time physical activity is associated with reduced all-cause mortality. However, this issue needs to be studied further, as no difference was seen in the low number of MZ pairs. Possibly this issue could be investigated using internationally pooled datasets.

It would be interesting to study the association between physical activity and type 2 diabetes in more depth. For example, to study the dose-response issue further, by analysing the data differently with more MET index categories. Analyses similar of those of the present study could also be conducted for different types of baseline physical activity, for example different intensities of activity or effect of work-related physical activity. Also, it would be interesting to combine the physical activity information from 1975 and 1981 to see what happens if changes in physical activity occur during this period and if so, what effects they have. Again, data from international twin registers could be pooled to study larger volumes of MZ pairs. It would also be interesting to combine the results of the diabetes study (study IV) with health-economic modelling and calculate the potential savings in health care costs that could be achieved by increased physical activity, e.g. in the reduced use of chronic medications, laboratory tests and in- and out-patient visits and in productivity at work.

The reimbursed medication registers could be more widely used to analyse other chronic conditions in the same fashion as was done for type 2 diabetes in this study (study IV). For example hypertension, asthma and depression/psychiatric medications could be studied using the reimbursed medication registers, as the participants self-reports showed these to have increased.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings of the present study can be summarized as follows:

1. Leisure-time physical activity protects against type 2 diabetes, also after controlled for genetics and childhood environment. Pairwise analyses showed that the BMI-adjusted hazard ratio was lower in the co-twins who were physically active (HR 0.54; 95% CI 0.37-0.78).
2. Consistent physical activity for 30 years during adulthood slowed down weight gain by 5.4 kg and resulted in 8.4 cm smaller waist circumference in the active compared to inactive co-twins.
3. Subjects who were physically active at baseline were more likely to show similar weight at the 30-year follow-up; weight maintenance was even more likely if activity was continued throughout adulthood.
4. The physically active co-twins had decreased premature mortality compared to their inactive co-twins among the DZ pairs.
5. The active co-twins tended to have less elevated blood pressure, psychiatric medications, better life satisfaction, less hospitalization, but more sports-related injuries. A physically active lifestyle thus outweighs the adverse effects even after taking familial effects into account.
6. Genetic factors may play a role in explaining some of the associations between disease occurrence and physical activity, as some of the findings were more salient among the dizygotic than monozygotic twin pairs discordant for physical activity.

YHTEENVETO

Vapaa-ajan liikunta, painonnousu ja terveys - yli 20 vuoden seurantatutkimus kaksosilla

Elämäntapasairauksiin luokitelluista tyypin 2 diabeteksesta ja lihavuudesta on tullut maailmanlaajuisia ongelmia. Näiden sairauksien lisääntymisen yhtenä syynä on liikkumattomuus. Liikunnan tiedetäänkin vaikuttavan ennaltaehkäisevästi näihin ja moniin muihin kroonisiin sairauksiin sekä vähentävän ennenaikaisia kuolemia. Myös perimän tiedetään vaikuttavan sekä liikunta-aktiivisuuteen että sairauksien esiintyvyyteen ja puhkeamiseen. Liikunnan vaikutusta eri sairauksien ennaltaehkäisyyn on tutkittu paljon laajoissa väestöä havainnoivissa pitkittäistutkimuksissa, mutta niissä ei ole otettu huomioon perintötekijöiden vaikutusta. Lisäksi pitkän seuranta-ajan omaavia satunnaistettuja kontrolloituja hoitotutkimuksia aiheesta ei juuri ole. Tämän väitöskirjatutkimuksen tavoitteena on saada selville, suojaako vapaa-ajan liikunta erilaisilta kroonisilta ja metabolisen oireyhtymän sairauksilta, ennenaikaisilta kuolemilta ja hidastaako liikunta tyypin 2 diabeteksen puhkeamista yli 20 vuoden seurannan aikana, kun geenit ja lapsuuden ympäristö otetaan huomioon. Geneettiset tekijät voidaan kontrolloida kaksostutkimusasetelmalla.

Näiden tavoitteiden saavuttamiseksi tutkimuksessa analysoitiin liikunnan suhteen eroavia kaksospareja. Aineisto perustuu suomalaiseen kaksoskohorttitutkimukseen, jossa ensimmäiset kyselyt tehtiin vuosina 1975 ja 1981. Vuoden 1975 tutkimuskohorttiin kuuluivat väestörekisterijärjestelmästä tunnistetut Suomessa ennen vuotta 1958 syntyneet samaa sukupuolta olevat kaksosparit. Kyselyt sisälsivät kysymyksiä mm. liikunta-aktiivisuudesta, jonka perusteella laskettiin MET indeksi (MET h/päivä). Tutkimukseen otettiin mukaan ne kaksosparit, joiden jäsenet olivat terveitä vuosina 1975 ja 1981 ja erosivat toisistaan liikunnan määrän ja rasittavuuden suhteen. Yhteensä 146 kaksosparia oli liikunnan suhteen eroavia molempina vuosina. Kuolemia seurattiin 1.1.1982 – 31.12.2004 välisenä aikana. Vuoden 2005 puhelinhaastatteluun otettiin mukaan kaikki suomenkieliset Suomessa asuvat ja elossa olevat liikunnan suhteen eroavat kaksosparit. Vuoden 2005 haastatteluun vastasi yhteensä 203 yksittäistä kaksosta sisältäen 95 kaksosparia (76 ditsygoottista eli epäidenttistä ja 19 monotsygoottista eli identtistä paria). Haastatteluun vastanneiden keski-ikä oli 58 vuotta (47–79). Haastattelu sisälsi kysymyksiä liikunnan jatkuvuudesta, painosta, sairauksista (mm. diabeteksesta, sydän- ja verisuonisairauksista, keuhkosairauksista ja TULES-vaivoista) ja lääkkeiden käytöstä. Liikunnan vaikutusta tyypin 2 diabeteksen ehkäisyyn haluttiin selvittää tarkemmin isommalla otannalla, joten yhteen osatutkimukseen otettiin mukaan kaikki vuoden 1975 kyselyyn vastanneet. Seurannan alussa vuonna 1975 kohorttiin kuului yhteensä 20 487 henkilöä, joilla ei ollut diabetesta, ja jotka olivat vastanneet liikunta-aktiivisuutta, pituutta ja painoa koskeviin kysymyksiin. MET-indeksin perusteella kaksoset jaettiin viiteen yhtä suureen luokkaan ja näitä luokkia käytettiin tyypin 2 diabeteksen ennustajina. Luokkaan I kuuluivat täysin inaktiiviset (<

0.59 MET h/päivä) ja luokkaan V erittäin aktiiviset (> 4.50 MET h/päivä). Tieto tyypin 2 diabeteksesta seuranta-ajalle 1.1.1976 – 31.12.2004 kerättiin kansallisista rekisteritiedostoista, lähinnä KELAn erityislääkekorvaustiedoista. Analyysit tehtiin yksilö- ja/tai parittaisanalyysein t-testiä, McNemarin testiä, logistista regressiota ja elinaika-analyysimallia käyttäen.

Tässä tutkimuksessa 146 liikunnan suhteen eroavan kaksosparin joukosta yhteensä 24 kaksosta kuoli (16 inaktiivista ja 8 aktiivista) vuoden 2004 loppuun mennessä. Tämä osoitti, että aktiivisilla kaksosilla oli pienentynyt riski kuolla ennenaikaisesti inaktiivisiin verrattuna (HR 0.39, luottamusväli 0.18 – 0.85). Tämä ero ei ollut nähtävissä identtisillä kaksosilla. Puhelinhaastattelun perusteella aktiivisilla kaksosilla oli vähemmän tyypin 2 diabetesta tai diabeteksen esiastetta, korkeaa verenpainetta sekä vähemmän psyykkisten sairauksien hoitoon käytettäviä lääkkeitä kuin inaktiiveilla kaksosilla. Lisäksi aktiiviset kaksoset olivat tyytyväisempiä elämäänsä ja olivat viettäneet vähemmän öitä sairaalassa inaktiivisiin verrattuna. Seurannan aikana aktiivisilla kaksosilla oli havaittavissa enemmän liikunnan yhteydessä ilmaantuvia vammoja kuin inaktiiveilla kaksosilla. Haastatteluun vastanneiden kaksosparien joukossa oli yhteensä 42 paria, jotka olivat liikunnan suhteen eroavia 30 vuoden ajan. Näiden parien osalta liikuntaa pysyvästi harrastaneet parien jäsenet olivat lihoneet keskimärin 5.4 kg vähemmän ja heillä oli 8.4 cm pienempi vyötärönympärys vuonna 2005 verrattuna heidän liikkumattomaan kaksosveljeensä/siskoonsa.

Tarkempi tyypin 2 diabeteksen seuranta koko kohortilla osoitti, että 28 vuoden aikana ilmaantui yhteensä 1082 tyypin 2 diabetes -tapausta. Yksilöanalyysien mukaan henkilöillä, joiden liikunta-aktiivisuus oli suurinta eli MET-luokissa III – V (HR 0.73, 0.78, 0.74) oli tilastollisesti merkitsevästi pienempi todennäköisyys saada tyypin 2 diabetes seurannan aikana kuin inaktiivisilla henkilöillä (MET-luokka I). Nämä erot eivät olleet merkitseviä, kun malli vakioitiin painoindeksillä. Parittaisanalyysi liikunnan suhteen eroavilla pareilla osoitti, että liikunnallisesti aktiivisemmilla kaksosilla (luokat II – V) oli pienempi todennäköisyys sairastua tyypin 2 diabetekseen seurannan aikana verrattuna kaksosparin inaktiivisiin jäseniin (HR 0.61, 0.59, 0.61, 0.61). Nämä erot säilyivät merkitsevinä myös painoindeksillä vakioimisen jälkeen. Painoindeksin huomioonottava parittaisanalyysi, jossa verrattiin täysin inaktiivisia (luokka I) kaikkiin aktiiveihin (luokat II-V yhdistettynä) osoitti, että vähäinenkin aktiivisuus puolitti riskin (HR 0.54, luottamusvälit 0.37-0.78) sairastua tyypin 2 diabetekseen seurannan aikana. Tulokset olivat samanlaiset tarkasteltaessa identtisiä ja epäidenttisiä pareja.

Tämän kaksospareilla tehdyn pitkittäistutkimuksen mukaan vapaa-ajan liikunta näyttää ennaltaehkäisevän ennen kaikkea metaboliseen oireyhtymään liitettyjä tekijöitä, painon nousua, lisääntynyttä vyötärönympärystä, korkeaa verenpainetta ja tyypin 2 diabetesta. Lisäksi aktiiviset henkilöt näyttävät olevan tyytyväisempiä elämäänsä seurannan aikana, vaikkakin liikuntaa harrastavilla vaikuttaa olevan enemmän liikunnan yhteydessä ilmaantuvia vammoja inaktiiveihin kaksosiinsa verrattuna. Liikunta näyttää ennaltaehkäisevän tyypin 2 diabetesta myös silloin, kun painoindeksi ja geneettiset tekijät on huomioitu. Jo

vähäinenkin vapaa-ajan liikunta näyttää suojaavan tyypin 2 diabetekseen sairastumiselta tai hidastavan sen puhkeamista. Muiden sairauksien osalta geneettiset tekijät saattavat osaksi selittää liikunnan ennaltaehkäiseviä vaikutuksia, koska tulokset olivat selkeämpiä epäidenttisillä kuin identtisillä kaksosilla, vaikkakin vähäinen identtisten kaksosparien määrä rajoittaa luotettavien johtopäätösten tekemistä. Näyttää kuitenkin siltä, että liikunnan positiiviset vaikutukset ovat huomattavasti suuremmat kuin negatiiviset vaikutukset.

REFERENCES

Aaltonen, S., Ortega-Alonso, A., Kujala, U. M. & Kaprio, J. 2010. A longitudinal study on genetic and environmental influences on leisure time physical activity in the Finnish twin cohort. Twin Res.Hum.Genet. 13 (5), 475-481.

ACSM 2010. ACSM's guidelines for exercise testing and prescription. (8th edition) Philadelphia: Lippincott Williams & Wilkins.

Andersen, L. G., Angquist, L., Gamborg, M., Byberg, L., Bengtsson, C., Canoy, D., Eriksson, J. G., Eriksson, M., Jarvelin, M. R., Lissner, L., et al. 2009. Birth weight in relation to leisure time physical activity in adolescence and adulthood: Meta-analysis of results from 13 Nordic cohorts. PLoS One 4 (12), e8192.

Andreasen, C. H., Stender-Petersen, K. L., Mogensen, M. S., Torekov, S. S., Wegner, L., Andersen, G., Nielsen, A. L., Albrechtsen, A., Borch-Johnsen, K., Rasmussen, S. S., Clausen, J. O., Sandbaek, A., Lauritzen, T., Hansen, L., Jorgensen, T., Pedersen, O. & Hansen, T. 2008. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 57 (1), 95-101.

Austin, M. A., Friedlander, Y., Newman, B., Edwards, K., Mayer-Davis, E. J. & King, M. C. 1997. Genetic influences on changes in body mass index: A longitudinal analysis of women twins. Obes.Res. 5 (4), 326-331.

Autenrieth, C. S., Baumert, J., Baumeister, S. E., Fischer, B., Peters, A., Doring, A. & Thorand, B. 2011. Association between domains of physical activity and all-cause, cardiovascular and cancer mortality. Eur.J.Epidemiol. 26 (2), 91-99.

Barbaric, M., Brooks, E., Moore, L. & Cheifetz, O. 2010. Effects of physical activity on cancer survival: A systematic review. Physiother.Can. 62 (1), 25-34.

Barengo, N. C., Hu, G., Kastarinen, M., Lakka, T. A., Pekkarinen, H., Nissinen, A. & Tuomilehto, J. 2005. Low physical activity as a predictor for antihypertensive drug treatment in 25-64-year-old populations in eastern and south-western Finland. J.Hypertens. 23 (2), 293-299.

Barengo, N. C., Kastarinen, M., Lakka, T., Nissinen, A. & Tuomilehto, J. 2006. Different forms of physical activity and cardiovascular risk factors among 24-64-year-old men and women in Finland. Eur.J.Cardiovasc.Prev.Rehabil. 13 (1), 51-59.

Barroso, I. 2005. Genetics of type 2 diabetes. Diabet.Med. 22 (5), 517-535.

Batra, V., Patkar, A. A., Berrettini, W. H., Weinstein, S. P. & Leone, F. T. 2003. The genetic determinants of smoking. Chest 123 (5), 1730-1739.

Battie, M. C., Videman, T., Levälahti, E., Gill, K. & Kaprio, J. 2007. Heritability of low back pain and the role of disc degeneration. Pain 131 (3), 272-280.

Berentzen, T., Petersen, L., Schnohr, P. & Sorensen, T. I. 2008. Physical activity in leisure-time is not associated with 10-year changes in waist circumference. Scand.J.Med.Sci.Sports 18 (6), 719-727.

Bigaard, J., Frederiksen, K., Tjonneland, A., Thomsen, B. L., Overvad, K., Heitmann, B. L. & Sorensen, T. I. 2005. Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. Int.J.Obes.(Lond) 29 (7), 778-784.

Bird, A. 2007. Perceptions of epigenetics. Nature 447 (7143), 396-398.

Blair, S. N., Cheng, Y. & Holder, J. S. 2001. Is physical activity or physical fitness more important in defining health benefits? Med.Sci.Sports Exerc. 33 (6 Suppl), S379-99; discussion S419-20.

Boden, G. & Shulman, G. I. 2002. Free fatty acids in obesity and type 2 diabetes: Defining their role in the development of insulin resistance and beta-cell dysfunction. Eur.J.Clin.Invest. 32 Suppl 3, 14-23.

Boomsma, D., Busjahn, A. & Peltonen, L. 2002. Classical twin studies and beyond. Nat.Rev.Genet. 3 (11), 872-882.

Brown, T., Avenell, A., Edmunds, L. D., Moore, H., Whittaker, V., Avery, L. & Summerbell, C. 2009. Systematic review of long-term lifestyle interventions to prevent weight gain and morbidity in adults. Obes.Rev. 10 (6), 627-638.

Brown, W. J., Burton, N. W. & Rowan, P. J. 2007. Updating the evidence on physical activity and health in women. Am.J.Prev.Med. 33 (5), 404-411.

Bruce, C. R., Kriketos, A. D., Cooney, G. J. & Hawley, J. A. 2004. Disassociation of muscle triglyceride content and insulin sensitivity after exercise training in patients with type 2 diabetes. Diabetologia 47 (1), 23-30.

Calle, E. E., Thun, M. J., Petrelli, J. M., Rodriguez, C. & Heath, C. W.,Jr 1999. Body-mass index and mortality in a prospective cohort of U.S. adults. N.Engl.J.Med. 341 (15), 1097-1105.

Carey, V. J., Walters, E. E., Colditz, G. A., Solomon, C. G., Willett, W. C., Rosner, B. A., Speizer, F. E. & Manson, J. E. 1997. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The nurses' health study. Am.J.Epidemiol. 145 (7), 614-619.

Carlson, S. A., Hootman, J. M., Powell, K. E., Macera, C. A., Heath, G. W., Gilchrist, J., Kimsey, C. D.,Jr & Kohl, H. W.,3rd 2006. Self-reported injury and physical activity levels: United States 2000 to 2002. Ann.Epidemiol. 16 (9), 712-719.

Carlsson, S., Andersson, T., Lichtenstein, P., Michaelsson, K. & Ahlbom, A. 2007. Physical activity and mortality: Is the association explained by genetic selection? Am.J.Epidemiol. 166, 255-259.

Casas, J. P., Cooper, J., Miller, G. J., Hingorani, A. D. & Humphries, S. E. 2006. Investigating the genetic determinants of cardiovascular disease using candidate genes and meta-analysis of association studies. Ann.Hum.Genet. 70 (Pt 2), 145-169.

Central Statistical Office of Finland 1972. Alphabetical list of occupations and classification of social class. Helsinki, Finland: Statistics Finland.

Chan, D. C., Watts, G. F., Barrett, P. H. & Burke, V. 2003. Waist circumference, waist-to-hip ratio and body mass index as predictors of adipose tissue compartments in men. QJM 96 (6), 441-447.

Chan, J. M., Rimm, E. B., Colditz, G. A., Stampfer, M. J. & Willett, W. C. 1994. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 17 (9), 961-969.

Corder, K., Ogilvie, D. & van Sluijs, E. M. 2009. Invited commentary: Physical activity over the life course--whose behavior changes, when, and why? Am.J.Epidemiol. 170 (9), 1078-81; discussion 1082-3.

Cornes, B. K., Lind, P. A., Medland, S. E., Montgomery, G. W., Nyholt, D. R. & Martin, N. G. 2009. Replication of the association of common rs9939609 variant of FTO with increased BMI in an Australian adult twin population but no evidence for gene by environment (G x E) interaction. Int.J.Obes.(Lond) 33 (1), 75-79.

Corrado, D., Migliore, F., Basso, C. & Thiene, G. 2006. Exercise and the risk of sudden cardiac death. Herz 31 (6), 553-558.

Cosca, D. D. & Navazio, F. 2007. Common problems in endurance athletes. Am.Fam.Physician 76 (2), 237-244.

Cymet, T. C. & Sinkov, V. 2006. Does long-distance running cause osteoarthritis? J.Am.Osteopath.Assoc. 106 (6), 342-345.

De Silva, N. M. & Frayling, T. M. 2010. Novel biological insights emerging from genetic studies of type 2 diabetes and related metabolic traits. Curr.Opin.Lipidol. 21 (1), 44-50.

Demakakos, P., Hamer, M., Stamatakis, E. & Steptoe, A. 2010. Low-intensity physical activity is associated with reduced risk of incident type 2 diabetes in older adults: Evidence from the English longitudinal study of ageing. Diabetologia 53 (9), 1877-1885.

Derks, E. M., Dolan, C. V. & Boomsma, D. I. 2006. A test of the equal environment assumption (EEA) in multivariate twin studies. Twin Res.Hum.Genet. 9 (3), 403-411.

Despres, J. P., Prud'homme, D., Pouliot, M. C., Tremblay, A. & Bouchard, C. 1991. Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. Am.J.Clin.Nutr. 54 (3), 471-477.

Droyvold, W. B., Holmen, J., Midthjell, K. & Lydersen, S. 2004. BMI change and leisure time physical activity (LTPA): An 11-y follow-up study in apparently healthy men aged 20-69 y with normal weight at baseline. Int.J.Obes.Relat.Metab.Disord. 28 (3), 410-417.

Duffy, D. L. 2000. The co-twin contol study. In T. D. Spector, H. Snieder & A. J. MacGregor (Eds.) Advances in twin and sib-pair analysis. London: Greenwich Medical Media, 53-66.

Duncan, G. E., Goldberg, J., Noonan, C., Moudon, A. V., Hurvitz, P. & Buchwald, D. 2008. Unique environmental effects on physical activity participation: A twin study. PLoS ONE [Electronic Resource] 3 (4), e2019.

Eckel, R. H., Grundy, S. M. & Zimmet, P. Z. 2005. The metabolic syndrome. The Lancet 365 (9468), 1415-1428.

Ekelund, U., Besson, H., Luan, J., May, A. M., Sharp, S. J., Brage, S., Travier, N., Agudo, A., Slimani, N., Rinaldi, S., et al. 2011. Physical activity and gain in

abdominal adiposity and body weight: Prospective cohort study in 288,498 men and women. Am.J.Clin.Nutr. 93 (4), 826-835.

Erikssen, G., Liestol, K., Bjornholt, J., Thaulow, E., Sandvik, L. & Erikssen, J. 1998. Changes in physical fitness and changes in mortality. Lancet 352 (9130), 759-762.

Evans, A., Van Baal, G. C., McCarron, P., DeLange, M., Soerensen, T. I., De Geus, E. J., Kyvik, K., Pedersen, N. L., Spector, T. D., Andrew, T., Patterson, C., Whitfield, J. B., Zhu, G., Martin, N. G., Kaprio, J. & Boomsma, D. I. 2003. The genetics of coronary heart disease: The contribution of twin studies. Twin Res. 6 (5), 432-441.

Fabsitz, R. R., Sholinsky, P. & Carmelli, D. 1994. Genetic influences on adult weight gain and maximum body mass index in male twins. Am.J.Epidemiol. 140 (8), 711-720.

Fagard, R., Brguljan, J., Staessen, J., Thijs, L., Derom, C., Thomis, M. & Vlietinck, R. 1995. Heritability of conventional and ambulatory blood pressures. A study in twins. Hypertension 26 (6 Pt 1), 919-924.

Fogelholm, M. & Kukkonen-Harjula, K. 2000. Does physical activity prevent weight gain - A systematic review. Obes.Rev. 1 (2), 95-111.

Fogelholm, M., Malmberg, J., Suni, J., Santtila, M., Kyrolainen, H., Mantysaari, M. & Oja, P. 2006. International physical activity questionnaire: Validity against fitness. Med.Sci.Sports Exerc. 38 (4), 753-760.

Folsom, A. R., Kushi, L. H. & Hong, C. P. 2000. Physical activity and incident diabetes mellitus in postmenopausal women. Am.J.Public Health 90 (1), 134-138.

Fox, C. S., Heard-Costa, N. L., Vasan, R. S., Murabito, J. M., D'Agostino RB, S., Atwood, L. D. & Framingham Heart Study. 2005. Genomewide linkage analysis of weight change in the Framingham Heart Study. J.Clin.Endocrinol.Metab. 90 (6), 3197-3201.

Franks, P. W. & Ling, C. 2010. Epigenetics and obesity: The devil is in the details. BMC Med. 8, 88.

Frayling, T. M., Timpson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M., Lindgren, C. M., Perry, J. R., Elliott, K. S., Lango, H., Rayner, N. W., et al. 2007. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316 (5826), 889-894.

Gesell, A. 1942. The method of co-twin control. Science 95 (2470), 446-448.

Gill, J. M. & Cooper, A. R. 2008. Physical activity and prevention of type 2 diabetes mellitus. Sports Med. 38 (10), 807-824.

Gluckman, P. D., Hanson, M. A. & Low, F. M. 2011. The role of developmental plasticity and epigenetics in human health. Birth Defects Res.C.Embryo.Today 93 (1), 12-18.

Glumer, C., Jorgensen, T., Borch-Johnsen, K. & Inter99 Study. 2003. Prevalences of diabetes and impaired glucose regulation in a Danish population: The Inter99 Study. Diabetes Care 26 (8), 2335-2340.

Goode, E. L., Cherny, S. S., Christian, J. C., Jarvik, G. P. & de Andrade, M. 2007. Heritability of longitudinal measures of body mass index and lipid and lipoprotein levels in aging twins. Twin Res.Hum.Genet. 10 (5), 703-711.

Goodpaster, B. H., Wolfe, R. R. & Kelley, D. E. 2002. Effects of obesity on substrate utilization during exercise. Obes.Res. 10 (7), 575-584.

Gudmundsson, H., Gudbjartsson, D. F., Frigge, M., Gulcher, J. R. & Stefansson, K. 2000. Inheritance of human longevity in Iceland. Eur.J.Hum.Genet. 8 (10), 743-749.

Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L. & Anis, A. H. 2009. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health 9, 88.

Guyton, A. C. & Hall, J. E. 2000. Textbook of medical physiology. (10th edition) Philadelphia, USA: W.B Saunders Company.

Haapanen, N., Miilunpalo, S., Pasanen, M., Oja, P. & Vuori, I. 1997a. Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. Am.J.Epidemiol. 145 (8), 762-769.

Haapanen, N., Miilunpalo, S., Vuori, I., Oja, P. & Pasanen, M. 1997b. Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. Int.J.Epidemiol. 26 (4), 739-747.

Hakanen, M., Raitakari, O. T., Lehtimäki, T., Peltonen, N., Pahkala, K., Sillanmäki, L., Lagstrom, H., Viikari, J., Simell, O. & Rönnemaa, T. 2009. FTO genotype is associated with body mass index after the age of seven years but not with energy intake or leisure-time physical activity. J.Clin.Endocrinol.Metab. 94 (4), 1281-1287.

Han, T. S., van Leer, E. M., Seidell, J. C. & Lean, M. E. 1995. Waist circumference action levels in the identification of cardiovascular risk factors: Prevalence study in a random sample. BMJ 311 (7017), 1401-1405.

Hankinson, A. L., Daviglus, M. L., Bouchard, C., Carnethon, M., Lewis, C. E., Schreiner, P. J., Liu, K. & Sidney, S. 2010. Maintaining a high physical activity level over 20 years and weight gain. JAMA 304 (23), 2603-2610.

Helakorpi, S., Laitalainen, E. & Uutela, A. 2010. Health behaviour and health among the Finnish adult population, Spring 2009. 7/2010. Helsinki.

Helmrich, S. P., Ragland, D. R., Leung, R. W. & Paffenbarger, R. S.,Jr 1991. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N.Engl.J.Med. 325 (3), 147-152.

Hernelahti, M., Levälahti, E., Simonen, R. L., Kaprio, J., Kujala, U. M., Uusitalo-Koskinen, A. L., Battie, M. C. & Videman, T. 2004. Relative roles of heredity and physical activity in adolescence and adulthood on blood pressure. J.Appl.Physiol. 97 (3), 1046-1052.

Herskind, A. M., McGue, M., Holm, N. V., Sorensen, T. I., Harvald, B. & Vaupel, J. W. 1996. The heritability of human longevity: A population-based study of 2872 Danish twin pairs born 1870-1900. Hum.Genet. 97 (3), 319-323.

Hill, J. O. & Melanson, E. L. 1999. Overview of the determinants of overweight and obesity: Current evidence and research issues. Med.Sci.Sports Exerc. 31 (11 Suppl), S515-21.

Hill, J. O. & Wyatt, H. R. 2005. Role of physical activity in preventing and treating obesity. J.Appl.Physiol. 99 (2), 765-770.

Hjelmborg, J. B., Fagnani, C., Silventoinen, K., McGue, M., Korkeila, M., Christensen, K., Rissanen, A. & Kaprio, J. 2008. Genetic influences on growth traits of BMI: A longitudinal study of adult twins. Obesity (Silver Spring) 16 (4), 847-852.

Hootman, J. M., Macera, C. A., Ainsworth, B. E., Addy, C. L., Martin, M. & Blair, S. N. 2002. Epidemiology of musculoskeletal injuries among sedentary and physically active adults. Med.Sci.Sports Exerc. 34 (5), 838-844.

Hu, F. B., Li, T. Y., Colditz, G. A., Willett, W. C. & Manson, J. E. 2003. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA 289 (14), 1785-1791.

Hu, F. B., Sigal, R. J., Rich-Edwards, J. W., Colditz, G. A., Solomon, C. G., Willett, W. C., Speizer, F. E. & Manson, J. E. 1999. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: A prospective study. JAMA 282 (15), 1433-1439.

Hu, G., Qiao, Q., Silventoinen, K., Eriksson, J. G., Jousilahti, P., Lindstrom, J., Valle, T. T., Nissinen, A. & Tuomilehto, J. 2003. Occupational, commuting, and leisure-time physical activity in relation to risk for type 2 diabetes in middle-aged Finnish men and women. Diabetologia 46 (3), 322-329.

Hu, H. H., Nayak, K. S. & Goran, M. I. 2011. Assessment of abdominal adipose tissue and organ fat content by magnetic resonance imaging. Obes.Rev. 12 (5), e504-15.

Hughes, V. A., Roubenoff, R., Wood, M., Frontera, W. R., Evans, W. J. & Fiatarone Singh, M. A. 2004. Anthropometric assessment of 10-y changes in body composition in the elderly. Am.J.Clin.Nutr. 80 (2), 475-482.

Hunt, M. S., Katzmarzyk, P. T., Perusse, L., Rice, T., Rao, D. C. & Bouchard, C. 2002. Familial resemblance of 7-year changes in body mass and adiposity. Obes.Res. 10 (6), 507-517.

Iachine, I. A., Holm, N. V., Harris, J. R., Begun, A. Z., Iachina, M. K., Laitinen, M., Kaprio, J. & Yashin, A. I. 1998. How heritable is individual susceptibility to death? The results of an analysis of survival data on Danish, Swedish and Finnish twins. Twin Res. 1 (4), 196-205.

Jebb, S. A. & Moore, M. S. 1999. Contribution of a sedentary lifestyle and inactivity to the etiology of overweight and obesity: Current evidence and research issues. Med.Sci.Sports Exerc. 31 (11 Suppl), S534-41.

Jeon, C. Y., Lokken, R. P., Hu, F. B. & van Dam, R. M. 2007. Physical activity of moderate intensity and risk of type 2 diabetes: A systematic review. Diabetes Care 30 (3), 744-752.

Kaprio, J. & Koskenvuo, M. 2002. Genetic and environmental factors in complex diseases: The older Finnish twin cohort. Twin Res. 5 (5), 358-365.

Kaprio, J., Koskenvuo, M., Langinvainio, H., Romanov, K., Sarna, S. & Rose, R. J. 1987. Genetic influences on use and abuse of alcohol: A study of 5638 adult Finnish twin brothers. Alcohol.Clin.Exp.Res. 11 (4), 349-356.

Kaprio, J., Koskenvuo, M. & Sarna, S. 1981. Cigarette smoking, use of alcohol, and leisure-time physical activity among same-sexed adult male twins. Prog.Clin.Biol.Res. 69 Pt C, 37-46.

Kaprio, J., Sarna, S., Koskenvuo, M. & Rantasalo, I. 1978. The Finnish Twin Registry: baseline characteristics. Section II. History of symptoms and illnesses, use of drugs, physical characteristics, smoking, alcohol and physical activity. Public Health Publication M 37. Helsinki.

Kaprio, J., Tuomilehto, J., Koskenvuo, M., Romanov, K., Reunanen, A., Eriksson, J., Stengard, J. & Kesäniemi, Y. A. 1992. Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 35 (11), 1060-1067.

Kay, S. J. & Fiatarone Singh, M. A. 2006. The influence of physical activity on abdominal fat: A systematic review of the literature. Obes.Rev. 7 (2), 183-200.

Kenfield, S. A., Stampfer, M. J., Giovannucci, E. & Chan, J. M. 2011. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J.Clin.Oncol. 29 (6), 726-732.

Kesäniemi, Y. K., Danforth, E.,Jr, Jensen, M. D., Kopelman, P. G., Lefebvre, P. & Reeder, B. A. 2001. Dose-response issues concerning physical activity and health: An evidence-based symposium. Med.Sci.Sports Exerc. 33 (6 Suppl), S351-8.

Kirjonen, J., Telama, R., Luukkonen, R., Kaaria, S., Kaila-Kangas, L. & Leino-Arjas, P. 2006. Stability and prediction of physical activity in 5-, 10-, and 28-year follow-up studies among industrial employees. Scand.J.Med.Sci.Sports 16 (3), 201-208.

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., Nathan, D. M. & Diabetes Prevention Program Research Group 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N.Engl.J.Med. 346 (6), 393-403.

Koh-Banerjee, P., Chu, N. F., Spiegelman, D., Rosner, B., Colditz, G., Willett, W. & Rimm, E. 2003. Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with 9-y gain in waist circumference among 16 587 US men. Am.J.Clin.Nutr. 78 (4), 719-727.

Koivumaa-Honkanen, H., Honkanen, R., Koskenvuo, M., Viinamäki, H. & Kaprio, J. 2002. Life dissatisfaction as a predictor of fatal injury in a 20-year follow-up. Acta Psychiatr.Scand. 105 (6), 444-450.

Koivumaa-Honkanen, H., Kaprio, J., Honkanen, R. J., Viinamäki, H. & Koskenvuo, M. 2005. The stability of life satisfaction in a 15-year follow-up of adult Finns healthy at baseline. BMC Psychiatry 5, 4.

Korhonen, T., Kujala, U. M., Rose, R. J. & Kaprio, J. 2009. Physical activity in adolescence as a predictor of alcohol and illicit drug use in early adulthood: A longitudinal population-based twin study. Twin Res.Hum.Genet. 12 (3), 261-268.

Kujala, U. M. 2011. Physical activity, genes, and lifetime predisposition to chronic diseases. Eur Rev Aging Phys Act 8, 31-36.

Kujala, U. M., Kaprio, J. & Koskenvuo, M. 2002. Modifiable risk factors as predictors of all-cause mortality: The roles of genetics and childhood environment. Am.J.Epidemiol. 156 (11), 985-993.

Kujala, U. M., Kaprio, J., Sarna, S. & Koskenvuo, M. 1998. Relationship of leisure-time physical activity and mortality: The Finnish twin cohort. JAMA 279 (6), 440-444.

Kujala, U. M., Sarna, S. & Kaprio, J. 2003. Use of medications and dietary supplements in later years among male former top-level athletes. Arch.Intern.Med. 163 (9), 1064-1068.

Kujala, U. M., Sarna, S., Kaprio, J. & Koskenvuo, M. 1996. Asthma and other pulmonary diseases in former elite athletes. Thorax 51 (3), 288-292.

Kupper, N., Willemsen, G., Riese, H., Posthuma, D., Boomsma, D. I. & de Geus, E. J. 2005. Heritability of daytime ambulatory blood pressure in an extended twin design. Hypertension 45 (1), 80-85.

Kuzuya, T., Nakagawa, S., Satoh, J., Kanazawa, Y., Iwamoto, Y., Kobayashi, M., Nanjo, K., Sasaki, A., Seino, Y., Ito, C., Shima, K., Nonaka, K., Kadowaki, T. & Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus 2002. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res.Clin.Pract. 55 (1), 65-85.

Kyvik, K. O. 2000. Generalisability and assumptions of twin studies. In T. D. Spector, H. Snieder & A. J. MacGregor (Eds.) Advances in twin and sib-pair analysis. London: Greenwich Medical Media, 53-66.

Laaksonen, D. E., Lindstrom, J., Lakka, T. A., Eriksson, J. G., Niskanen, L., Wikstrom, K., Aunola, S., Keinänen-Kiukaanniemi, S., Laakso, M., Valle, T. T., et al. 2005. Physical activity in the prevention of type 2 diabetes: The Finnish diabetes prevention study. Diabetes 54 (1), 158-165.

Lagerros, Y. T. & Lagiou, P. 2007. Assessment of physical activity and energy expenditure in epidemiological research of chronic diseases. Eur.J.Epidemiol. 22 (6), 353-362.

Laitinen, T., Räsänen, M., Kaprio, J., Koskenvuo, M. & Laitinen, L. A. 1998. Importance of genetic factors in adolescent asthma: A population-based twin-family study. Am.J.Respir.Crit.Care Med. 157 (4 Pt 1), 1073-1078.

Lakka, T. A. & Salonen, J. T. 1997. The physical activity questionnaires of the Kuopio ischemic heart disease study (KIHD). A collection of physical activity questionnaires for health-related research. Medicine and Science in Sports and Exercise, Med Sci Sports Exerc 29, S46-58.

Lakka, T. A. & Salonen, J. T. 1992. Intra-person variability of various physical activity assessments in the Kuopio ischaemic heart disease risk factor study. Int.J.Epidemiol. 21 (3), 467-472.

Lakka, T. A., Venäläinen, J. M., Rauramaa, R., Salonen, R., Tuomilehto, J. & Salonen, J. T. 1994. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. N.Engl.J.Med. 330 (22), 1549-1554.

LaMonte, M. J., Blair, S. N. & Church, T. S. 2005. Physical activity and diabetes prevention. J.Appl.Physiol. 99 (3), 1205-1213.

Lauderdale, D. S., Fabsitz, R., Meyer, J. M., Sholinsky, P., Ramakrishnan, V. & Goldberg, J. 1997. Familial determinants of moderate and intense physical activity: A twin study. Med.Sci.Sports Exerc. 29 (8), 1062-1068.

Lee, I. M., Djousse, L., Sesso, H. D., Wang, L. & Buring, J. E. 2010. Physical activity and weight gain prevention. JAMA 303 (12), 1173-1179.

Lee, I. M., Hsieh, C. C. & Paffenbarger, R. S.,Jr 1995. Exercise intensity and longevity in men. The Harvard Alumni Health Study. JAMA 273 (15), 1179-1184.

Lee, I. M. & Skerrett, P. J. 2001. Physical activity and all-cause mortality: What is the dose-response relation? Med.Sci.Sports Exerc. 33 (6 Suppl), S459-71; discussion S493-4.

Lee, J., Chen, L., Snieder, H., Chen da, F., Lee, L. M., Liu, G. F., Wu, T., Tang, X., Zhan, S. Y., Cao, W. H., Lv, J., Gao, W. J. & Hu, Y. H. 2010. Heritability of obesity-related phenotypes and association with adiponectin gene polymorphisms in the Chinese national twin registry. Ann.Hum.Genet. 74 (2), 146-154.

Lees, S. J. & Booth, F. W. 2004. Sedentary death syndrome. Can.J.Appl.Physiol. 29 (4), 447-60; discussion 444-6.

Lehtovirta, M., Pietiläinen, K. H., Levälahti, E., Heikkilä, K., Groop, L., Silventoinen, K., Koskenvuo, M. & Kaprio, J. 2010. Evidence that BMI and type 2 diabetes share only a minor fraction of genetic variance: A follow-up study of 23,585 monozygotic and dizygotic twins from the Finnish twin cohort study. Diabetologia 53 (7), 1314-1321.

Leon, A. S., Connett, J., Jacobs, D. R.,Jr & Rauramaa, R. 1987. Leisure-time physical activity levels and risk of coronary heart disease and death. The multiple risk factor intervention trial. JAMA 258 (17), 2388-2395.

Leskinen, T., Rinnankoski-Tuikka, R., Rintala, M., Seppänen-Laakso, T., Pöllänen, E., Alen, M., Sipilä, S., Kaprio, J., Kovanen, V., Rahkila, P., Oresic, M., Kainulainen, H. & Kujala, U. M. 2010. Differences in muscle and adipose tissue gene expression and cardio-metabolic risk factors in the members of physical activity discordant twin pairs. PLoS One 5 (9), e12609.

Leskinen, T., Sipilä, S., Alen, M., Cheng, S., Pietiläinen, K. H., Usenius, J. P., Suominen, H., Kovanen, V., Kainulainen, H., Kaprio, J. & Kujala, U. M. 2009. Leisure-time physical activity and high-risk fat: A longitudinal population-based twin study. Int.J.Obes.(Lond) 33 (11), 1211-1218.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., Collins, R. & Prospective Studies Collaboration 2002. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. The Lancet 360 (9349), 1903-1913.

Li, S., Zhao, J. H., Luan, J., Ekelund, U., Luben, R. N., Khaw, K. T., Wareham, N. J. & Loos, R. J. 2010. Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. PLoS Med. 7 (8), e1000332.

Li, S., Zhao, J. H., Luan, J., Langenberg, C., Luben, R. N., Khaw, K. T., Wareham, N. J. & Loos, R. J. 2011. Genetic predisposition to obesity leads to increased risk of type 2 diabetes. Diabetologia 54 (4), 776-782.

Liu, G., Zhu, H., Lagou, V., Gutin, B., Stallmann-Jorgensen, I. S., Treiber, F. A., Dong, Y. & Snieder, H. 2010. FTO variant rs9939609 is associated with body mass index and waist circumference, but not with energy intake or physical activity in European- and African-American youth. BMC Med.Genet. 11, 57.

Lollgen, H., Bockenhoff, A. & Knapp, G. 2009. Physical activity and all-cause mortality: An updated meta-analysis with different intensity categories. Int.J.Sports Med. 30 (3), 213-224.

Loos, R. J. & Bouchard, C. 2008. FTO: The first gene contributing to common forms of human obesity. Obes.Rev. 9 (3), 246-250.

Loos, R. J. & Bouchard, C. 2003. Obesity--is it a genetic disorder? J.Intern.Med. 254 (5), 401-425.

Loos, R. J., Derom, C., Derom, R. & Vlietinck, R. 2005. Determinants of birthweight and intrauterine growth in liveborn twins. Paediatr.Perinat.Epidemiol. 19 Suppl 1, 15-22.

MacGregor, A. J., Andrew, T., Sambrook, P. N. & Spector, T. D. 2004. Structural, psychological, and genetic influences on low back and neck pain: A study of adult female twins. Arthritis Rheum. 51 (2), 160-167.

Maes, H. H., Neale, M. C. & Eaves, L. J. 1997. Genetic and environmental factors in relative body weight and human adiposity. Behav.Genet. 27 (4), 325-351.

Magliano, D. J., Shaw, J. E., Shortreed, S. M., Nusselder, W. J., Liew, D., Barr, E. L., Zimmet, P. Z. & Peeters, A. 2008. Lifetime risk and projected population prevalence of diabetes. Diabetologia 51 (12), 2179-2186.

Mainous, A. G.,3rd, Baker, R., Koopman, R. J., Saxena, S., Diaz, V. A., Everett, C. J. & Majeed, A. 2007. Impact of the population at risk of diabetes on projections of diabetes burden in the United States: An epidemic on the way. Diabetologia 50 (5), 934-940.

Malecki, M. T. & Klupa, T. 2005. Type 2 diabetes mellitus: From genes to disease. Pharmacol.Rep. 57 Suppl, 20-32.

Manson, J. E., Rimm, E. B., Stampfer, M. J., Colditz, G. A., Willett, W. C., Krolewski, A. S., Rosner, B., Hennekens, C. H. & Speizer, F. E. 1991. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. The Lancet 338 (8770), 774-778.

Marenberg, M. E., Risch, N., Berkman, L. F., Floderus, B. & de Faire, U. 1994. Genetic susceptibility to death from coronary heart disease in a study of twins. N.Engl.J.Med. 330 (15), 1041-1046.

McArdle, W., Katch, F. & Katch, V. 2001. Exercise physiology:energy, nutrition, and human performance. (5th ed edition) Baltimore, USA: Lippincott Williams & Wilkins.

McCaffery, J. M., Papandonatos, G. D., Bond, D. S., Lyons, M. J. & Wing, R. R. 2009. Gene X environment interaction of vigorous exercise and body mass index among male Vietnam-era twins. Am.J.Clin.Nutr. 89 (4), 1011-1018.

Meigs, J. B., Cupples, L. A. & Wilson, P. W. 2000. Parental transmission of type 2 diabetes: The Framingham offspring study. Diabetes 49 (12), 2201-2207.

Misra, A. & Vikram, N. K. 2003. Clinical and pathophysiological consequences of abdominal adiposity and abdominal adipose tissue depots. Nutrition 19 (5), 457-466.

Monrad, R. N., Grunnet, L. G., Rasmussen, E. L., Malis, C., Vaag, A. & Poulsen, P. 2009. Age-dependent nongenetic influences of birth weight and adult body fat on insulin sensitivity in twins. J.Clin.Endocrinol.Metab. 94 (7), 2394-2399.

Morris, J. N., Everitt, M. G., Pollard, R., Chave, S. P. & Semmence, A. M. 1980. Vigorous exercise in leisure-time: Protection against coronary heart disease. Lancet 2 (8206), 1207-1210.

Morseth, B., Jorgensen, L., Emaus, N., Jacobsen, B. K. & Wilsgaard, T. 2011. Tracking of leisure time physical activity during 28 yr in adults. The Tromso study. Med.Sci.Sports Exerc. 43 (7), 1229-1234.

Mustelin, L., Silventoinen, K., Pietiläinen, K., Rissanen, A. & Kaprio, J. 2009. Physical activity reduces the influence of genetic effects on BMI and waist circumference: A study in young adult twins. Int.J.Obes.(Lond) 33 (1), 29-36.

Nelson, T. L., Brandon, D. T., Wiggins, S. A. & Whitfield, K. E. 2006. Genetic and environmental influences on body fat and blood pressure in African-American adult twins. Int.J.Obes.(Lond) 30 (2), 243-250.

Nieminen, M. M., Kaprio, J. & Koskenvuo, M. 1991. A population-based study of bronchial asthma in adult twin pairs. Chest 100 (1), 70-75.

Nocon, M., Hiemann, T., Muller-Riemenschneider, F., Thalau, F., Roll, S. & Willich, S. N. 2008. Association of physical activity with all-cause and cardiovascular mortality: A systematic review and meta-analysis. Eur.J.Cardiovasc.Prev.Rehabil. 15 (3), 239-246.

Nyman, T., Mulder, M., Iliadou, A., Svartengren, M. & Wiktorin, C. 2010. High heritability for concurrent low back and neck-shoulder pain - a study of twins. Spine (Phila Pa.1976).

Oguma, Y., Sesso, H. D., Paffenbarger, R. S.,Jr & Lee, I. M. 2002. Physical activity and all cause mortality in women: A review of the evidence. Br.J.Sports Med. 36 (3), 162-172.

Okura, Y., Urban, L. H., Mahoney, D. W., Jacobsen, S. J. & Rodeheffer, R. J. 2004. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J.Clin.Epidemiol. 57 (10), 1096-1103.

Ortega-Alonso, A., Sipilä, S., Kujala, U. M., Kaprio, J. & Rantanen, T. 2009. Genetic influences on change in BMI from middle to old age: A 29-year follow-up study of twin sisters. Behav.Genet. 39 (2), 154-164.

Paffenbarger, R. S.,Jr & Hyde, R. T. 1984. Exercise in the prevention of coronary heart disease. Prev.Med. 13 (1), 3-22.

Paffenbarger, R. S.,Jr & Lee, I. M. 1997. Intensity of physical activity related to incidence of hypertension and all-cause mortality: An epidemiological view. Blood Press.Monit. 2 (3), 115-123.

Pan, X. R., Li, G. W., Hu, Y. H., Wang, J. X., Yang, W. Y., An, Z. X., Hu, Z. X., Lin, J., Xiao, J. Z., Cao, H. B., Liu, P. A., Jiang, X. G., Jiang, Y. Y., Wang, J. P., Zheng, H., Zhang, H., Bennett, P. H. & Howard, B. V. 1997. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and diabetes study. Diabetes Care 20 (4), 537-544.

Parsons, T. J., Power, C. & Manor, O. 2006. Longitudinal physical activity and diet patterns in the 1958 British birth cohort. Med.Sci.Sports Exerc. 38 (3), 547-554.

Petersen, L., Andersen, P. K. & Sorensen, T. I. 2008. Genetic and environmental effects on mortality before age 70 years. Epidemiology 19 (3), 472-476.

Philippaerts, R. M., Westerterp, K. R. & Lefevre, J. 1999. Doubly labelled water validation of three physical activity questionnaires. Int.J.Sports Med. 20 (5), 284-289.

Physical Activity Guidelines Advisory Committee 2008. Physical Activity Guidelines Advisory Committee Report, 2008. Washington, DC.

Pietiläinen, K. H., Kaprio, J., Borg, P., Plasqui, G., Yki-Järvinen, H., Kujala, U. M., Rose, R. J., Westerterp, K. R. & Rissanen, A. 2008. Physical inactivity and obesity: A vicious circle. Obesity (Silver Spring) 16 (2), 409-414.

Pischon, T., Boeing, H., Hoffmann, K., Bergmann, M., Schulze, M. B., Overvad, K., van der Schouw, Y. T., Spencer, E., Moons, K. G., Tjonneland, A., et al. 2008. General and abdominal adiposity and risk of death in Europe. N.Engl.J.Med. 359 (20), 2105-2120.

Plomin, R., DeFries, J. C., McClearn, G. E. & McGuffin, P. 2000. Behavioral Genetics. (4 th edition) New York: Worth Publishers.

Poulsen, P., Grunnet, L. G., Pilgaard, K., Storgaard, H., Alibegovic, A., Sonne, M. P., Carstensen, B., Beck-Nielsen, H. & Vaag, A. 2009. Increased risk of type 2 diabetes in elderly twins. Diabetes 58 (6), 1350-1355.

Qin, L., Knol, M. J., Corpeleijn, E. & Stolk, R. P. 2010. Does physical activity modify the risk of obesity for type 2 diabetes: A review of epidemiological data. Eur.J.Epidemiol. 25 (1), 5-12.

Ramachandran, A., Snehalatha, C., Mary, S., Mukesh, B., Bhaskar, A. D., Vijay, V. & Indian Diabetes Prevention Programme (IDPP) 2006. The Indian diabetes prevention programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 49 (2), 289-297.

Rankinen, T. & Bouchard, C. 2007. Invited commentary: Physical activity, mortality, and genetics. Am.J.Epidemiol. 166 (3), 260-262.

Rejeski, W. J. & Mihalko, S. L. 2001. Physical activity and quality of life in older adults. J.Gerontol.A Biol.Sci.Med.Sci. 56 Spec No 2, 23-35.

Rethorst, C. D., Wipfli, B. M. & Landers, D. M. 2009. The antidepressive effects of exercise: A meta-analysis of randomized trials. Sports Med. 39 (6), 491-511.

Reunanen, A., Virta, L. & Klaukka T. 2008. Tyypin 2 diabeetikkoja on jo yli puoli miljoonaa (already over half a million type 2 diabetics). Suomen Lääkärilehti (Finnish Medical Journal) 21, 1952-1955.

Revicki, D. A. & Israel, R. G. 1986. Relationship between body mass indices and measures of body adiposity. Am.J.Public Health 76 (8), 992-994.

Rönnemaa, T., Koskenvuo, M., Marniemi, J., Koivunen, T., Sajantila, A., Rissanen, A., Kaitsaari, M., Bouchard, C. & Kaprio, J. 1997. Glucose metabolism in identical twins discordant for obesity. the critical role of visceral fat. J.Clin.Endocrinol.Metab. 82 (2), 383-387.

Rose, G. A. & Blackburn, H. 1968. Cardiovascular survey methods. Monogr.Ser.World Health Organ. 56, 1-188.

Rosengren, A. & Wilhelmsen, L. 1997. Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the primary prevention study in Goteborg. Ann.Epidemiol. 7 (1), 69-75.

Ross, R., Janssen, I., Dawson, J., Kungl, A. M., Kuk, J. L., Wong, S. L., Nguyen-Duy, T. B., Lee, S., Kilpatrick, K. & Hudson, R. 2004. Exercise-induced reduction in obesity and insulin resistance in women: A randomized controlled trial. Obes.Res. 12 (5), 789-798.

Sarna, S., Kaprio, J., Sistonen, P. & Koskenvuo, M. 1978. Diagnosis of twin zygosity by mailed questionnaire. Hum.Hered. 28 (4), 241-254.

Schmitz, K. H., Jacobs, D. R.,Jr, Leon, A. S., Schreiner, P. J. & Sternfeld, B. 2000. Physical activity and body weight: Associations over ten years in the CARDIA study. Coronary artery risk development in young adults. Int.J.Obes.Relat.Metab.Disord. 24 (11), 1475-1487.

Schousboe, K., Visscher, P. M., Erbas, B., Kyvik, K. O., Hopper, J. L., Henriksen, J. E., Heitmann, B. L. & Sorensen, T. I. 2004. Twin study of genetic and environmental influences on adult body size, shape, and composition. Int.J.Obes.Relat.Metab.Disord. 28 (1), 39-48.

Schousboe, K., Willemsen, G., Kyvik, K. O., Mortensen, J., Boomsma, D. I., Cornes, B. K., Davis, C. J., Fagnani, C., Hjelmborg, J., Kaprio, J., De Lange, M., Luciano, M., Martin, N. G., Pedersen, N., Pietiläinen, K. H., Rissanen, A., Saarni, S., Sorensen, T. I., Van Baal, G. C. & Harris, J. R. 2003. Sex differences in heritability of BMI: A comparative study of results from twin studies in eight countries. Twin Res. 6 (5), 409-421.

Scuteri, A., Sanna, S., Chen, W. M., Uda, M., Albai, G., Strait, J., Najjar, S., Nagaraja, R., Orru, M., Usala, G., et al. 2007. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. 3 (7), e115.

Selmer, R. 1992. Blood pressure and twenty-year mortality in the city of Bergen, Norway. Am.J.Epidemiol. 136 (4), 428-440.

September, A. V., Schwellnus, M. P. & Collins, M. 2007. Tendon and ligament injuries: The genetic component. Br.J.Sports Med. 41 (4), 241-6; discussion 246.

Shaw, K., Gennat, H., O'Rourke, P. & Del Mar, C. 2006. Exercise for overweight or obesity. Cochrane Database Syst.Rev. (4) (4), CD003817.

Shephard, R. J. 2003. Limits to the measurement of habitual physical activity by questionnaires. Br.J.Sports Med. 37 (3), 197-206; discussion 206.

Silventoinen, K., Hasselbalch, A. L., Lallukka, T., Bogl, L., Pietiläinen, K. H., Heitmann, B. L., Schousboe, K., Rissanen, A., Kyvik, K. O., Sorensen, T. I. & Kaprio, J. 2009. Modification effects of physical activity and protein intake on heritability of body size and composition. Am.J.Clin.Nutr. 90 (4), 1096-1103.

Silventoinen, K. & Kaprio, J. 2009. Genetics of tracking of body mass index from birth to late middle age: Evidence from twin and family studies. Obes.Facts 2 (3), 196-202.

Silventoinen, K., Rokholm, B., Kaprio, J. & Sorensen, T. I. 2010. The genetic and environmental influences on childhood obesity: A systematic review of twin and adoption studies. Int.J.Obes.(Lond) 34 (1), 29-40.

Silventoinen, K., Sammalisto, S., Perola, M., Boomsma, D. I., Cornes, B. K., Davis, C., Dunkel, L., De Lange, M., Harris, J. R., Hjelmborg, J. V., Luciano, M., Martin, N. G., Mortensen, J., Nistico, L., Pedersen, N. L., Skytthe, A., Spector, T. D., Stazi, M. A., Willemsen, G. & Kaprio, J. 2003. Heritability of adult body height: A comparative study of twin cohorts in eight countries. Twin Res. 6 (5), 399-408.

Slattery, M. L., Jacobs, D. R.,Jr & Nichaman, M. Z. 1989. Leisure time physical activity and coronary heart disease death. The US railroad study. Circulation 79 (2), 304-311.

Slentz, C. A., Houmard, J. A. & Kraus, W. E. 2009. Exercise, abdominal obesity, skeletal muscle, and metabolic risk: Evidence for a dose response. Obesity 17, S27–S33.

Sorensen, T. I., Nielsen, G. G., Andersen, P. K. & Teasdale, T. W. 1988. Genetic and environmental influences on premature death in adult adoptees. N.Engl.J.Med. 318 (12), 727-732.

Spector, T. D., Cicuttini, F., Baker, J., Loughlin, J. & Hart, D. 1996. Genetic influences on osteoarthritis in women: A twin study. BMJ 312 (7036), 940-943.

Spector, T. D. & MacGregor, A. J. 2004. Risk factors for osteoarthritis: Genetics. Osteoarthritis Cartilage 12 Suppl A, S39-44.

Speliotes, E. K., Willer, C. J., Berndt, S. I., Monda, K. L., Thorleifsson, G., Jackson, A. U., Allen, H. L., Lindgren, C. M., Luan, J., Magi, R., et al. 2010. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat.Genet. 42 (11), 937-948.

Sternfeld, B., Wang, H., Quesenberry, C. P.,Jr, Abrams, B., Everson-Rose, S. A., Greendale, G. A., Matthews, K. A., Torrens, J. I. & Sowers, M. 2004. Physi-

cal activity and changes in weight and waist circumference in midlife women: Findings from the study of women's health across the nation. Am.J.Epidemiol. 160 (9), 912-922.

Stubbe, J. H., Boomsma, D. I., Vink, J. M., Cornes, B. K., Martin, N. G., Skytthe, A., Kyvik, K. O., Rose, R. J., Kujala, U. M., Kaprio, J., Harris, J. R., Pedersen, N. L., Hunkin, J., Spector, T. D. & de Geus, E. J. 2006. Genetic influences on exercise participation in 37.051 twin pairs from seven countries. PLoS ONE 1 (1).

Stubbe, J. H., de Moor, M. H., Boomsma, D. I. & de Geus, E. J. 2007. The association between exercise participation and well-being: A co-twin study. Prev.Med. 44 (2), 148-152.

Stumvoll, M., Goldstein, B. J. & van Haeften, T. W. 2005. Type 2 diabetes: Principles of pathogenesis and therapy. Lancet 365 (9467), 1333-1346.

Sullivan, P. F., Neale, M. C. & Kendler, K. S. 2000. Genetic epidemiology of major depression: Review and meta-analysis. Am.J.Psychiatry 157 (10), 1552-1562.

Terry, D. F., Wilcox, M. A., McCormick, M. A., Pennington, J. Y., Schoenhofen, E. A., Andersen, S. L. & Perls, T. T. 2004. Lower all-cause, cardiovascular, and cancer mortality in centenarians' offspring. J.Am.Geriatr.Soc. 52 (12), 2074-2076.

The Social Insurance Institution of Finland 2010. Reimbursements for medicine expences. Available in: http://www.kela.fi/in/internet/english.nsf/NET/131003131216MH?OpenDocument. Accessed: 2011 March 21.

Thomas, D. 2002. Statistical Methods in Genetic Epidemiology. USA: Oxford University Press.

Tresierras, M. A. & Balady, G. J. 2009. Resistance training in the treatment of diabetes and obesity: Mechanisms and outcomes. J.Cardiopulm.Rehabil.Prev. 29 (2), 67-75.

Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hämäläinen, H., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., Uusitupa, M. & Finnish Diabetes Prevention Study Group 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N.Engl.J.Med. 344 (18), 1343-1350.

U.S. Department of Health and Human Services 1996. Physical activity and health: A report of the surgeon general. Atlanta, GA.

Uusitupa, M., Tuomilehto, J. & Puska, P. 2011. Are we really active in the prevention of obesity and type 2 diabetes at the community level? Nutr.Metab.Cardiovasc.Dis. 21 (5), 380-389.

Vanhees, L., Lefevre, J., Philippaerts, R., Martens, M., Huygens, W., Troosters, T. & Beunen, G. 2005. How to assess physical activity? how to assess physical fitness? Eur.J.Cardiovasc.Prev.Rehabil. 12 (2), 102-114.

Vazquez, G., Duval, S., Jacobs, D. R.,Jr & Silventoinen, K. 2007. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: A meta-analysis. Epidemiol.Rev. 29, 115-128.

vB Hjelmborg, J., Iachine, I., Skytthe, A., Vaupel, J. W., McGue, M., Koskenvuo, M., Kaprio, J., Pedersen, N. L. & Christensen, K. 2006. Genetic influence on human lifespan and longevity. Hum.Genet. 119 (3), 312-321.

Vimaleswaran, K. S., Li, S., Zhao, J. H., Luan, J., Bingham, S. A., Khaw, K. T., Ekelund, U., Wareham, N. J. & Loos, R. J. 2009. Physical activity attenuates the body mass index-increasing influence of genetic variation in the FTO gene. Am.J.Clin.Nutr. 90 (2), 425-428.

Vimaleswaran, K. S. & Loos, R. J. 2010. Progress in the genetics of common obesity and type 2 diabetes. Expert Rev.Mol.Med. 12, e7.

Voight, B. F., Scott, L. J., Steinthorsdottir, V., Morris, A. P., Dina, C., Welch, R. P., Zeggini, E., Huth, C., Aulchenko, Y. S., Thorleifsson, G., et al. 2010. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat.Genet. 42 (7), 579-589.

Wang, Y., Rimm, E. B., Stampfer, M. J., Willett, W. C. & Hu, F. B. 2005. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am.J.Clin.Nutr. 81 (3), 555-563.

Wang, Y., Simar, D. & Fiatarone Singh, M. A. 2009. Adaptations to exercise training within skeletal muscle in adults with type 2 diabetes or impaired glucose tolerance: A systematic review. Diabetes Metab.Res.Rev. 25 (1), 13-40.

Warburton, D. E., Nicol, C. W. & Bredin, S. S. 2006. Health benefits of physical activity: The evidence. CMAJ 174 (6), 801-809.

Westendorp, R. G., van Heemst, D., Rozing, M. P., Frolich, M., Mooijaart, S. P., Blauw, G. J., Beekman, M., Heijmans, B. T., de Craen, A. J., Slagboom, P. E. & Leiden Longevity Study Group 2009. Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden longevity study. J.Am.Geriatr.Soc. 57 (9), 1634-1637.

WHO 2011a. Diabetes, Fact sheet N°312. Available in: http://www.who.int/mediacentre/factsheets/fs312/en/index.html.

WHO 2011b. Obesity and overweight, Fact sheet N°311. Available in: http://www.who.int/mediacentre/factsheets/fs311/en/index.html.

WHO 2010a. Ageing. Available in: http://www.who.int/topics/ageing/en/index.html.

WHO 2010b. Global recommendations on physical activity for health. Switzerland.

WHO 2008. Waist circumference and waist–hip ratio: report of a WHO expert consultation, Geneva, 8–11, December 2008. Geneva.

WHO 2006a. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia : report of a WHO/IDF consultation. Geneva.

WHO 2006b. Obesity and overweight. Available in: http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/.

Wienke, A., Herskind, A. M., Christensen, K., Skytthe, A. & Yashin, A. I. 2005. The heritability of CHD mortality in Danish twins after controlling for smoking and BMI. Twin Res.Hum.Genet. 8 (1), 53-59.

Wienke, A., Holm, N. V., Skytthe, A. & Yashin, A. I. 2001. The heritability of mortality due to heart diseases: A correlated frailty model applied to Danish twins. Twin Res. 4 (4), 266-274.

Wild, S., Roglic, G., Green, A., Sicree, R. & King, H. 2004. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 27 (5), 1047-1053.

Williams, R. L. 2000. A note on robust variance estimation for cluster-correlated data. Biometrics 56 (2), 645-646.

Winters-Hart, C. S., Brach, J. S., Storti, K. L., Trauth, J. M. & Kriska, A. M. 2004. Validity of a questionnaire to assess historical physical activity in older women. Med.Sci.Sports Exerc. 36 (12), 2082-2087.

Witham, M. D. & Avenell, A. 2010. Interventions to achieve long-term weight loss in obese older people: A systematic review and meta-analysis. Age Ageing 39 (2), 176-184.

Woodcock, J., Franco, O. H., Orsini, N. & Roberts, I. 2011. Non-vigorous physical activity and all-cause mortality: Systematic review and meta-analysis of cohort studies. Int.J.Epidemiol. 40 (1), 121-138.

Wu, T., Gao, X., Chen, M. & van Dam, R. M. 2009. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: A meta-analysis. Obes.Rev. 10 (3), 313-323.

Yusuf, S., Hawken, S., Ounpuu, S., Bautista, L., Franzosi, M. G., Commerford, P., Lang, C. C., Rumboldt, Z., Onen, C. L., Lisheng, L., Tanomsup, S., Wangai, P.,Jr, Razak, F., Sharma, A. M., Anand, S. S. & INTERHEART Study Investigators 2005. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: A case-control study. The Lancet 366 (9497), 1640-1649.

Zdravkovic, S., Wienke, A., Pedersen, N. L., Marenberg, M. E., Yashin, A. I. & de Faire, U. 2004. Genetic influences on CHD-death and the impact of known risk factors: Comparison of two frailty models. Behav.Genet. 34 (6), 585-592.

Zdravkovic, S., Wienke, A., Pedersen, N. L., Marenberg, M. E., Yashin, A. I. & De Faire, U. 2002. Heritability of death from coronary heart disease: A 36-year follow-up of 20 966 Swedish twins. J.Intern.Med. 252 (3), 247-254.

Zierath, J. R. 2002. Invited review: Exercise training-induced changes in insulin signaling in skeletal muscle. J.Appl.Physiol. 93 (2), 773-781.

ORIGINAL PAPERS

I

PHYSICAL ACTIVITY, MORBIDITY AND MORTALITY IN TWINS: A 24-YEAR PROSPECTIVE FOLLOW-UP

by

Waller K, Kujala UM, Rantanen T, Kauppinen M, Silventoinen K, Koskenvuo M, Kaprio J. 2010

European Journal of Epidemiology 25(10),731-739

Eur J Epidemiol (2010) 25:731–739
DOI 10.1007/s10654-010-9493-x

GENETIC EPIDEMIOLOGY

Physical activity, morbidity and mortality in twins: a 24-year prospective follow-up

Katja Waller · Urho M. Kujala · Taina Rantanen · Markku Kauppinen · Karri Silventoinen · Markku Koskenvuo · Jaakko Kaprio

Received: 29 August 2008 / Accepted: 16 July 2010 / Published online: 3 August 2010

Abstract The aim of this study was to find out whether persistent leisure-time physical activity, adjusted for genetic liability and childhood experiences, protect against occurrence of specific chronic diseases and all-cause mortality. Study design was a 24-year prospective follow-up after 6-year physical activity discordance in twin pairs. From 5,663 healthy adult twin pairs, 146 pairs (including 29 mozygotic) discordant for both intensity and volume of leisure physical activity at baseline in both 1975 and 1981 were systematically identified. Mortality and occurrence of chronic diseases (diabetes, hypertension, coronary heart disease defined according to reimbursable medication status) were followed for the period 1.1.1983–31.12.2006 for mortality and 1.1.1983–31.12.2004 for diseases. By end of follow-up, 19 inactive and 10 active co-twins had died. In the whole sample, HR of death adjusted for social class was 2.08 (95% CI 1.06–4.09) for inactive vs. active co-twins, the HR being 2.67 (95% CI 1.15–6.20) among DZ pairs with no mortality difference among the smaller number of discordant MZ pairs. The reimbursable medication analyses showed a tendency of higher risk for inactive vs. active co-twins. Among DZ pairs, HR of diabetes medication adjusted for social class was 2.73 (95% CI 0.62–12.00) and HR of hypertension medication was 2.14 (95% CI 0.94–4.89). This study supports the earlier findings that physical activity is associated with reduced mortality. However the difference was seen only in DZ pairs and therefore some residual genetic confounding effects on mortality cannot be excluded.

Keywords Morbidity · Mortality · Physical activity · Prospective follow-up · Twin studies

Abbreviations
DZ Dizygotic
MZ Monozygotic

Introduction

A sedentary lifestyle is one of the ten leading causes of death and disability in the world, and approximately two million deaths every year are estimated to be attributable to physical inactivity [1]. The protective effect of physical activity on coronary heart disease and all-cause mortality has been reported in many observational studies [2–13]. The present evidence shows an inverse curvilinear dose–response relation between physical activity and all-cause mortality [14, 15]. However, this association has only been investigated in observational studies and no randomized controlled trials are available to support the findings [14, 15]. This association could also be affected by genetic factors predisposing to sedentariness [16, 17], which also

K. Waller (✉) · U. M. Kujala · T. Rantanen · M. Kauppinen
Department of Health Sciences, University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland
e-mail: katja.waller@jyu.fi

T. Rantanen · M. Kauppinen
Finnish Centre for Interdisciplinary Gerontology, University of Jyväskylä, Jyväskylä, Finland

K. Silventoinen · M. Koskenvuo · J. Kaprio
Department of Public Health, University of Helsinki, Helsinki, Finland

J. Kaprio
Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland

affects lifespan. A Swedish twin study by Carlsson et al. [12] found that physical activity independently protects against death. This study was able to tackle the issue of genetic influence and shared environment, but the study was conducted among healthy and already chronically diseased subjects. Therefore, as stated by Rankinen and Bouchard in the commentary [17], this study cannot be used to conclude the matter.

The underlying causes of difference in mortality between physically inactive and active subjects are mainly deaths from metabolic syndrome and cardiovascular diseases. Genetic selection and shared environmental factors may play a role towards both physical activity and mortality. For example if a person due to his/her genetic susceptibility becomes ill, gains weight or has naturally low aerobic fitness this may lead to inactivity and cause selection bias in observational studies. Various studies have shown that physical fitness and ability to achieve high levels of physical activity have genetic components [11, 18, 19]. Childhood environment has also been shown to play a modest role in adult exercise behaviour [16]. Some evidence show that inherited biological characteristics facilitate some individuals to exercise and therefore favour them with lower morbidity and mortality [11, 20, 21]. Twin [22] and adoption [23] studies have shown that genetics may also have an important role as the underlying cause for mortality, for example Swedish and Danish twin studies have suggested that the age at death from CAD has moderate to high heritability [24–27]. Although Herskind et al. [28] estimated in a Danish twin study that the heritability of longevity is quite low; i.e. 0.2, it was found in an analysis of Nordic twin data to increase after age 60 [29].

In epidemiological studies, genetic selection and childhood environment may be important confounders when studying the effect of physical activity on mortality as explained in the previous paragraph. It is difficult to conduct a randomised controlled trial of the effect of physical activity on morbidity and mortality with a long enough follow-up period. Therefore we followed twin pairs prospectively for 24 years, after initial 6-year baseline discordance in intensity and volume of leisure-time physical activity, to study the association between physical activity and all-cause mortality. A second aim was to study the chronic disease mechanisms underlying the possible mortality difference by studying differences in the occurrence of diabetes, hypertension and coronary heart disease as well as difference in cancer incidences between inactive and active co-twins. Our twin pair study design takes into account genetic predisposition (monozygotic twins) and childhood home environment (monozygotic and dizygotic twins). Monozygotic (MZ) pairs are genetically identical at the sequence level and these genetic factors are controlled for, while dizygotic (DZ) twins share on average half of their segregating genes. Both (DZ and MZ) pairs nearly always share the same childhood environment and therefore childhood home environment is controlled for among both types of twins.

Methods

Subjects

The Finnish Twin Cohort includes all same-sex twin pairs born in Finland before 1958 and with both co-twins alive in 1967 [30]. For this study, the initial inclusion criteria were employment (including women working at home and students) in 1981 and complete data on leisure-time physical activity required for MET index calculations gathered by postal surveys in 1975 and 1981. The subjects were between 24 and 60 years of age on January 1, 1982 ($n = 17{,}968$) [11]. All pairs in which at least one of the twins did not respond to both questionnaires, had died or had a chronic disease, except hypertension, by the end of 1982 were excluded [8, 11, 30]. The healthy cohort comprised 5,663 same-sex twin pairs (3,551 dizygotic, 1,772 monozygotic and 340 pairs with unknown zygosity) [11]. Zygosity determination was based on an accurate and validated questionnaire method [31]. Finally, included in this study were 146 same-sex twin pairs who were discordant for leisure-time physical activity in both participation in vigorous activity and volume of activity in 1975 and 1981. The mean age of the subjects was 38.1 years at the beginning of the follow-up (1.1.1983). The final study cohort (146 pairs) consisted of 65 male and 81 female pairs, of which 29 were monozygotic, 116 dizygotic and one of uncertain zygosity.

Assessment of predictors

The subjects had been mailed similar questionnaires in 1975 and 1981. These included questions on weight, height, physical activity, occupation, alcohol use, smoking and physician-diagnosed diseases. Among those for whom addresses were known (93.5% of subjects) in 1975, the response rate for twin pairs was 87.6%. The response rate among those responding in 1975 and alive in 1981 was 90.7% in 1981. Physical activity habits assessed by identical questions in 1975 and 1981 were used as the baseline predictor in the present study. These data are considered to be valid on the bases of earlier studies [8, 32–35]. Our earlier analysis showed high correlations between physical activity questions and physical activity data obtained by interview [36]. In other prospective studies using the entire twin cohort, low activity metabolic equivalent (MET)

index has been shown to be a predictor of mortality, type 2 diabetes, coronary heart disease and hospitalization [8, 11, 37–39].

For the current study, 146 same-sex twin pairs were comprehensively selected from the entire Finnish Twin Cohort on the basis of discordance for leisure-time physical activity both for participation in vigorous activity and volume of activity (MET index) in 1975 and 1981. Assessment of participation in vigorous physical activity in 1975 and 1981 was based on the following question: Is your leisure-time physical activity about as strenuous on average as: (1) walking, (2) alternately walking and jogging, (3) jogging (light running), (4) running. Those who chose alternatives 2, 3 or 4 were classified as participating in vigorous activity. Assessment of the MET index was based on a series of structured questions [8, 32] on leisure physical activity (monthly frequency, mean duration and mean intensity of sessions) and physical activity during the journey to and from work. The index was calculated by assigning a MET score to each activity and by calculating the product of that activity: intensity x duration x frequency [8]. The MET index was expressed as the sum-score of leisure MET hours/day. Subjects whose volume of activity was $\geq$2 MET hours/day (corresponding to about 30 min walking per day) were classified as physically active compared to their inactive co-twins whose level of activity was $<$2 MET hours/day. In 1975 the leisure-time MET index for 146 twin pairs was 4.59 MET hours/day for active and 0.71 MET hours/day for inactive co-twins. In 1981 the MET index was 5.80 MET hours/day for active and 0.84 MET hours/day for inactive co-twins. Similar MET values were seen for men, women, and MZ and DZ pairs.

For the present study self-reported smoking status, use of alcohol, work-related physical activity at baseline in 1981 and social class in 1975 were used as covariates. Smoking status was coded into four categories (never smoked, former smoker, occasional smoker, and current (daily) smoker) determined from responses to detailed smoking history questions [34]. Alcohol use was a dichotomous index of binge drinking and defined by whether the subject had drunk at least five drinks on a single occasion, at least monthly [33]. Social class had six categories (for categories see Table 1), and the classification was based on job title according to the Central Statistical Office of Finland [40]. Work-related physical activity was used as a categorical variable with four-point ordinal scale [11]. A four-question ordinal scale on life satisfaction (LS) yielded a sum-score ranging between 4 and 20, with an increasing score indicating a decrease in life satisfaction [41]. The life satisfaction scale correlates well ($r > 0.6$) with depressiveness on the Beck Depression Inventory [41].

Mortality assessment

All-cause mortality during the follow-up was analysed. The mortality follow-up began on January 1, 1983 and continued until December 31, 2006. For mortality assessment the dates of death were available from the Population Register Centre of Finland.

Assessment of reimbursed medication

To investigate the most likely causal pathways between physical activity and reduced mortality, type 2 diabetes, hypertension and coronary heart disease reimbursable medications were analysed. The reimbursable medication follow-up began on January 1, 1983 and continued until December 31, 2004. Reimbursable medication information for the 146 pairs was obtained from the Social Insurance Institution of Finland, which is the agency responsible for basic social security covering all residents of Finland [42]. The Social Insurance Institution of Finland reimburses whole or part of the cost of necessary medications to patients who have a medical certificate based on a diagnosis by a physician indicating the presence of a severe chronic disease [43]. Although the register is not sensitive to cases of a mild disease, it has very high validity and the possibility of false positive cases is unlikely [42]. The date of being granted the right to reimbursable medication was used in the analysis.

Assessment of cancers

Information on cancers (primary site and time of diagnosis) was obtained from the population-based Finnish Cancer Registry. The cancer follow-up began on January 1, 1983 and continued until December 31, 2004. Having cancer was determined according to the first diagnoses. Cancers that physical activity is known to protect against, i.e. breast cancer and colon cancer [44, 45], were also analysed separately as one group.

Statistical analysis

First, we conducted a mortality analysis and calculated hazard ratios (HR) with their 95% confidence intervals (CI) for 146 physical activity discordant twin pairs using the Cox proportional hazard model clustering for family. We then adjusted the model for social class, smoking status and alcohol use at baseline by adding one covariate at the time into the model. Similar analyses were carried out for reimbursable medications and occurrence of cancers. Follow-ups for all the endpoints were started on January 1, 1983, which allows for a lag of 1 year from the second physical activity assessment. The follow-up ended on

Table 1 Baseline characteristics in 1975 and 1981 for 146 twin pairs

Characteristics	146 pairs in 1975			146 pairs in 1981		
	Inactive	Active	*P* value	Inactive	Active	*P* value
Age (SD)	30.1 (8.1)	30.1 (8.1)		36.1 (8.1)	36.1 (8.1)	
Height (SD)	168.5 (8.5)	169.5 (8.5)	0.027	168.8 (8.6)	169.6 (8.3)	0.065
Weight (SD)	64.6 (12.4)	64.9 (10.9)	0.73	68.1 (13.2)	66.3 (10.9)	0.036
BMI (SD)	22.6 (3.1)	22.5 (2.5)	0.59	23.8 (3.4)	23.0 (2.5)	0.003
Ever regular smoker, *N* (%)	83 (56.8%)	67 (45.9%)	0.037	85 (58.2%)	65 (44.5%)	0.008
Pack years smoked (SD)	4.2 (6.2)	2.6 (4.9)	<0.001	6.9 (9.8)	3.4 (6.6)	<0.001
Years smoked (SD)	9.9 (7.0)	7.7 (5.7)	0.003	15.0 (7.3)	11.5 (7.5)	0.002
Alcohol grams/day (SD)	8.1 (13.4)	9.0 (15.4)	0.49	8.4 (13.4)	7.5 (9.4)	0.46
Binge drinking, *N* (%)	30 (20.8%)	34 (23.6%)	0.59	36 (24.8%)	30 (20.7%)	0.39
Diagnosed hypertension, *N* (%)	8 (5.6%)	8 (5.6%)	1.00	15 (10.3%)	9 (6.2%)	0.26
Life satisfaction (SD)[a]	8.8 (2.7)	8.0 (2.5)	0.004	8.6 (2.6)	8.2 (2.9)	0.28
Marital status, *N* (%)			0.097			0.089
Single	42 (28.8%)	57 (39.0%)		28 (19.2%)	27 (18.5%)	
Married	91 (62.3%)	83 (56.8%)		102 (69.9%)	99 (67.8%)	
Divorced	6 (4.1%)	4 (2.7%)		6 (4.1%)	1 (0.7%)	
Cohabiting	5 (3.4%)	2 (1.4%)		9 (6.2%)	17 (11.6%)	
Widowed	2 (1.4%)	0		1 (0.7%)	2 (1.4%)	
Work-related physical activity, *N* (%)			0.019			0.012
Sedentary	47 (32.4%)	57 (39.3%)		48 (33.3%)	64 (44.4%)	
Standing or walking at work	26 (17.9%)	32 (22.1%)		23 (16.0%)	30 (20.8%)	
Light manual labour	61 (42.1%)	52 (35.9%)		51 (35.4%)	43 (29.9%)	
Heavy manual labour	11 (7.6%)	4 (2.8%)		22 (15.3%)	7 (4.9%)	
Social class, *N* (%)						
Upper white-collar worker	11 (7.5%)	13 (8.9%)				
Clerical worker	48 (32.9%)	51 (34.9%)				
Skilled worker	48 (32.9%)	52 (35.6%)				
Unskilled worker	11 (7.5%)	11 (7.5%)				
Farmer	19 (13.0%)	3 (2.1%)				
Other (students, army, retired, unknown)	9 (6.2%)	16 (11.0%)				

Plus-minus values are means ± SD

[a] The life satisfaction index was a four-question scale with sum-score ranging from 4 to 20, with an increasing score indicating a decrease in life satisfaction

December 31, 2006 or at emigration or death and for the medication analyses at the time when reimbursable medication status was granted or for cancer analysis at the time of the first cancer diagnosis or at end of follow-up (31.12.2004). All of these analyses were then carried out separately for MZ and DZ pairs. Three co-twins were excluded from all of the analyses, as they had emigrated before the follow-up start date, and 10 co-twins were excluded from the hypertension and a combination medication analyses, as these subjects had been granted hypertension reimbursable medication before the follow-up start date. Active co-twins were used as the reference group in all of the analyses. To test whether the hazard ratios differed by zygosity, a test of interaction between physical activities within discordant pairs and zygosity (MZ vs. DZ) was used. Data were analyzed with SPSS 14.0 for Windows [46] and STATA 9.0 [47] statistical packages.

Results

The baseline characteristics of the study cohort for 1975 and 1981 are shown in Table 1. In both years there were more inactive co-twins who had ever smoked regularly and whose work-related physical activity was heavier when compared with active co-twins. Inactive co-twins had higher BMI in 1981 compared to their active co-twins. Inactive co-twins were less satisfied with their life in 1975, but this was not seen in 1981.

Twenty-nine co-twins died during the follow-up (1.1.1983–31.12.2006). Mean age for all deaths was 57.1 years, inactive co-twins died on average at age of 56 and active at age of 59.3 years. All together 19 inactive and 10 active co-twins died, including 16 inactive and 7 active DZ co-twins and 3 inactive and 3 active MZ co-twins. Among the 29 individuals who died during the follow-up, both co-twins in 4 pairs died, including 2 active and 2 inactive co-twin who died before their co-twins. Figure 1 shows the survival curves for inactive and active co-twins. Inactive co-twins had increased risk of death when compared with their active co-twins (HR = 1.95, 95% CI 0.99–3.84). After adjusting for social class, the HR was 2.08 (95% CI 1.06–4.09). When adjusted for work-related physical activity instead of social class the HR was 1.97 (95% CI 1.01–3.85). Although the study had a fairly low number of subjects and a low number of outcomes, we adjusted the model for other covariates. The hazard ratios remained similar after the further adjustments (Table 2). The hazard ratios increased even further when the analyses were done for DZ pairs only, the HR adjusted for social class being 2.67 (95% CI 1.15–6.20). When analysing MZ pairs, no differences were seen between inactive and active co-twins. The result of the activity discordance × zygosity interaction test for mortality was not significant.

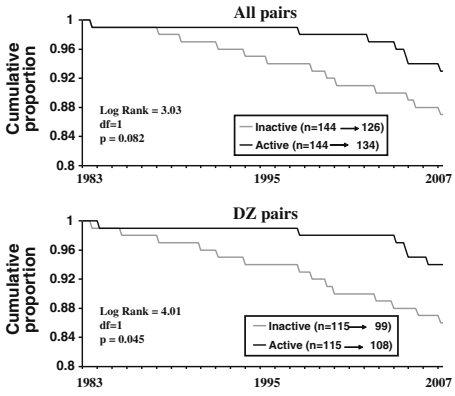

Fig. 1 Survival curves for mortality for all physical activity discordant pairs and for physical activity discordant DZ pairs

Table 2 Hazard ratios for death, cancers and reimbursable drug use for inactive co-twins compared with active co-twins, adjusted for variables in 1975 (social class) or variables in 1981 (alcohol and smoking)

	Discordant			Social class adj.			Social class, alcohol and smoking adj.		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
All pairs									
Mortality	1.95	0.99–3.84	0.054	2.08	1.06–4.10	0.034	2.04	0.94–4.42	0.072
Diabetes[a]	1.39	0.47–4.13	0.55	1.25	0.40–3.88	0.70	1.22	0.40–3.74	0.73
Hypertension[a]	1.57	0.78–3.13	0.21	1.50	0.73–3.08	0.27	1.71	0.82–3.57	0.16
CHD[a]	1.21	0.54–2.72	0.65	1.08	0.40–2.91	0.89	0.96	0.21–4.43	0.96
All med.[b]	1.20	0.73–1.96	0.47	1.14	0.67–1.92	0.63	1.27	0.71–2.26	0.43
Cancers[c]	1.37	0.61–3.06	0.45	1.42	0.61–3.33	0.42	1.34	0.49–3.65	0.57
DZ pairs									
Mortality	2.41	1.05–5.54	0.039	2.67	1.15–6.20	0.022	2.61	1.08–6.29	0.033
Diabetes[a]	2.91	0.74–11.4	0.13	2.73	0.62–12.00	0.18	2.61	0.58–11.73	0.21
Hypertension[a]	2.19	1.00–4.78	0.049	2.14	0.94–4.89	0.072	1.97	0.80–4.87	0.14
CHD[a]	1.08	0.41–2.86	0.88	0.84	0.21–3.40	0.80	1.06	0.34–3.28	0.93
All med.[b]	1.49	0.85–2.62	0.17	1.39	0.73–2.65	0.32	1.46	0.72–2.96	0.30
Cancers[c]	1.50	0.63–3.60	0.36	1.52	0.60–3.85	0.38	1.56	0.54–4.53	0.41
MZ pairs									
Mortality	0.96	0.35–2.60	0.93						
Hypertension[a]	0.44	0.08–2.57	0.36						
All med.[b]	0.59	0.21–1.68	0.33						
Cancers[c]	0.97	0.13–7.32	0.98						

CI denotes confidence interval

[a] Reimbursable medication

[b] All medications includes diabetes, hypertension and CHD reimbursable medications

[c] Any cancer

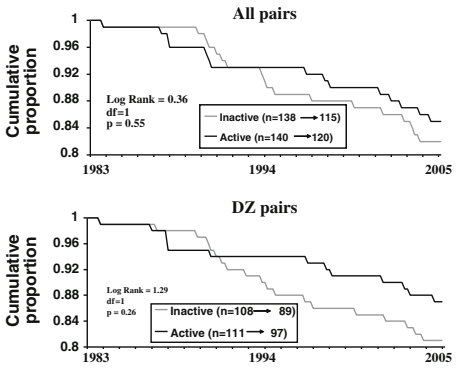

Fig. 2 Survival curves for combined medication variable for all physical activity discordant pairs and for physical activity discordant DZ pairs

The reimbursable medication analyses showed that among the 146 pairs, 23 inactive and 20 active co-twins (19 inactive and 14 active DZ co-twins) had at least one of the studied reimbursable medications. Among the individual medication groups, 8 inactive and 6 active co-twins had medication for diabetes (8 inactive and 3 active DZ co-twins), 18 inactive and 12 active co-twins (16 inactive and 8 active DZ co-twins) had medication for hypertension, and 7 inactive and 6 active co-twins (5 inactive and 5 active DZ co-twins) had medication for coronary heart disease. The reimbursable medication analyses showed a tendency for higher hazard ratios for inactive vs. active co-twins. Figure 2 shows the survival curves for the combined medication variable for inactive and active co-twins. Among DZ pairs, inactive co-twins had higher risk for hypertension medication during the follow-up compared to their active co-twins (HR = 2.19, 95% CI 1.00–4.78), when adjusting for work-related physical activity HR was 2.21 (95% CI 1.02–4.79). Again, no differences were seen within MZ pairs.

The cancer analyses showed that 12 inactive and 9 active co-twins (10 inactive and 7 active DZ co-twins) had at least one cancer in any site during the follow-up. The analyses showed that inactive co-twins had a slightly (but statistically non-significantly) increased risk for any cancer (Table 2) compared to their active co-twins (HR adjusted for social class = 1.42, 95% CI 0.61–3.33). The physical activity-related cancer analyses showed that 7 individuals, 4 inactive and 3 active co-twins, had either breast or colon cancer.

Discussion

Our over 24-year follow-up twin study assessed the relationship between physical activity and all-cause mortality. The all-cause mortality assessment showed that inactive co-twins were more likely to die earlier than their active co-twins including when childhood family environment was controlled for. Our study also investigated the possible disease mechanisms underlying the all-cause mortality difference by studying the risk of having reimbursable medication for type 2 diabetes, hypertension or coronary heart disease. The medication analyses showed a tendency for higher hazard ratios for inactive co-twins, especially for hypertension medication.

In an earlier study, we interviewed 111 pairs of twins from the original sample of 146 pairs and found that the discordant pattern of physical activity continued for a subgroup of 42 pairs for 30 years [36]. That study showed that the adulthood physical activity habits are often maintained for long time, and thus it is possible that the continuation of physical activity habits partly explains the difference in mortality. However, incipient disease from other causes can reduce the ability to exercise and thus attenuate within-pair differences in physical activity over time.

As expected, premature mortality was reduced with physical activity. This finding is in accordance with earlier studies [2–10, 12, 48]. Although a similar study including partly the same study population was conducted by Kujala et al. [11], the present study concentrated on a smaller, but more discordant group of twins over a longer follow-up period. The main difference between the studies was more strict determination of leisure-time physical activity between discordant pairs taking into account both intensity and volume of leisure-time physical activity in the present study compared with the earlier study by Kujala et al. [11]. Also new cases of death had occurred since the previous study. Both analyses showed an association between high physical activity and reduced mortality in DZ twin pairs but not in MZ pairs [11], although the present study used survival analyses methods for pairwise analyses which were not used in the previous study. Lately published Physical Activity Guidelines Advisory Committee Report, 2008 [15] shows that physical activity is clearly associated with reduced all-cause mortality, but our study indicates that there is a possible genetic pleiotropy underlying physical activity and mortality. The present study clearly shows and supports the extant literature that this issue needs to be studied further, maybe among internationally pooled datasets. In the present study, we in addition examined morbidity underlying the mortality differences.

Few review studies have estimated that energy expenditure of at least 1,000 kcal/week is likely to decrease mortality rates [10, 14], although both reviews acknowledged that a lesser volume of physical activity could also have beneficial effects on all-cause mortality. In our study, active co-twins exercised at least 2 MET hours/day (on

average 4.59 MET hours/day in 1975 and 5.80 MET hours/day in 1981) and the intensity of activity was vigorous in two separate baseline years. This indicates that the activity level of these twins was relatively high during this 6-year period.

The mortality difference found in our study could partly be due to differences in type 2 diabetes, hypertension or coronary heart disease as a slight increase in the use of medications for these was seen among inactive co-twins. The use of hypertension medication in particular was higher among inactive co-twins. It is known that physical inactivity is a risk factor for hypertension [49, 50], and increased blood pressure is a predictor of mortality [51–53]. However, we were not able to confirm that physical activity is the major reason for this difference as we did not obtain similar results for MZ pairs, and therefore the possibility of genetic selection towards premature mortality remains. On the other hand, the number of MZ pairs was very small. The actual causes of death were available until the end of 2003. Among the 15 inactive co-twins who died by the end of 2003, the causes of death were 7 cancers, 3 cardio- or cerebrovascular diseases, 2 suicides, 1 disease of respiratory system, 1 alcohol related disease and 1 accidental fall. So, increased prevalence of T2D and CVD does not alone explain the increased mortality of physically inactive co-twins. However, a number of these causes of death are associated with physically inactive lifestyle, such as some cancers [15], CVD [2, 3, 15], pulmonary disease [54], alcohol related problems [55] and accidental falls [15].

The strengths of our study were a very long follow-up period and twin study design. We partly controlled for genetic factors and the childhood environment by studying twin pairs comprehensively selected from the large Finnish Twin Cohort. Another strength of the study was the 6-year baseline assessment period during which physical activity discordance was assessed twice, indicating a true and long-term difference in this particular health habit before the follow-up period began.

One of the limitations of the study was the low mortality rate as only 9.9% of the original sample had died; likewise the number of outcomes was small for medications and cancers. Our relatively young and healthy (exclusion of subjects with any disease but hypertension) study population at baseline contributed to this low rate of outcomes. Finally, one of the co-twins of each pair was relatively active indicating the existence of a healthy lifestyle for at least half of the subjects, while the other half were genetically closely related. One other possible limitation relates to childhood environment as the twins might have some differences in non-shared environmental effects outside home.

The optimal study design for this type of analysis would have been to use a large sample of activity-discordant MZ pairs. However, we did not have sufficient numbers of discordant MZ pairs, even in this large twin cohort that initially included all same-sex Finnish twin pairs who were born in Finland before 1958. So for the main analyses, the MZ pairs were pooled together with the DZ pairs. Among the baseline cohort of 5,663 (31% MZ and 63% DZ) healthy twin pairs a sub-sample of 146 (20% MZ and 80% DZ) pairs were selected for the follow-up study. The reduced number of MZ pairs in our sample is probably due to the finding that MZ pairs consistently discordant for common traits are rare [8, 36, 56]. In addition, high heritability of persistent physical activity makes it difficult to find MZ twin pairs discordant both for physical activity and mortality. The number of MZ pairs, the relatively small overall sample size and the small number of outcome events among MZ twin pairs does not make it possible to draw conclusions separately for MZ pairs. This is an unfortunate study limitation. The significant difference in the DZ pairs suggests that the association between physical activity and the outcome variables is not due to childhood environmental effects, but we cannot of course exclude the effect of genetic predisposition on the results. A Swedish twin study by Carlsson et al. [12] found a difference in mortality among activity-discordant MZ pairs, but their study had limitations as they did not exclude subjects with chronic diseases at baseline [12, 17]. Although we only had a small number of MZ pairs, the study shows that it is important to investigate the genes which are associated with both physical activity and the underlying causes of diseases.

Conclusion

This study supports the earlier findings that physical activity is associated with reduced mortality. However the difference was only seen in dizygotic pairs and therefore some residual confounding due to genetic effects on mortality cannot be excluded.

Acknowledgments This study was supported by the Finnish Ministry of Education, the Juho Vainio Foundation and University of Jyväskylä. The Finnish Twin Cohort study was supported by the GENOMEUTWIN project (supported by the European Union Contract No. QLG2-CT-2002-01254) and the Finnish Twin Cohort Study is part of the Academy of Finland Centre of Excellence in Complex Disease Genetics.

Conflict of interest The authors have no potential conflicts of interest related to the funding.

References

1. WHO. Sedentary lifestyle: A global public health problem. http://www.who.int/moveforhealth/advocacy/information_sheets/sedentary/en/. 2006.

2. Morris JN, Everitt MG, Pollard R, Chave SP, Semmence AM. Vigorous exercise in leisure-time: protection against coronary heart disease. Lancet. 1980;2:1207–10.
3. Paffenbarger RS Jr, Hyde RT. Exercise in the prevention of coronary heart disease. Prev Med. 1984;13:3–22.
4. Leon AS, Connett J, Jacobs DR Jr, Rauramaa R. Leisure-time physical activity levels and risk of coronary heart disease and death: the multiple risk factor intervention trial. JAMA. 1987;258:2388–95.
5. Slattery ML, Jacobs DR Jr, Nichaman MZ. Leisure time physical activity and coronary heart disease death: the US railroad study. Circulation. 1989;79:304–11.
6. Lee IM, Hsieh CC, Paffenbarger RS Jr. Exercise intensity and longevity in men: the harvard alumni health study. JAMA. 1995;273:1179–84.
7. Rosengren A, Wilhelmsen L. Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the primary prevention study in goteborg. Ann Epidemiol. 1997;7:69–75.
8. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of leisure-time physical activity and mortality: the finnish twin cohort. JAMA. 1998;279:440–4.
9. Erikssen G, Liestol K, Bjornholt J, Thaulow E, Sandvik L, Erikssen J. Changes in physical fitness and changes in mortality. Lancet. 1998;352:759–62.
10. Oguma Y, Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and all cause mortality in women: a review of the evidence. Br J Sports Med. 2002;36:162–72.
11. Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of all-cause mortality: The roles of genetics and childhood environment. Am J Epidemiol. 2002;156:985–93.
12. Carlsson S, Andersson T, Lichtenstein P, Michaelsson K, Ahlbom A. Physical activity and mortality: Is the association explained by genetic selection? Am J Epidemiol. 2007;166:255–9.
13. Savela S, Koistinen P, Tilvis RS, Strandberg AY, Pitkala KH, Salomaa VV, Miettinen TA, Strandberg TE. Leisure-time physical activity, cardiovascular risk factors and mortality during a 34-year follow-up in men. Eur J Epidemiol. 2010. doi: 10.1007/s10654-010-9483-z.
14. Lee IM, Skerrett PJ. Physical activity and all-cause mortality: What is the dose-response relation? Med Sci Sports Exerc. 2001;33:S459–71. Discussion S493–4.
15. Physical Activity Guidelines Advisory Committee. Physical activity guidelines advisory committee report, 2008. Washington, DC: U.S. Department of Health and Human Services; 2008.
16. Stubbe JH, Boomsma DI, Vink JM, Cornes BK, Martin NG, Skytthe A, Kyvik KO, Rose RJ, Kujala UM, Kaprio J, Harris JR, Pedersen NL, Hunkin J, Spector TD, de Geus EJ. Genetic influences on exercise participation in 37.051 twin pairs from seven countries. PLoS ONE 2006; 1. doi: 10.1371/journal.pone.0000022.
17. Rankinen T, Bouchard C. Invited commentary: physical activity, mortality, and genetics. Am J Epidemiol. 2007;166:260–2.
18. Bouchard C, Dionne FT, Simoneau JA, Boulay MR. Genetics of aerobic and anaerobic performances. Exerc Sport Sci Rev. 1992;20:27–58.
19. Stubbe JH, Boomsma DI, De Geus EJ. Sports participation during adolescence: a shift from environmental to genetic factors. Med Sci Sports Exerc. 2005;37:563–70.
20. Kujala UM, Marti P, Kaprio J, Hernelahti M, Tikkanen H, Sarna S. Occurrence of chronic disease in former top-level athletes. predominance of benefits, risks or selection effects? Sports Med. 2003;33:553–61.
21. Karjalainen J, Tikkanen H, Hernelahti M, Kujala UM. Muscle fiber-type distribution predicts weight gain and unfavorable left ventricular geometry: a 19 year follow-up study. BMC Cardiovasc Disord. 2006;6:2.
22. Iachine IA, Holm NV, Harris JR, Begun AZ, Iachina MK, Laitinen M, Kaprio J, Yashin AI. How heritable is individual susceptibility to death? The results of an analysis of survival data on danish, swedish and finnish twins. Twin Res. 1998;1:196–205.
23. Petersen L, Andersen PK, Sorensen TI. Genetic and environmental effects on mortality before age 70 years. Epidemiology. 2008;19:472–6.
24. Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med. 1994;330:1041–6.
25. Wienke A, Holm NV, Skytthe A, Yashin AI. The heritability of mortality due to heart diseases: a correlated frailty model applied to danish twins. Twin Res. 2001;4:266–74.
26. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. J Intern Med. 2002;252:247–54.
27. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, de Faire U. Genetic influences on CHD-death and the impact of known risk factors: comparison of two frailty models. Behav Genet. 2004;34:585–92.
28. Herskind AM, McGue M, Holm NV, Sorensen TI, Harvald B, Vaupel JW. The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870–1900. Hum Genet. 1996;97:319–23.
29. Hjelmborg vBJ, Iachine I, Skytthe A, Vaupel JW, McGue M, Koskenvuo M, Kaprio J, Pedersen NL, Christensen K. Genetic influence on human lifespan and longevity. Hum Genet. 2006;119:312–21.
30. Kaprio J, Pulkkinen L, Rose RJ. Genetic and environmental factors in health-related behaviors: studies on finnish twins and twin families. Twin Res. 2002;5:366–71.
31. Sarna S, Kaprio J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. Hum Hered. 1978;28:241–54.
32. Kaprio J, Sarna S, Koskenvuo M, Rantasalo I. The finnish twin registry: baseline characteristics. Section II. History of symptoms and illnesses, use of drugs, physical characteristics, smoking, alcohol and physical activity. Helsinki: University of Helsinki, Department of Public Health; 1978.
33. Kaprio J, Koskenvuo M, Langinvainio H, Romanov K, Sarna S, Rose RJ. Genetic influences on use and abuse of alcohol: a study of 5638 adult finnish twin brothers. Alcohol Clin Exp Res. 1987;11:349–56.
34. Kaprio J, Koskenvuo M. A prospective study of psychological and socioeconomic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and non-smokers. J Clin Epidemiol. 1988;41:139–50.
35. Kujala UM, Kaprio J, Taimela S, Sarna S. Prevalence of diabetes, hypertension, and ischemic heart disease in former elite athletes. Metabolism. 1994;43:1255–60.
36. Waller K, Kaprio J, Kujala UM. Associations between long-term physical activity, waist circumference and weight gain: a 30-year longitudinal twin study. Int J Obes. 2008;32:353–61.
37. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Future hospital care in a population-based series of twin pairs discordant for physical activity behavior. Am J Public Health. 1999;89:1869–72.
38. Kaprio J, Kujala UM, Koskenvuo M, Sarna S. Physical activity and other risk factors in male twin-pairs discordant for coronary heart disease. Atherosclerosis. 2000;150:193–200.
39. Kujala UM, Kaprio J, Koskenvuo M. Diabetes in a population-based series of twin pairs discordant for leisure sedentariness. Diabetologia. 2000;43:259.
40. Central Statistical Office of Finland. Alphabetical list of occupations and classification of social class. Helsinki, Finland: Statistics Finland; 1972.

41. Koivumaa-Honkanen H, Honkanen R, Koskenvuo M, Viinamaki H, Kaprio J. Life dissatisfaction as a predictor of fatal injury in a 20-year follow-up. Acta Psychiatr Scand. 2002;105:444–50.
42. Kujala UM, Sarna S, Kaprio J. Use of medications and dietary supplements in later years among male former top-level athletes. Arch Intern Med. 2003;163:1064–8.
43. The Social Insurance Institution of Finland. Medicines. http://www.kela.fi/in/internet/english.nsf/NET/131003131216MH?openDocument. 2006.
44. Thune I, Furberg AS. Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. Med Sci Sports Exerc. 2001;33:S530–50. discussion S609–10.
45. Kruk J, Aboul-Enein HY. Physical activity in the prevention of cancer. Asian Pac J Cancer Prev. 2006;7:11–21.
46. SPSS. SPSS 14.0 for windows. Chicago: SPSS, Inc; 2005.
47. STATA. STATA base reference manual. College Station: STATA press; 2005.
48. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15:239–46.
49. Barengo NC, Hu G, Kastarinen M, Lakka TA, Pekkarinen H, Nissinen A, Tuomilehto J. Low physical activity as a predictor for antihypertensive drug treatment in 25–64-year-old populations in eastern and south-western finland. J Hypertens. 2005;23:293–9.
50. Paffenbarger RS Jr, Lee IM. Intensity of physical activity related to incidence of hypertension and all-cause mortality: an epidemiological view. Blood Press Monit. 1997;2:115–23.
51. Selmer R. Blood pressure and twenty-year mortality in the city of bergen, norway. Am J Epidemiol. 1992;136:428–40.
52. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13.
53. Menotti A, Lanti M, Kafatos A, Nissinen A, Dontas A, Nedeljkovic S, Kromhout D, Seven Countries Study. The role of a baseline casual blood pressure measurement and of blood pressure changes in middle age in prediction of cardiovascular and all-cause mortality occurring late in life: a cross-cultural comparison among the european cohorts of the seven countries stud. J Hypertens. 2004;22:1683–90.
54. Kujala UM, Sarna S, Kaprio J, Koskenvuo M. Asthma and other pulmonary diseases in former elite athletes. Thorax. 1996;51:288–92.
55. Korhonen T, Kujala UM, Rose RJ, Kaprio J. Physical activity in adolescence as a predictor of alcohol and illicit drug use in early adulthood: a longitudinal population-based twin study. Twin Res Hum Genet. 2009;12:261–8.
56. Lauderdale DS, Fabsitz R, Meyer JM, Sholinsky P, Ramakrishnan V, Goldberg J. Familial determinants of moderate and intense physical activity: a twin study. Med Sci Sports Exerc. 1997;29:1062–8.

II

EFFECT OF PHYSICAL ACTIVITY ON HEALTH IN TWINS: A 30-YEAR LONGITUDINAL STUDY

by

Waller K, Kujala UM, Kaprio J, Koskenvuo M, Rantanen T. 2010

Medicine & Science in Sport & Exercise 42(4), 658-664

Effect of Physical Activity on Health in Twins: A 30-yr Longitudinal Study

KATJA WALLER[1], URHO M. KUJALA[1], JAAKKO KAPRIO[2,3,4], MARKKU KOSKENVUO[2], and TAINA RANTANEN[1,5]

[1]Department of Health Sciences, University of Jyväskylä, Jyväskylä, FINLAND; [2]Department of Public Health, University of Helsinki, Helsinki, FINLAND; [3]Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, FINLAND; [4]Institute for Molecular Medicine, University of Helsinki, Helsinki, FINLAND; and [5]The Gerontology Research Centre, University of Jyväskylä, Jyväskylä, FINLAND

ABSTRACT

WALLER, K., U. M. KUJALA, J. KAPRIO, M. KOSKENVUO, and T. RANTANEN. Effect of Physical Activity on Health in Twins: A 30-yr Longitudinal Study. *Med. Sci. Sports Exerc.*, Vol. 42, No. 4, pp. 658–664, 2010. **Purpose**: The aim of this study was to investigate whether persistent leisure-time physical activity, adjusted for genetic liability and childhood experiences, protects against chronic diseases, early signs of disability, and loss of life satisfaction. **Methods**: From 5663 healthy adult twin pairs, we identified 146 pairs who were discordant for both intensity and volume of leisure physical activity in 1975 and 1981. Of them, both members of 95 pairs were alive and participated in our follow-up study in 2005 when chronic diseases (such as diabetes, cardiovascular disease, and osteoarthritis), life satisfaction, and disability were assessed by a structured telephone interview. The mean age of the participants was 58 yr (range = 47–79 yr) in 2005. Paired tests were used in the analyses. **Results**: At the end of follow-up, the active cotwins had a decreased risk of reporting at least one chronic diseases, whereas active monozygotic (MZ) twins had two or more chronic diseases significantly less often than their inactive cotwins (odds ratio [OR] = 0.14, $P = 0.031$). Overall, the risk for type 2 diabetes or glucose intolerance (OR = 0.09, $P = 0.022$) and elevated blood pressure (OR = 0.46, $P = 0.039$) was decreased among the active cotwins. These effects were seen clearly among dizygotic twins but not always among small number of monozygotic twins. The active cotwins reported greater life satisfaction ($P = 0.047$) and tended to be less likely to be hospitalized ($P = 0.065$), although active cotwins had somewhat more sports-related injuries (OR = 1.9, $P = 0.051$) than inactive cotwins. Studied disability variables did not differ between the active and the inactive cotwins. **Conclusions**: Physical activity reduces the risk for chronic diseases and helps in maintaining life satisfaction. However, genetic factors may play a role in this association because some findings emerged more clearly among dizygotic than monozygotic twins discordant for physical activity. **Key Words:** LEISURE-TIME PHYSICAL ACTIVITY, MORBIDITY, CHRONIC DISEASE, FOLLOW-UP STUDIES, TWIN STUDY

Observational follow-up studies have provided substantial evidence that physical activity plays an important role in the prevention of several chronic diseases, such as cardiovascular disease, CHD, type 2 diabetes, and hypertension (19,23,29,36). Although physical activity has many positive outcomes for health, adverse effects include an increased rate of musculoskeletal injuries (11).

Genetic selection can also play a role in accounting for the relationship between physical activity and chronic disease. Physical fitness and the ability to achieve high levels of physical activity have a genetic component (4,17,33). The review by Casas et al. (7) clearly demonstrated that CAD has a genetic component and that different risk factors for CAD have high heritability. Significant genetic influences on cholesterol levels, smoking, and hypertension have repeatedly been shown (3,7,22). Twin studies have shown that age at death from CAD has a strong genetic component, particularly early onset of CAD (27). A genetic predisposition also underlies the increased tendency for weight gain and other metabolic syndrome–related conditions (2,25). Interestingly, some evidence is now available that inherited biological characteristics make it easier for some individuals

Address for correspondence: Katja Waller, M.Sc., Department of Health Sciences, University of Jyväskylä, P.O. Box 35 (LL227) 40014 Jyväskylä, Finland; E-mail: katja.waller@jyu.fi.
Submitted for publication February 2009.
Accepted for publication August 2009.

0195-9131/10/4204-0658/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e3181bdeea3

to exercise and also favor them with lower morbidity and mortality (15,17,20).

Despite recent progress in defining the individual genes underlying the genetic component identified from family and twin studies, known genes account only for a small fraction of the estimated heritability for common diseases and physical activity. Thus, twin and family studies still remain a powerful tool for investigating the role of genetic and environmental factors in risk factor–disease relationships. Dizygotic (DZ) twins share half of their segregating genes, whereas monozygotic (MZ) pairs are genetically identical. Both kinds of pairs nearly always have the same childhood environment. By studying outcomes in twin pairs discordant for an exposure, such as physical activity, the possible confounding role of genetic and early childhood experiences can be controlled for.

We followed the Finnish Twin Cohort for 30 yr to study the associations between physical activity, chronic diseases, life satisfaction, and preclinical disability in healthy twin pairs discordant for leisure-time physical activity. Given the current knowledge of both positive and negative effects of physical activity on some conditions, we were interested in gaining an overview of the whole spectrum of health-related conditions. The aim of the study was to see whether baseline physical activity protects broadly from morbidity assessed using wide range of diseases and associated measures.

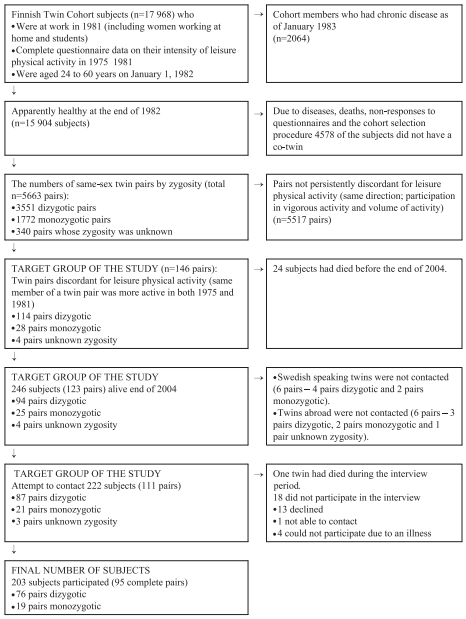

FIGURE 1—Flow chart of participants.

METHODS

Participants. The Finnish Twin Cohort consists of all same-sex twin pairs born in Finland before 1958 with both cotwins alive in 1967 (12). Figure 1 shows the flow of the participants. For the present study, the initial inclusion criteria were employment in 1981 and complete questionnaire data on leisure physical activity in 1975 and 1981. The subjects were aged from 24 to 60 yr on January 1, 1982 (n = 17,968 individuals). All pairs in which at least one cotwin did not respond to the questionnaires, had died, or had a chronic disease, except hypertension, by the end of 1982 were excluded (12,17). The healthy cohort comprised 5663 same-sex twin pairs (17). Determination of zygosity was based on an accurate and validated questionnaire method (32).

For this study, we selected 146 same-sex twin pairs who were discordant for leisure-time physical activity for both participation in vigorous activity and volume of activity in 1975 and 1981. The final study sample at the 2005 follow-up comprised 111 twin pairs because only those pairs in which both twins were still alive were included (24 cotwins from 146 pairs, 16 inactive and 8 active, had died by the end of 2004; Waller, K, et al., unpublished observations, 2009). In addition, we required that both were known to be living in Finland and spoke Finnish as their mother tongue, which resulted in the exclusion of 12 pairs. An attempt was made to contact all 222 subjects. Of these, 203 subjects (95 complete pairs, 54 women) took part in the interview because one died during the interview period and 18 did not participate. The mean age of the subjects was 58 yr (range = 47–79 yr) at interview.

Assessment of exposure variables. The questionnaires in 1975 and 1981 included identical questions on weight, height, physical activity, occupation, alcohol use, smoking, and physician-diagnosed diseases. Among the twin pairs whose addresses could be identified (93.5% of subjects), the response rate was 87.6% in 1975, and the reresponse rate was 90.7% in 1981.

Physical activity habits elicited by identical questions in 1975 and 1981 were used as the main exposure in the present study. This information is considered to be valid on the basis of earlier studies (13,14,19). Participation in vigorous physical activity was assessed by the following question: Is your physical activity during leisure time about as strenuous on average as 1) walking, 2) alternately walking and jogging, 3) jogging (light run), and 4) running? Those who chose alternative 2, 3, or 4 were classified as participating in vigorous activity. Assessment of leisure activity volume (MET index) was based on a series of structured questions (14,19) on leisure physical activity (monthly frequency, mean duration, and mean intensity of

physical activity sessions) and physical activity during commuting to and from work. The index was calculated by assigning a multiple of resting metabolic rate (MET score) to each activity and by calculating the total volume of activity using the following formula: intensity × duration × frequency (19). The MET index was expressed as the sum score of leisure MET-hours per day. Those subjects whose volume of activity was ≥2 MET·h·d^{-1} (corresponding to about 30 min walking per day) and participated in vigorous activity (alternatives 2, 3, or 4) were classified as physically active. This had to be true at both time points (1975 and 1981), and their cotwin had to be inactive at both time points. Figure 2 shows the MET indices for active and inactive cotwins in 1975 and 1981.

The MET index was validated in a previous study (35) by comparing the questions used for calculating MET index to a 12-month detailed physical activity questionnaire conducted by telephone interview. The intraclass correlation between these two was relatively high: the intraclass correlation between the MET index 2005 (same as the original questions used in 1975 and 1981) and the detailed 12-month physical activity MET index was 0.68 ($P < 0.001$) for leisure-time physical activity and 0.93 ($P < 0.001$) for work journey.

Follow-up assessment and outcomes. In 2005, after being sent an invitation letter and giving their informed consent to participate in the study, subjects were interviewed by telephone. The study was approved by the ethics committee of the University of Jyväskylä. All outcome assessments (interview and data entry) were carried out by researchers blinded to the subjects' baseline status. Two experienced and trained interviewers interviewed each twin in a pair at random. The average duration of the interview was 50 min and included questions on physical activity habits, functional limitations, use of medications, and occurrence of chronic diseases.

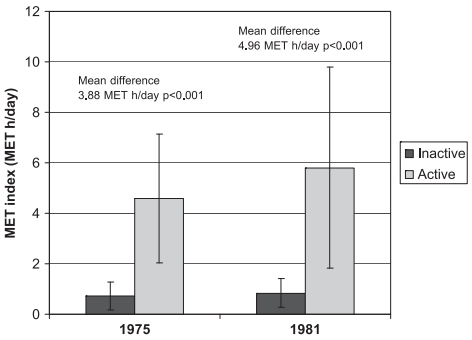

FIGURE 2—Leisure-time MET indices for 146 comprehensively selected twin pairs discordant for both intensity and volume of physical activity in 1975 and 1981. Similar results were seen for men, women, and MZ and DZ pairs.

TABLE 1. 1975 baseline characteristics for 95 twin pairs.

Characteristics	Inactive	Active	P
Age (mean ± SD)	28.5 ± 6.9	28.5 ± 6.9	
Height (mean ± SD)	169.2 ± 8.4	169.5 ± 8.1	0.53
Weight (mean ± SD)	63.2 ± 12.1	63.7 ± 10.2	0.65
Body mass index (mean ± SD)	22.0 ± 2.8	22.1 ± 2.3	0.66
Ever regular smoker (*n* (%))	51 (53.7%)	43 (45.3%)	0.22
Pack-years smoked (mean ± SD)	3.1 ± 4.8	1.9 ± 3.4	0.008
Alcohol grams per day (mean ± SD)	7.2 ± 14.4	7.6 ± 11.8	0.74
Diagnosed hypertension (*n* (%))	7 (7.4%)	5 (5.3%)	0.75
Life satisfaction (mean ± SD)[a]	8.8 ± 2.5	8.0 ± 2.7	0.026
Marital status (*n* (%))			0.027
Single	28 (29.5%)	41 (43.2%)	
Married	62 (65.3%)	52 (54.7%)	
Divorced	5 (5.3%)	2 (2.1%)	
Work-related physical activity in 1975 (*n* (%))			0.19
Sedentary	28 (29.8%)	33 (34.7%)	
Standing or walking at work	14 (14.9%)	20 (21.1%)	
Light manual labor	46 (48.9%)	39 (41.1%)	
Heavy manual labor	6 (6.4%)	3 (3.2%)	
Social class (*n* (%))			0.26
Upper white collar	6 (6.3%)	8 (8.4%)	
Clerical work	28 (29.5%)	25 (26.3%)	
Skilled workers	33 (34.7%)	39 (41.1%)	
Unskilled workers	7 (7.4%)	8 (8.4%)	
Farmer	14 (14.7%)	2 (2.1%)	
Other (students, conscript, retired, unknown)	7 (7.4%)	13 (13.7)	
MET index[b]	0.71 ± 0.54	4.23 ± 2.23	<0.001

[a] The life satisfaction index was a four-question scale with a sum score ranging between 4 and 20, with an increasing score indicating a decrease in life satisfaction.
[b] MET index includes leisure-time physical activity and work journey activity.

The follow-up interview included a four-question dyspnea scale concerning whether the subject became breathless during walking and performing daily tasks (31). This scale has five response categories (from 0 = no breathlessness to 4 = breathless during daily tasks). A four-question scale on life satisfaction yielded a sum score ranging between 4 and 20, with an increasing score indicating a decrease in life satisfaction (16). The life satisfaction scale correlates well ($r > 0.6$) with depressiveness on the Beck Depression Inventory (16).

Subjects were asked if they had specific physician-diagnosed diseases; for example, "Has your doctor ever told you that you have rheumatoid arthritis?" Information about individually asked diseases can be found in the Results section. Glucose intolerance and type 2 diabetes were assessed in the interview with the question, "Has your doctor told you that you have diabetes?" Responses were classified as no, yes (type 2 diabetes), or no but has been diagnosed as having elevated blood glucose (impaired glucose tolerance or impaired fasting glycemia). The latter responses were classified as having prediabetes. Subjects were also asked whether they had specific musculoskeletal diseases or conditions (rheumatoid arthritis, osteoarthritis (knee, hip, or other), sports-related injuries, sciatica, and tension neck). Finally, the presence of other physician-diagnosed diseases was assessed with an open question, "Do you have any other physician-diagnosed diseases?"

Recent hospitalizations were investigated with the question, "How many days have you spent in hospital during the last 3 years?" Only inpatient visits were counted.

Mobility was assessed with 6–12 questions ranging from preclinical mobility limitations, such as task modification, to frank disability and inability (24,26). This scale is reliable (κ coefficient between 0.47 and 1.00) (24), and it has been validated against objective measurements of muscle power and walking speed (26).

Statistical analysis. As we were studying occurrence of diseases among twin pairs discordant for physical activity, all the statistical analyses were based on pairwise tests. To compare differences in outcome measurements between the inactive and the active cotwins, we used paired samples *t*-test, we used McNemar's test and conditional logistic regression. The level of significance was set at $P < 0.05$, and all the *P* values reported are two sided. Data were analyzed with SPSS 14.0 (SPSS Inc., Chicago, IL) or Stata 9.0 (StataCorp, College Station, TX).

RESULTS

Table 1 shows the baseline characteristics for 95 pairs. In 1975, a slightly higher proportion of the active cotwins were single, and a slightly higher proportion of the inactive cotwins were married. Baseline characteristics show that the inactive subjects smoked or had smoked more than their active cotwins. The active cotwins reported greater life satisfaction at baseline. No other differences were seen between inactive and active cotwins at baseline.

The active cotwins remained more satisfied with their life at the end of follow-up: mean life satisfaction was 6.5 for the active cotwins and 7.1 for the inactive cotwins (paired *t*-test $P = 0.047$). Rather similar results were obtained for the DZ pairs (6.4 vs 6.9, $P = 0.12$) and the MZ pairs (6.8 vs 7.9, $P = 0.24$). Inactive cotwins had a tendency toward dyspnea at follow-up when compared with their active cotwins ($P = 0.067$), more so in the DZ pairs ($P = 0.10$) than that in the MZ pairs ($P = 1.00$).

The results for physician-diagnosed diseases in inactive and active cotwins are shown in Table 2. Among MZ twin pairs, the active cotwins had a reduced risk of having at least two chronic diseases (with the exception of hypertension) because one active MZ and seven inactive MZ cotwins had two or more chronic diseases (odds ratio [OR] = 0.14, $P = 0.031$), although the difference was not significant when MZ and DZ pairs were taken together (OR = 0.54, $P = 0.19$). No differences were seen in the cumulative incidence of diagnosed hypertension between the inactive and active cotwins when studying new cases of hypertension since 1975. Overall, the active cotwins had a decreased risk for elevated blood pressure (OR = 0.46, $P = 0.039$; DZ, OR = 0.44, 95% CI = 0.19–1.02; MZ, OR = 0.5, 95% CI = 0.09–2.73). The active cotwins also had a decreased risk for type 2 diabetes or prediabetes (OR = 0.09, $P = 0.022$; DZ, OR = 0.1, 95% CI = 0.01–0.78; MZ, no difference). Although statistically nonsignificant, the active twins showed a lower prevalence of type 2 diabetes, any pulmonary disease, and other physician-diagnosed diseases.

We observed some differences in selected musculoskeletal problems between the inactive and the active cotwins (Table 3). The active cotwins had a marginally nonsignificant increased risk for at least one sports-related injury (OR = 1.9, $P = 0.051$) compared with their inactive cotwins, the finding being more salient in the DZ pairs (OR = 2.2, 95% CI = 1.07–4.45) than that in the MZ pairs

TABLE 2. Chronic and other physician-diagnosed diseases for 95 pairs.

Disease	Inactive, *n* (%)	Active, *n* (%)	OR	95% CI	*P*
At least one chronic disease[a]	41 (43.2)	41 (43.2)	1.00	0.56–1.78	1.00
At least two chronic diseases[a]	25 (26.3)	19 (20.0)	0.7	0.35–1.39	0.31
At least one chronic diseases[a] except hypertension	45 (47.4)	42 (44.2)	0.88	0.49–1.57	0.66
At least two chronic diseases[a] except hypertension	15 (15.8)	9 (9.5)	0.54	0.21–1.35	0.19
Prediabetes	7 (7.4)	1 (1.1)	0.14	0.02–1.16	0.07
Type 2 diabetes	7 (7.4)	3 (3.2)	0.2	0.02–1.71	0.14
Type 2 diabetes or prediabetes	14 (14.7)	4 (4.2)	0.09	0.01–0.70	0.022
Cardiovascular disease[a]	5 (5.3)	7 (7.4)	1.67	0.40–6.97	0.48
CHD including myocardial infarction	4 (4.2)	5 (5.3)	1.5	0.25–8.98	0.66
Stroke or intermittent claudication	1 (1.1)	2 (2.1)	2	0.18–2.06	0.57
Cardiac failure	0	2 (2.1)			
BP medication in 2005[b]	18 (21.4)	19 (22.6)	1.09	0.48–2.47	0.84
Elevated BP or BP medication in 2005[b]	43 (51.2)	31 (36.9)	0.46	0.22–0.96	0.039
Pulmonary disease[a]	8 (8.4)	3 (3.2)	0.33	0.09–1.23	0.099
Asthma	7 (7.4)	2 (2.1)	0.29	0.06–1.38	0.12
COPD	1 (1.1)	0			
Chronic bronchitis	2 (2.1)	2 (2.1)	1		1
Gastric ulcer	6 (6.3)	6 (6.3)	1		1
Depression	9 (9.5)	9 (9.5)	1		1
Other physician-diagnosed chronic disease[c]	30 (31.6)	21 (22.1)	0.57	0.28–1.16	0.12

[a] At least one of the following listed below.
[b] New cases since 1975. If the person had hypertension as assessed by questionnaire or had medication for hypertension in 1975, he or she was excluded from the analyses; 84 pairs included in the analyses.
[c] Includes diseases such as cancer, 8 individuals (of which breast cancer, 4 individuals); different allergies, 7 individuals; osteoporosis, 5 individuals; thyroid gland problem, 5 individuals; eye problems, 5 individuals (glaucoma, 3 individuals); and migraine, 3 individuals.
BP, blood pressure.

TABLE 3. Selected musculoskeletal problems for 95 pairs.

Disease	Inactive, *n* (%)	Active, *n* (%)	OR	95% CI	*P*
Arthritis[a]	22 (23.2)	27 (28.4)	1.38	0.68–2.83	0.37
Rheumatoid arthritis	1 (1.1)	4 (4.2)	4	0.45–35.79	0.22
Osteoarthritis[a]	22 (23.2)	25 (26.3)	1.21	0.60–2.46	0.59
Hip osteoarthritis	5 (5.3)	4 (4.2)	0.75	0.17–3.35	0.71
Knee osteoarthritis	10 (10.5)	11 (11.6)	1.13	0.43–2.92	0.81
Any other osteoarthritis[b]	10 (10.5)	17 (17.9)	2.17	0.82–5.70	0.12
Sciatica	29 (30.5)	22 (23.2)	0.68	0.35–1.31	0.25
Tension neck	11 (11.6)	9 (9.5)	0.78	0.29–2.09	0.62
Injuries typical for athletes[a]	29 (30.5)	42 (44.2)	1.87	0.997–3.49	0.051
Acute injuries	24 (25.3)	31 (32.6)	1.44	0.76–2.72	0.27
Tendon rupture (Achilles or other)	6 (6.3)	5 (5.3)	0.8	0.22–2.98	0.74
Achilles tendon	2 (2.1)	2 (2.1)	1		1
Other tendon	4 (4.2)	3 (3.2)	0.67	0.11–4.00	0.66
Knee or ankle injury	20 (21.1)	30 (31.6)	1.77	0.90–3.49	0.10
Knee meniscus	5 (5.3)	8 (8.4)	1.75	0.51–5.98	0.37
Knee ligament	5 (5.3)	5 (5.3)	1		1
Ankle ligament	13 (13.7)	21 (22.1)	1.8	0.83–3.90	0.14
Stress injury or tendonitis (Achilles or other)	10 (10.5)	17 (17.9)	1.88	0.80–4.42	0.15
Achilles tendon inflammation	4 (4.2)	6 (6.3)	1.5	0.42–5.32	0.53
Other tendon inflammation	7 (7.4)	12 (12.6)	1.83	0.68–4.96	0.23

[a] At least one of the following listed below.
[b] The other osteoarthritis includes osteoarthritis in hand (15 individuals), shoulder (6 individuals), neck (6 individuals), back (4 individuals), toes (3 individuals), and wrists (1 individual).

(OR = 1, 95% CI = 0.25–4.0). For individual sports-related injuries, the active cotwins again had a statistically nonsignificant increased risk for getting an ankle ligament injury (OR = 1.8, $P = 0.14$; DZ, OR = 2.17, 95% CI = 0.82–5.70; MZ, OR = 1.3, 95% CI = 0.34–4.66). The risk for conditions other than knee or hip osteoarthritis and sciatica did not differ between active and inactive twins (Table 3).

Of 95 pairs, 23 inactive and 13 active cotwins had been hospitalized within the last 3 yr before the interview for a total of 171 and 95 nights, respectively. On average, the inactive cotwins spent 1.8 nights and the active cotwins spent 1 night (paired *t*-test $P = 0.16$) in the hospital during that period. The active cotwins had a nonsignificant decreased risk for having been hospitalized (OR = 0.47, $P = 0.065$) and did not differ by zygosity (DZ, OR = 0.54, 95% CI = 0.22–1.35; MZ, OR = 0.33, 95% CI = 0.07–1.65).

The results of the preclinical disability analyses did not reach statistical significance between inactive and active cotwins. However, there was a tendency for the inactive cotwins to have more difficulties and to report more task modification in daily activities compared with their active cotwins. For example, active cotwins were less likely to have made changes in walking for 2 km (OR = 0.53, 95% CI = 0.22–1.35, $P = 0.19$).

DISCUSSION

Our 30-yr longitudinal follow-up study on twins discordant for physical activity found greater life satisfaction among the active than the inactive cotwins. The inactive cotwins reported breathlessness more often than their active cotwins. Abnormalities in glucose metabolism (diabetes or prediabetes) and elevated blood pressure were less common among the active cotwins. The active cotwins had also been hospitalized less often and for shorter times. In contrast, the active cotwins showed a tendency to having more sports-related injuries at follow-up than their inactive cotwins.

In line with our results, similar effects of physical activity on several different diseases, for instance, diabetes or prediabetes and hypertension, have been reported in previous studies (5,29,36). Although we did not find a difference in the reported diagnoses of depression between inactive and active cotwins in our study, the active cotwins reported greater life satisfaction. In their review in 2001, Rejeski and Mihalko (30) found a lack of consistency in the results of previous studies on physical activity and life satisfaction in older adults with only some studies reporting positive effects.

When studying differences between inactive and active subjects, it would be reasonable to expect differences to be seen first in fitness and body fatness. In the present study, we documented a trend to higher frequency of breathlessness during specific daily tasks in the inactive compared with active cotwins. In our earlier study, we documented an association between long-term physical activity and lower weight gain in our twin sample (35). Next, a difference is usually seen in insulin sensitivity, as in the present study, where a difference was seen in DZ but not in MZ pairs, suggesting a possible gene–physical activity interaction, such as documented for the FTO gene (1) for physical activity in body mass index and glucose metabolism parameters. In our earlier study, among the same cohort, we found that discordance pattern in physical activity had continued for 30 yr in a subgroup of 42 pairs (35). That study showed that adulthood physical activity habits are often maintained for a long period, and thus it is possible that the continuation of physical activity habits partly explains the difference in the occurrence of chronic diseases in the present study.

As expected, the active cotwins seem to have more musculoskeletal problems and sports-related injuries. Hootman et al. (11) studied subjects who participated in recreational

sports and found that 25% of their subjects had sustained a musculoskeletal injury within the 12 months preceding the survey. Over 83% of these injuries were physical activity related, and 66% were located in the lower extremities. Although in our study active cotwins had slightly more injuries, the number of injuries in real life could have been even higher because only injuries that had been diagnosed by a physician were included in our study. It is very likely that only the more severe sports-related or musculoskeletal injuries were reported to a physician, therefore excluding less severe injuries from our study.

No differences were seen in the amount of hip or knee osteoarthritis between the inactive and the active cotwins. Although former athletes have higher incidence rates of osteoarthritis in the lower limb compared with controls (8,34), this relationship has not been confirmed among recreationally physically active people (10,29). Our active cotwins were not high-level athletes, and therefore the intensity and the duration of their activity may not have been high enough to cause them significantly more osteoarthritis.

The need of hospital care can be seen as a summary measure of the impact of morbidity on different diseases and injuries. The findings that physically active members of the twins pairs tended to need hospital care less often and for a shorter duration than their inactive cotwins agree with earlier analyses of larger cohorts (18) and studies of former athletes (21). Although no overall effect was observed on the preclinical disability scale, there was a tendency for inactive cotwins to have more difficulties and to report more task modification in daily activities. It seems that the benefits of a physically active lifestyle are higher than the adverse effects.

Study strengths and limitations. The strengths of our study were a very long follow-up period and twin study design. We partly controlled for genetic factors and childhood environment by studying twin pairs comprehensively selected from the large Finnish Twin Cohort. Although we started with a large population-based twin cohort, the number of twin pairs discordant for physical activity was relatively small. The small sample size is a limitation, especially when studying diseases as outcomes. The reason for finding a low number of twin pairs discordant for disease could be due to either diseases occurring in both cotwins for genetic reasons or having a relatively young and healthy study cohort at baseline (mean age of subjects was 28.5 yr in 1975). Because of the small numbers, we were not able to adjust the results of analyses with known covariates. The study design adjusts for gender, age, and shared familial factors, and it is known that twins show similarity in their health habits more often than do unrelated subjects. We did adjust most conditions for smoking (results not shown), but this did not change our results.

A further study limitation is that the medical information was self-reported rather than based on data gathered from medical registers or subjects' formal medical notes. However, studies have shown that agreement between self-reported medical history and medical records is generally good, especially with respect to well-known chronic diseases (9,28). Recall bias due to subjects not remembering all their diseases is an issue if the recall is different between active and inactive twins; active subjects may have a better memory for injuries and musculoskeletal disorders because these would have affected an important part of their life more than that in the case of inactive subjects, thus biasing our risk estimates upward. Also, subjects with severe dementia and subjects who had died did not participate. In DZ pairs, but not in MZ pairs, a higher number of inactive than active members of twin pairs had died before the end of our follow-up (Waller, K, et al., unpublished observations, 2009). Although another study limitation was self-reported physical activity data at baseline, these type physical activity questions have been commonly used in the epidemiological studies. In a study by Kujala et al. (19), the same physical activity questions predicted morbidity and mortality in a fashion consistent with other studies using somewhat different measures providing external validation to the questions.

The ideal study method would have been to study the occurrence of diseases in a large number of MZ pairs discordant for physical activity. However, because the sample size was small and only few diseases were present, it is not possible to draw separate conclusions for MZ twins. Therefore, we cannot totally exclude the effect of genetic selection bias on some of the results. The evidence on whether genetic selection explains, for example, the association between high physical activity and low mortality is conflicting. In a study among Swedish twins, in which no exclusion criteria regarding baseline diseases were imposed, genetic selection did not explain this association (6), whereas in a study of healthy twins from the Finnish Twin Cohort (17), genetic selection partially explained the association.

CONCLUSION

Our longitudinal twin pair study found that the benefits of a physically active lifestyle outweigh the adverse effects even after taking familial effects into account. Physical activity reduces the risk for chronic diseases and helps in maintaining life satisfaction. However, genetic factors may play a role in explaining some of the association between disease occurrence and physical activity because some of the findings were more salient among DZ than MZ twin pairs discordant for physical activity.

This study was supported by the Finnish Ministry of Education, the Juho Vainio Foundation, and the University of Jyväskylä. The Finnish Twin Cohort Study is part of the Academy of Finland Centre of Excellence in Complex Disease Genetics.

The authors have no potential conflicts of interest related to the funding.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Andreasen CH, Stender-Petersen KL, Mogensen MS, et al. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. *Diabetes*. 2008;57(1): 95–101.
2. Barroso I. Genetics of type 2 diabetes. *Diabet Med*. 2005;22(5): 517–35.
3. Batra V, Patkar AA, Berrettini WH, Weinstein SP, Leone FT. The genetic determinants of smoking. *Chest*. 2003;123(5):1730–9.
4. Bouchard C, Dionne FT, Simoneau JA, Boulay MR. Genetics of aerobic and anaerobic performances. *Exerc Sport Sci Rev*. 1992; 20:27–58.
5. Brown WJ, Burton NW, Rowan PJ. Updating the evidence on physical activity and health in women. *Am J Prev Med*. 2007; 33(5):404–11.
6. Carlsson S, Andersson T, Lichtenstein P, Michaelsson K, Ahlbom A. Physical activity and mortality: is the association explained by genetic selection? *Am J Epidemiol*. 2007;166:255–9.
7. Casas JP, Cooper J, Miller GJ, Hingorani AD, Humphries SE. Investigating the genetic determinants of cardiovascular disease using candidate genes and meta-analysis of association studies. *Ann Hum Genet*. 2006;70(pt 2):145–69.
8. Conaghan PG. Update on osteoarthritis part 1: current concepts and the relation to exercise. *Br J Sports Med*. 2002;36(5):330–3.
9. Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I. Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. *Am J Epidemiol*. 1997;145(8):762–9.
10. Hart LE, Haaland DA, Baribeau DA, Mukovozov IM, Sabljic TF. The relationship between exercise and osteoarthritis in the elderly. *Clin J Sport Med*. 2008;18(6):508–21.
11. Hootman JM, Macera CA, Ainsworth BE, Addy CL, Martin M, Blair SN. Epidemiology of musculoskeletal injuries among sedentary and physically active adults. *Med Sci Sports Exerc*. 2002; 34(5):838–44.
12. Kaprio J, Koskenvuo M. Genetic and environmental factors in complex diseases: the older Finnish Twin Cohort. *Twin Res*. 2002; 5(5):358–65.
13. Kaprio J, Koskenvuo M, Langinvainio H, Romanov K, Sarna S, Rose RJ. Genetic influences on use and abuse of alcohol: a study of 5638 adult Finnish twin brothers. *Alcohol Clin Exp Res*. 1987; 11(4):349–56.
14. Kaprio J, Sarna S, Koskenvuo M, Rantasalo I. The Finnish Twin Registry: baseline characteristics. Section II. History of symptoms and illnesses, use of drugs, physical characteristics, smoking, alcohol and physical activity. Helsinki: University of Helsinki, Department of Public Health; 1978. pp. 120–2.
15. Karjalainen J, Tikkanen H, Hernelahti M, Kujala UM. Muscle fiber-type distribution predicts weight gain and unfavorable left ventricular geometry: a 19 year follow-up study. *BMC Cardiovasc Disord*. 2006;6(1):2.
16. Koivumaa-Honkanen H, Honkanen R, Koskenvuo M, Viinamaki H, Kaprio J. Life dissatisfaction as a predictor of fatal injury in a 20-year follow-up. *Acta Psychiatr Scand*. 2002;105(6):444–50.
17. Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. *Am J Epidemiol*. 2002;156(11):985–93.
18. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Future hospital care in a population-based series of twin pairs discordant for physical activity behavior. *Am J Public Health*. 1999;89(12): 1869–72.
19. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of leisure-time physical activity and mortality: the Finnish Twin Cohort. *JAMA*. 1998;279(6):440–4.
20. Kujala UM, Marti P, Kaprio J, Hernelahti M, Tikkanen H, Sarna S. Occurrence of chronic disease in former top-level athletes. Predominance of benefits, risks or selection effects? *Sports Med*. 2003;33(8):553–61.
21. Kujala UM, Sarna S, Kaprio J, Koskenvuo M. Hospital care in later life among former world-class Finnish athletes. *JAMA*. 1996; 276(3):216–20.
22. Kupper N, Willemsen G, Riese H, Posthuma D, Boomsma DI, de Geus EJ. Heritability of daytime ambulatory blood pressure in an extended twin design. *Hypertension*. 2005;45(1):80–5.
23. LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl Physiol*. 2005;99(3):1205–13.
24. Leinonen R, Heikkinen E, Hirvensalo M, et al. Customer-oriented counseling for physical activity in older people: study protocol and selected baseline results of a randomized-controlled trial (ISRCTN 07330512). *Scand J Med Sci Sports*. 2007;17(2):156–64.
25. Loos RJ, Bouchard C. Obesity—is it a genetic disorder? *J Intern Med*. 2003;254(5):401–25.
26. Mänty M, Heinonen A, Leinonen R, et al. Construct and predictive validity of a self-reported measure of preclinical mobility limitation. *Arch Phys Med Rehabil*. 2007;88(9):1108–13.
27. Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. *N Engl J Med*. 1994;330(15):1041–6.
28. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol*. 2004; 57(10):1096–103.
29. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report, 2008*. Washington, DC: U.S. Department of Health and Human Services; 2008. G2:4–12, G3:9–15.
30. Rejeski WJ, Mihalko SL. Physical activity and quality of life in older adults. *J Gerontol A Biol Sci Med Sci*. 2001;56 Spec No 2: 23–35.
31. Rose GA, Blackburn H. Cardiovascular survey methods. *Monogr Ser World Health Organ*. 1968;56:1–188.
32. Sarna S, Kaprio J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. *Hum Hered*. 1978;28(4):241–54.
33. Stubbe JH, Boomsma DI, De Geus EJ. Sports participation during adolescence: a shift from environmental to genetic factors. *Med Sci Sports Exerc*. 2005;37(4):563–70.
34. Vignon E, Valat JP, Rossignol M, et al. Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). *Joint Bone Spine*. 2006;73(4):442–55.
35. Waller K, Kaprio J, Kujala UM. Associations between long-term physical activity, waist circumference and weight gain: a 30-year longitudinal twin study. *Int J Obes*. 2008;32:353–61.
36. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801–9.

III

ASSOCIATIONS BETWEEN LONG-TERM PHYSICAL ACTIVITY, WAIST CIRCUMFERENCE AND WEIGHT GAIN: A 30-YEAR LONGITUDINAL TWIN STUDY

by

Waller K, Kaprio J, Kujala UM. 2008

International Journal of obesity 32, 353-361

International Journal of Obesity (2008) 32, 353–361
 0307-0565/08 $30.00
www.nature.com/ijo

ORIGINAL ARTICLE

Associations between long-term physical activity, waist circumference and weight gain: a 30-year longitudinal twin study

K Waller[1], J Kaprio[2] and UM Kujala[1]

[1]*Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland and* [2]*Department of Public Health, University of Helsinki and Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland*

Background and objective: Physical activity level and obesity are both partly determined by genes and childhood environment. To determine the associations between long-term leisure-time physical activity, weight gain and waist circumference and whether these are independent of genes and childhood effects.
Design and subjects: The study design is a 30-year follow-up twin study in Finland. For this study, 146 twin pairs were comprehensively identified from the large Finnish Twin Cohort. These twin pairs were discordant for both intensity and volume of leisure physical activity in 1975 and 1981 and were healthy in 1981. At follow-up in 2005, both members of 89 pairs were alive and participated in a structured telephone interview. In the interview self-measured weight and waist circumference, and physical activity level for the whole follow-up were assessed. Paired tests were used in the statistical analyses.
Main outcome measures: Waist circumference at 30-year follow-up (2005) and change in weight from 1975 to 2005.
Results: In the 42 twin pairs discordant for physical activity at all time points during the 30-year period, the mean weight gain from 1975 through 2005 was 5.4 kg (95% confidence interval (CI) 2.0–8.9) less in the active compared to inactive co-twins (paired *t*-test, $P=0.003$). In 2005, the mean waist circumference was 8.4 cm (95% CI 4.0–12.7) less in the active compared with inactive co-twins ($P<0.001$). These trends were similar for both monozygotic and dizygotic twin pairs. Pairwise differences in weight gain and waist circumference were not seen in the 47 twin pairs, who were not consistently discordant for physical activity.
Conclusion: Persistent participation in leisure-time physical activity is associated with decreased rate of weight gain and with a smaller waist circumference to a clinically significant extent even after partially controlling for genetic liability and childhood environment.
International Journal of Obesity (2008) **32,** 353–361; doi:10.1038/sj.ijo.0803692; published online 24 July 2007

Keywords: weight gain; waist circumference; physical activity; twins; longitudinal study

Introduction

Over one billion of the world's population can be considered to be overweight (body mass index, BMI $\geqslant$ 25 kg/m^2), including 300 million obese individuals (BMI $\geqslant$ 30 kg/m^2).[1] Both obesity, and particularly the accumulation of intra-abdominal adipose tissue, are considered to be risk factors for the development of several metabolic disorders such as glucose intolerance, dyslipidemia and hypertension,[2,3] as well as for mortality.[4]

Correspondence: K Waller, Department of Health Sciences, PO Box 35, University of Jyväskylä, FIN-40014 Jyväskylä, Finland.
E-mail: katja.waller@sport.jyu.fi
Received 8 September 2006; revised 29 May 2007; accepted 4 June 2007; published online 24 July 2007

Various studies have shown that physical fitness and the ability to achieve high levels of physical activity have a genetic component.[5–7] Genetic predisposition also underlies the tendency for weight change and other metabolic syndrome-related diseases.[8–11] A large twin study across eight countries confirmed that genetics, non-shared environment and gender have an important role in variation in BMI.[12] The Framingham family study[13] found that the heritability of long-term weight change is 0.24, while twin studies have estimated higher values.[14] Since the gene pool changes slowly, the causes of the obesity epidemic are mainly environmental,[10,15] and it has been suggested that a sedentary lifestyle could be as important as diet in the development of obesity.[16,17] While there is accumulating evidence to show that the rate of weight gain is reduced by

physical activity,[18,19] more long-term studies controlling for different associated factors are needed.

We followed the Finnish Twin Cohort for 30 years to study the associations between physical activity and adult weight gain, waist circumference and other indicators of metabolic syndrome in twin pairs discordant for leisure-time physical activity. Our twin pair study design takes into account genetic predisposition and childhood environment. It is important to be able to take into account genetic and childhood effects as both physical activity and weight gain are influenced by these. Dizygotic (DZ) twins share on average half of their segregating genes, while monozygotic (MZ) pairs are genetically identical. Both kinds of pairs nearly always have the same childhood environment. Among our data of 146 pairs, twin pairs lived together until a mean age of 19.3 years, with no difference by zygosity or whether the difference in physical activity persisted throughout adult life or not.

Methods

Subjects

The Finnish Twin Cohort includes all same-sex twin pairs born in Finland before 1958 and with both co-twins alive in 1967.[20] For the present analysis, initial inclusion criteria were employment (including women working at home and students) in 1981 and complete questionnaire data on leisure physical activity in 1975 and 1981. All pairs where at least one of the twins had died or had a chronic disease, except hypertension, by the end of 1982 were excluded.[6,20,21] The healthy cohort comprised 5663 same-sex twin pairs (3551 DZ, 1772 MZ and 340 pairs with unknown zygosity).[6] Zygosity determination was based on an accurate and validated questionnaire method.[22]

Among these 5663 twin pairs, 146 pairs were discordant for leisure-time physical activity for both participation in vigorous activity and volume of activity in both 1975 and 1981 (for determination see later). The final study sample at the 2005 follow-up comprised 111 twin pairs (222 subjects) as only those pairs were included in which both twins were still alive, both were known to be living in Finland and both spoke Finnish as their mother tongue. Of these 222 subjects, one had died during the interview period and 18 did not participate in the interview due to illness (4), unwillingness (13) or unavailability (1). Therefore, 203 subjects took part in the interview. Those 203 subjects included 89 twin pairs (40 male, 49 female, 72 DZ, 17 MZ pairs) all of whom had completed all the physical activity questions in the interview in 2005.

Assessment of predictors

The subjects had been mailed similar questionnaires in 1975 and 1981. These included questions on weight, height, physical activity, occupation, alcohol use, smoking and physician-diagnosed diseases. Physical activity habits elicited by identical questions in 1975 and 1981 were used as the baseline predictor in the present study.

Assessment of vigorous physical activity was based on the following question: Is your physical activity during leisure time about as strenuous on average as: (1) walking, (2) alternately walking and jogging, (3) jogging, (4) running. Those who chose 2, 3 or 4 were classified as engaging in vigorous activity. Assessment of leisure activity volume (MET index) was based on a series of structured questions on leisure physical activity (monthly frequency, mean duration and mean intensity of sessions) and physical activity during journeys to and from work. The index was calculated by assigning a multiple of resting metabolic rate (MET score) to each activity and by calculating the product of activity, intensity $\times$ duration $\times$ frequency.[21] The MET index was expressed as the sum-score of leisure MET h/day. Those subjects whose volume of activity was $\geqslant 2$ MET h/day (corresponding to about 30 min walking per day) were classified as physically active.[6] Among the 89 pairs who were included in the final study sample and who were discordant for leisure-time physical activity in both 1975 and 1981, the mean difference between the active and inactive co-twins was 3.55 MET h/day in 1975 (paired *t*-test, $P<0.001$) and 4.93 in 1981 ($P<0.001$). Similar results were seen for male, female, MZ and DZ pairs. In prospective studies using the original twin cohort, the MET index has been shown to be a predictor of mortality, type 2 diabetes, coronary heart disease and need of hospital care.[6,21,23–25]

Follow-up assessment of physical activity level

After being sent an invitation letter, subjects were interviewed by telephone in 2005. Subjects provided an informed consent to participate in the study and the ethics committee of the University of Jyväskylä approved the study. All outcome assessments (including interview and data entry) were carried out blinded to baseline status. Two experienced and trained interviewers interviewed at random one co-twin from each pair. The interview included questions on weight, height, waist circumference, physical activity habits and occurrence of chronic diseases. The mean duration of the interviews was 50 min.

The interview included questions on current and past physical activity. Physical activity level was assessed by two sets of questions. The first, a shorter retrospective assessment (years 1980, 1985, 1990, 1995, 2000 and 2005) of physical activity volume (including calculation of MET index) and participation in vigorous physical activity, used the same questions as in 1975 and 1981. The mean MET index for all six measurements between 1980 and 2005 was calculated. To increase recall, subjects were asked their marital and work status for each year before the retrospective physical activity questions.[26] The intraclass correlation (ICC) between the questionnaire-based leisure physical activity MET index in 1981 (questionnaire responses from year 1981) and the

interview-based retrospective MET index in 1980 (interviewed in 2005) was 0.56 ($P<0.001$).

The second, a detailed assessment of leisure-time physical activity volume over the previous 12 months (12-month MET index), was done using a modified version of the Kuopio Ischemic Heart Disease Risk Factor Study Questionnaire.[27] The assessment included questions on leisure physical activities (termed conditioning activities in earlier publications[28]), physical activities during journeys to and from work as well as daily activities such as gardening and berry picking. Each activity included a question on monthly frequency, mean duration and mean intensity of sessions. The ICC between the shorter 2005 MET index and the detailed 12-month physical activity MET index was 0.68 ($P<0.001$) for leisure-time physical activity and 0.93 ($P<0.001$) for work journey.

Assessment of anthropometrics

In the interview, subjects were asked their current weight, height and waist circumference. Self-reported height and weight have been validated against measured values.[12,29] The BMI (kg/m^2) was calculated. Change in weight was calculated by subtracting the weight in 1975 or 1981 from the weight in 2005.

As the amount of abdominal fat can be estimated by measuring waist circumference,[30] subjects were sent a tape measure before the interviews. They were asked to measure their waist circumference in the standing position according to an instruction clarified with a picture. The measurement was to be done at the narrowest part of the waist; if this could not be found, they were instructed to measure midway between the iliac crest and the lowest rib. In a separate validation study, a healthcare professional measured the circumference blinded to the subjects' ($N=24$) measurement, and the ICC between these was 0.97 ($P<0.001$).

Statistical analysis

As we studied twin pairs, all the statistical analyses were based on pairwise tests. First, analyses were conducted on all 89 pairs. Second, we carried out specific analyses for the 42 pairs who had remained consistently discordant for physical activity over the 30-year follow-up and for 47 pairs who were not consistently discordant (discordance not in the same direction at one or more time points). The main results are also reported by gender and zygosity. To compare differences in outcome measurements between inactive and active co-twins, paired samples *t*-test, McNemar's test and conditional logistic regression were used. The level of significance was set at $P<0.05$ and all reported *P*-values are two-sided. Data were analyzed with the use of either SPSS 12.0 or Stata 8.0.

Results

No statistically significant pairwise differences were found between inactive and active co-twins in anthropometry, marital or socio-economic status at the baseline in 1975 (Table 1). In 1975, the inactive members of the twin pairs tended to be more often involved in heavier manual work compared to their active co-twins. This was not observed in 2005, as statistically non-significant differences were mainly seen in retirement and lighter work.

We found 42 pairs (5 MZ, 4 female and 1 male, and 37 DZ, 17 female and 20 male, pairs) who were consistently discordant for physical activity at all the 5-year time points across the 30-year period, and 47 pairs (12 MZ, 7 female and 5 male, and 35 DZ, 21 female and 14 male, pairs) who were not consistently discordant. Figure 1 shows the differences in MET indices between inactive and active co-twins from 1980 through 2005. DZ twin pairs seemed to stay discordant for longer and the discordances appear greater when compared with MZ pairs (Figure 2). The mean MET index from 1980 through 2005 was significantly higher in active than inactive co-twins in all twin pairs as well as in all subgroups (Table 2, Figure 3). Significant differences between inactive and active co-twins were observed in leisure-time physical activity but not in daily activities.

Table 1 1975 baseline characteristics of 89 twin pairs[a]

Characteristics	*Inactive*	*Active*	*P-value*
Age (mean, range)	29 (18–48)	29 (18–48)	
Height	169.3±8.5	169.5±8.5	0.67
Weight	63.5±12.5	63.9±10.5	0.72
Ever smoked regularly by 1975 (*N*, %)	47 (52.8%)	40 (44.9%)	0.28
Alcohol, g/day (mean±s.d.)	6.1±9.3	6.7±8.5	0.62
Diagnosed hypertension (*N*, (%))	3 (3.4%)	5 (5.6%)	0.69
Marital status (N, %)			0.16
Single	26 (29.2%)	38 (42.7%)	
Married	56 (62.9%)	48 (53.9%)	
Divorced	5 (5.6%)	2 (2.2%)	
Cohabiting	2 (2.3%)	1 (1.2%)	
Work-related physical activity (N, %)			0.13
Sedentary	26 (29.5%)	31 (34.8%)	
Standing or walking at work	12 (13.6%)	20 (22.5%)	
Light manual labor	45 (51.1%)	34 (39.3%)	
Heavy manual labor	5 (5.7%)	3 (3.4%)	
Occupational group (N, %)			0.31
Upper white-collar	5 (5.6%)	8 (9.0%)	
Clerical work	26 (29.2%)	24 (27.0%)	
Skilled workers	31 (34.8%)	36 (40.4%)	
Unskilled workers	7 (7.9%)	7 (7.9%)	
Farmer	13 (14.6%)	2 (2.2%)	
Other (students, army, retired, unknown)	7 (7.9%)	12 (13.5%)	

Abbreviation: CI, confidence interval. [a]± Values are means±s.d.

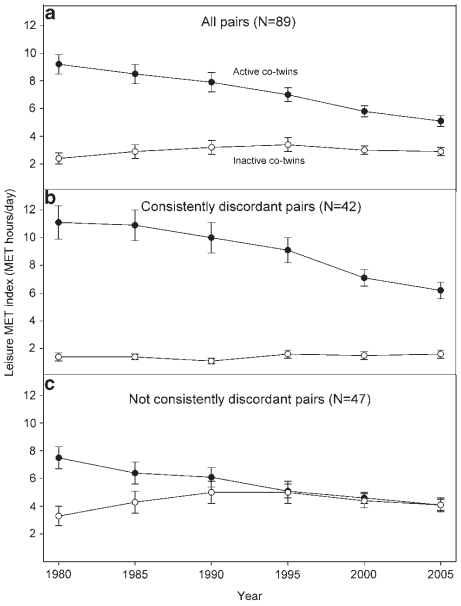

Figure 1 Leisure-time MET indices (mean ± s.e.) in inactive and active members of the twin pairs from 1980 through 2005. In (**a**) and (**b**) a significant difference ($P<0.001$) between inactive and active co-twins is seen in all measured years, but in (**c**), a significant difference is seen only in 1980 ($P<0.001$) and 1985 ($P<0.05$).

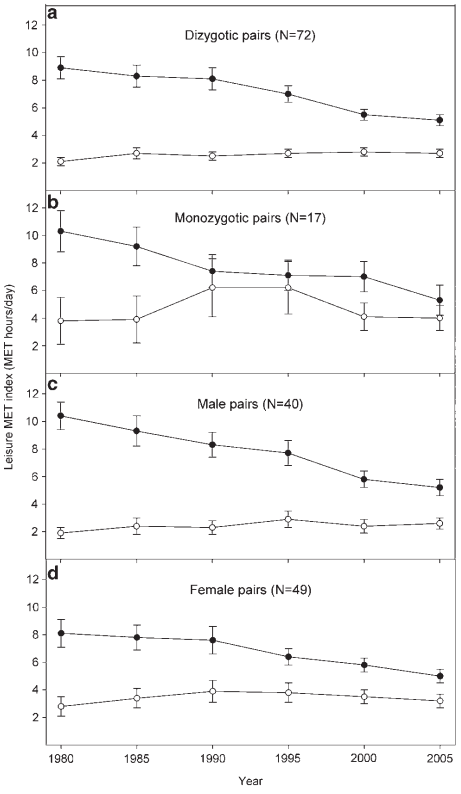

Figure 2 Leisure-time MET indices (mean ± s.e.) in inactive and active members of the twin pairs from 1980 through 2005. In (**a**), (**c**) and (**d**), significant difference ($P<0.01$) between inactive and active co-twins is seen in all the years measured, but in (**b**), a significant difference ($P<0.01$) is seen only in 1980 and 1985.

An increase in weight over time was seen in both inactive and active co-twins (Table 3). Among all 89 pairs, the active members gained 2.8 kg less weight during the 30-year follow-up than their inactive co-twins ($P=0.01$). Trends for weight gain were similar for male, female, DZ and MZ pairs (Figure 3). Among the 42 consistently discordant twin pairs, the active twins gained significantly less weight (5.4 kg, 95% confidence interval (CI) 1.95–8.87 kg, $P=0.003$) during 30-year follow-up when compared with their inactive co-twins, with similar trends in DZ (4.4 kg, 95% CI 0.90–7.96 kg, $P=0.02$) and MZ (12.6 kg, 95% CI −4.12 to 29.32 kg, $P=0.11$) pairs. However, the results for pairs not consistently discordant for physical activity did not show any differences between inactive and active co-twins in 2005.

In 2005, waist circumference was 4.1 cm smaller (95% CI 1.4–6.7 cm, $P=0.003$) in active than in inactive co-twins (Table 3). Again, trends were similar for male, female, DZ and MZ pairs. Among the consistently discordant twin pairs (Figure 4) waist circumference was 8.4 cm smaller (95% CI 4.0–12.7 cm, $P<0.001$) among active co-twins with similar trends in DZ (7.8 cm, 95% CI 3.71–11.84 cm, $P<0.001$), MZ (12.6 cm, 95% CI −18.47 to 43.67 cm, $P=0.32$), male and female pairs. However, no pairwise difference was seen in waist circumference among pairs not consistently discordant.

Inactive co-twins had a higher risk of major weight gain ($\geqslant$15 kg) during the 30-year follow-up (OR 2.18, 95% CI 1.07–4.45, $P=0.03$) compared to their active co-twins, the risk becoming even higher when further adjusted for weight and smoking in 1975 (OR 2.49, 95% CI 1.12–5.52, $P=0.025$). Inactive co-twins also had an increased but statistically non-significant risk of being obese (BMI $\geqslant$30) in 2005 (OR 2.75, 95% CI 0.88–8.64, $P=0.08$). Among 42 consistently discordant pairs, inactive co-twins had an even higher risk of

Table 2 MET indices (MET h/day) for all pairs, consistently discordant and not consistently discordant pairs[a]

Variable	*Inactive*	*Active*	*Mean difference (95% CI)*	T-*test*, P-*value*
All 89 pairs				
Mean MET index 1980–2005	3.0±3.1	7.2±4.4	4.27 (3.16 to 5.38)	<0.001
Daily activities 12-month MET index	1.9±2.9	1.9±2.7	−0.02 (−0.80 to 0.77)	0.96
Leisure time 12-month MET index	3.0±2.5	5.3±4.7	2.22 (1.15 to 3.30)	<0.001
Total 12-month MET index	5.0±4.1	7.2±5.4	2.20 (1.00 to 3.41)	<0.001
Consistently discordant pairs (42 pairs)				
Mean MET index 1980–2005	1.4±1.2	9.1±4.9	7.65 (6.20 to 9.10)	<0.001
Daily activities 12-month MET index	1.6±2.7	2.6±3.6	1.01 (−0.27 to 2.28)	0.12
Leisure time 12-month MET index	1.9±1.5	6.1±5.9	4.14 (2.38 to 5.90)	<0.001
Total 12-month MET index	3.5±3.3	8.7±6.7	5.15 (3.53 to 6.77)	<0.001
Not consistently discordant pairs (47 pairs)				
Mean MET index 1980–2005	4.4±3.6	5.6±3.2	1.25 (0.15 to 2.34)	0.03
Daily activities 12-month MET index	2.2±3.1	1.3±1.4	−0.94 (−1.86 to −0.01)	0.05
Leisure time 12-month MET index	4.0±2.9	4.5±3.2	0.51 (−0.62 to 1.64)	0.37
Total 12-month MET index	6.3±4.3	5.9±3.5	−0.43 (−1.86 to 1.01)	0.55

Abbreviation: CI, confidence interval. [a]± Values are means±s.d. Mean MET index 1980–2005 calculated from the shorter retrospective physical activity assessment. 12-month = 12-month detailed physical activity assessment. Leisure time 12-month MET index includes work journey and leisure time physical activities. Total = leisure time+work journey+daily activities.

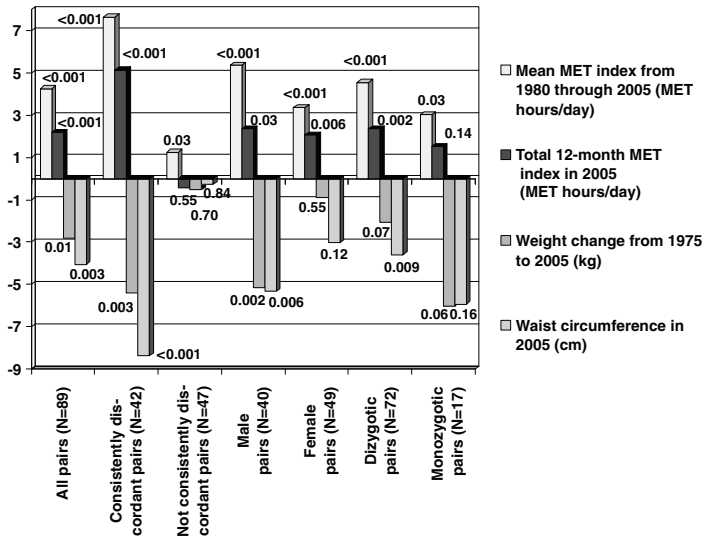

Figure 3 Pairwise differences between inactive and active co-twins in mean MET index, total 12-month MET index in 2005, weight change and waist circumference. Mean differences and *P*-values from paired *t*-test between inactive and active members of twin pairs for mean MET index from 1980 through 2005, total 12-month MET index in 2005, weight change from 1975 through 2005 and waist circumference.

major weight gain (OR 4.3, 95% CI 1.24–15.21, $P=0.02$) than their active co-twins, the risk being further increased when adjusted for weight and smoking in 1975 (OR 7.99, 95% CI 1.04–61.12, $P=0.045$). They also had an increased risk of obesity in 2005 (OR 4.5, 95% CI 0.97–20.8, $P=0.06$).

Discussion

Our study shows that physical activity in adults is associated with decreased weight gain and with smaller waist circumference in twin pairs consistently discordant for leisure-time

Table 3 Anthropometric measurements for all pairs, consistently discordant and not consistently discordant pairs[a]

Variable	*Inactive*	*Active*	*Mean difference (95% CI)*	T-*test*, P-*value*
All 89 pairs				
Height, 1975 (cm)	169.3±8.5	169.5±8.5	0.24 (−0.86 to 1.34)	0.67
Weight, 1975 (kg)	63.5±12.5	63.9±10.5	0.39 (−1.74 to 2.53)	0.72
Weight, 1981 (kg)	67.1±13.7	65.2±10.7	−1.99 (−4.35 to 0.37)	0.10
Weight, 2005 (kg)	74.7±15.1	72.3±11.7	−2.43 (−5.21 to 0.36)	0.09
Change in weight, 1975–1981 (kg)	3.6±4.7	1.3±3.8	−2.38 (−3.54 to −1.22)	<0.001
Change in weight, 1981–2005 (kg)	7.6±7.3	7.1±5.9	−0.44 (−2.30 to 1.42)	0.64
Change in weight, 1975–2005 (kg)	11.2±9.0	8.4±7.1	−2.82 (−4.98 to −0.66)	0.01
BMI, 1975	22.0±2.9	22.2±2.3	0.14 (−0.49 to 0.77)	0.66
BMI, 1981	23.3±3.4	22.6±2.4	−0.73 (−1.46 to 0.01)	0.05
BMI, 2005	25.9±3.9	25.1±3.0	−0.80 (−1.70 to 0.10)	0.08
Waist circumference (cm)	90.7±12.1	86.7±10.2	−4.05 (−6.67 to −1.42)	0.003
Consistently discordant pairs (42 pairs)				
Height, 1975 (cm)	169.7±8.5	169.3±8.5	−0.39 (−2.22 to 1.44)	0.67
Weight, 1975 (kg)	65.9±12.9	64.4±10.1	−1.50 (−4.88 to 1.88)	0.38
Weight, 1981 (kg)	69.9±14.6	65.0±9.7	−4.86 (−8.72 to −0.99)	0.02
Weight, 2005 (kg)	78.9±15.4	72.0±11.8	−6.91 (−11.19 to −2.62)	0.002
Change in weight, 1975–1981 (kg)	4.0±5.4	0.6±4.2	−3.36 (−5.42 to −1.29)	0.002
Change in weight, 1981–2005 (kg)	9.0±8.5	7.0±6.6	−2.05 (−5.01 to 0.91)	0.17
Change in weight, 1975–2005 (kg)	13.0±10.1	7.6±7.8	−5.41 (−8.87 to −1.95)	0.003
BMI, 1975	22.7±2.9	22.4±2.2	−0.30 (−1.24 to 0.65)	0.53
BMI, 1981	24.2±3.6	22.6±2.2	−1.57 (−2.77 to −0.37)	0.01
BMI, 2005	27.1±4.0	25.1±3.4	−2.05 (−3.48 to −0.61)	0.006
Waist circumference (cm)	94.2±12.4	85.8±10.2	−8.37 (−12.73 to −4.00)	<0.001
Not consistently discordant pairs (47 pairs)				
Height, 1975 (cm)	168.9±8.6	169.7±8.6	0.79 (−0.57 to 2.14)	0.25
Weight, 1975 (kg)	61.4±11.8	63.5±10.9	2.09 (−0.63 to 4.80)	0.13
Weight, 1981 (kg)	64.7±12.4	65.3±11.7	0.57 (−2.18 to 3.33)	0.68
Weight, 2005 (kg)	71.0±13.9	72.6±11.6	1.58 (−1.79 to 4.94)	0.35
Change in weight, 1975–1981 (kg)	3.3±3.9	1.8±3.5	−1.51 (−2.72 to −0.29)	0.02
Change in weight, 1981–2005 (kg)	6.3±5.8	7.3±5.4	1.00 (−1.35 to 3.36)	0.40
Change in weight, 1975–2005 (kg)	9.6±7.6	9.1±6.5	−0.51 (−3.14 to 2.13)	0.70
BMI, 1975	21.4±2.8	21.9±2.3	0.53 (−0.34 to 1.39)	0.23
BMI, 1981	22.6±3.1	22.6±2.6	0.01 (−0.88 to 0.89)	0.99
BMI, 2005	24.8±3.5	25.1±2.7	0.32 (−0.76 to 1.39)	0.56
Waist circumference (cm)	87.7±11.1	87.4±10.2	−0.28 (−3.09 to 2.54)	0.84

Abbreviations: BMI, body mass index; CI, confidence interval. [a]± Values are means±s.d. The body mass index is the weight in kilograms divided by the square of the height in meters. Change in weight 1975–1981 is weight in 1981–weight in 1975 and respectively for 1981–2005 and for 1975–2005.

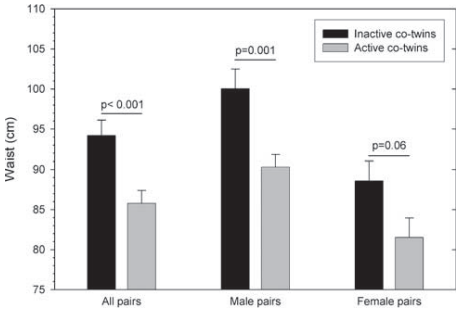

Figure 4 Waist circumference (mean±s.e.) difference for 42 consistently discordant pairs, for 21 consistently discordant male pairs and for 21 consistently discordant female pairs.

physical activity habits over 30 years. Trends were similar for both monozygotic and dizygotic twin pairs. The findings were most likely due to physical activity and not primarily influenced by genes or childhood environment.

The optimal study design for analysis would have been to use a large sample of activity-discordant monozygotic pairs; but we did not have sufficient numbers of discordant monozygotic pairs even in this large twin cohort. So, for the main analyses the monozygotic twin pairs were pooled with the dizygotic pairs. Among the baseline cohort of 5663 (31% MZ and 63% DZ) healthy twin pairs, a sub-sample of 111 pairs were invited for a follow-up study, of which 89 (19% MZ and 81% DZ) twin pairs completed the follow-up. These twin pairs were then, based on the follow-up information, further divided into two groups, consistently discordant (12% MZ and 88% DZ) and not consistently discordant (26% MZ and 74% DZ) for physical activity. As

indicated above, the number of monozygotic pairs in the sample constitutes a reduced proportion (19%) in the included sample than in the total cohort (31%). This is further reduced in the consistently discordant pairs (12%) indicating that consistently discordant monozygotic pairs are rare. The finding is in accordance with earlier twin studies[21,31] and consistent with strong genetic influences on physical activity.[32,33] In our study we also see that existing discordance seems to last for a shorter time among monozygotic pairs than in dizygotic pairs (Figure 2). The same genes may predict lower weight gain as well as make it easier for some individuals to exercise more. However, we observed that when activity discordance continues, the trend is the same for both zygosities in all our outcome measurements, even though the number of monozygotic pairs did not permit strong inference. As the trend was the same in both monozygotic and dizygotic pairs and the outcome difference was relatively high also among monozygotic pairs (12.6 kg in weight gain and 12.6 cm in waist circumference), it is likely that the association is also present in genetically controlled conditions. The significant difference in dizygotic pairs indicates that the association between physical activity and the outcome variables are not due to childhood environmental effects.

In line with our study, a decreased rate of weight gain with physical activity has been found in other studies,[34–39] although with shorter follow-ups and based on analyses of unrelated individuals. Haapanen *et al*.[35] found that inactive subjects had significantly higher risk of gaining $\geqslant 5$ kg during a 10-year follow-up when compared with more active subjects. Sternfeld *et al*.[38] found that decreased activity over a 3-year follow-up was associated with higher weight gain (2.7 kg) in women. They also found that physical activity was inversely related to waist circumference. Hill and Wyatt[19] proposed that physical activity is important for weight maintenance because of its impact on energy expenditure, effects on body composition through enhancing fat-free mass and increasing total fat oxidation.

Weight may increase once participation in physical activity is reduced, indicating the need to adjust diet during periods of inactivity. This was seen in the not consistently discordant pairs, while weight was significantly different between the inactive and active co-twins in 1981 but no longer in 2005. However, it is noteworthy that the weight increase from 1975 to 2005 tended to be lower in both of the not consistently discordant twin pair members (means 9.1 and 9.6 kg) compared to inactive members of the consistently discordant pairs (13.0 kg). Thus, on the basis of non-paired analyses, and also in accordance with Schmitz *et al*.,[36] periodical participation in physical activity also seems to slow down long-term weight gain. If looking at the truly prospective design (activity discordance 1975–1981 and weight gain 1981–2005), the weight gain was similar for both inactive and active co-twins ($P = 0.64$) among all 89 pairs. This could be explained by converging amounts of physical activity, as most active co-twins decreased the amount of activity and inactive co-twins slightly increased it or remained the same. Even though the prospective design did not show a difference in weight gain between inactive and active co-twins, the final cross-sectional design showed a significant difference in waist circumference at follow-up. This could partly be explained by reverse causality as decrease in weight might lead to increased participation in physical activity. In our study, even a small increase in exercise habits in passive co-twins seemed to slow down weight gain, although persistent activity was more beneficial. The correlation between pairwise differences in mean MET and in weight gain was significant ($r = -0.28$, $P = 0.008$) reinforcing the dose–response relationship between long-term physical activity and a slow rate of weight gain.

It has been shown that exercise without weight loss is associated with a substantial reduction in total and abdominal fat.[40] As expected, waist circumference was clearly lower in active compared with inactive co-twins (Figure 4). A 10-cm difference in waist circumference has high clinical significance as the outcome measurement has a strict association with other metabolic syndrome manifestations.[3] According to a study by Han *et al*.,[41] the risk of having at least one other CVD risk factor was higher (OR = 4.57, 95% CI 3.48–5.99) for men who had a waist circumference $\geqslant 102$ cm compared to men with waist circumference < 94 cm, whereas in women, the risk was higher (OR = 2.55 95% CI 2.02–3.23) if waist circumference was $\geqslant 88$ cm when compared with women who had waist circumference < 80 cm. However, a study by Wang *et al*.[42] showed that men who had waist circumference $\geqslant 96.5$ cm had higher risk (age-adjusted RR = 5.0, 95% CI 3.4–7.2) of type 2 diabetes compared to men who had waist circumference < 86.4 cm. A twin study by Rönnemaa *et al*.[43] found that among identical twins discordant for obesity, only those who differed most in visceral fat level had major alterations in insulin sensitivity and glucose tolerance. Aside from prevention of obesity and abdominal fat, physical activity has other benefits such as increased cardiovascular fitness, prevention of type 2 diabetes and coronary heart disease.[44,45] It is also important to remember that the most direct effect of physical training is the increase in fitness, which is also known to reduce disease risk.[46,47] Expectedly, we also found that inactive co-twins tended to become breathless easier during walking and daily tasks when compared with active co-twins ($P = 0.06$ for paired difference, results not shown).

Strengths and limitations

The strengths of our study were a very long follow-up period and twin study design. We partly controlled for genetic factors and the childhood environment by studying twin pairs comprehensively selected from the large Finnish Twin Cohort. One of the study limitations is the lack of comprehensive data on dietary habits. It would have been

impossible to collect reliable dietary data for so long period with current data collection methods. A small number of MZ twin pairs allowed us to only compare whether the trends were similar to DZ twins. The direction was same in 4 out of 5 consistently discordant MZ pairs.

Retrospective physical activity data collection presents some limitations, but we observed moderate correlations between the different physical activity assessments in the study. Also this type of data collection method is commonly used in the epidemiological physical activity research.[48] It would have been difficult to measure total energy expenditure for 30 years to validate the retrospective physical activity assessment. To maximize the participation rate and minimize the selection bias, an interview-based study was conducted, leaving weight, height and waist circumference to be measured by the participants. Although self-measurements are a limitation, they have shown to be valid and clinically relevant.

Conclusion

In conclusion, our findings give further evidence that persistent long-term participation in leisure-time physical activity is associated with decreased rate of weight gain and smaller waist circumference in adults. A 10-cm reduction in waist circumference across the population would produce significant benefits for public health.

Acknowledgements

This study was supported by the Finnish Ministry of Education, the Juho Vainio Foundation and the Yrjö Jahnsson Foundation. The Finnish Twin Cohort study was supported by the GENOMEUTWIN project (supported by the European Union Contract No. QLG2-CT-2002-01254) and the Finnish Twin Cohort Study is part of the Academy of Finland Centre of Excellence in Complex Disease Genetics.

The authors have no potential conflicts of interest related to the funding.

References

1 World Health Organization (WHO). *Obes Overweight* 2006, http: www.who.int/dietphysicalactivity/publications/facts/obesity/en/ ed. 2006.
2 Misra A, Vikram NK. Clinical and pathophysiological consequences of abdominal adiposity and abdominal adipose tissue depots. *Nutrition* 2003; **19**: 457–466.
3 Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; **365**: 1415–1428.
4 Bigaard J, Frederiksen K, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL *et al*. Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. *Int J Obes (Lond)* 2005; **29**: 778–784.
5 Bouchard C, Dionne FT, Simoneau JA, Boulay MR. Genetics of aerobic and anaerobic performances. *Exerc Sport Sci Rev* 1992; **20**: 27–58.
6 Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. *Am J Epidemiol* 2002; **156**: 985–993.
7 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.
8 Austin MA, Friedlander Y, Newman B, Edwards K, Mayer-Davis EJ, King MC. Genetic influences on changes in body mass index: a longitudinal analysis of women twins. *Obes Res* 1997; **5**: 326–331.
9 Hunt MS, Katzmarzyk PT, Perusse L, Rice T, Rao DC, Bouchard C. Familial resemblance of 7-year changes in body mass and adiposity. *Obes Res* 2002; **10**: 507–517.
10 Loos RJ, Bouchard C. Obesity—is it a genetic disorder? *J Intern Med* 2003; **254**: 401–425.
11 Barroso I. Genetics of type 2 diabetes. *Diabet Med* 2005; **22**: 517–535.
12 Schousboe K, Willemsen G, Kyvik KO, Mortensen J, Boomsma DI, Cornes BK *et al*. Sex differences in heritability of BMI: a comparative study of results from twin studies in eight countries. *Twin Res* 2003; **6**: 409–421.
13 Fox CS, Heard-Costa NL, Vasan RS, Murabito JM, D'Agostino RBS, Atwood LD *et al*. Genomewide linkage analysis of weight change in the Framingham Heart Study. *J Clin Endocrinol Metab* 2005; **90**: 3197–3201.
14 Fabsitz RR, Sholinsky P, Carmelli D. Genetic influences on adult weight gain and maximum body mass index in male twins. *Am J Epidemiol* 1994; **140**: 711–720.
15 Lees SJ, Booth FW. Sedentary death syndrome. *Can J Appl Physiol* 2004; **29**: 447–460; discussion 444–6.
16 Hill JO, Melanson EL. Overview of the determinants of overweight and obesity: current evidence and research issues. *Med Sci Sports Exerc* 1999; **31**: S515–S521.
17 Jebb SA, Moore MS. Contribution of a sedentary lifestyle and inactivity to the etiology of overweight and obesity: Current evidence and research issues. *Med Sci Sports Exerc* 1999; **31**: S534–S541.
18 Fogelholm M, Kukkonen-Harjula K. Does physical activity prevent weight gain—a systematic review. *Obes Rev* 2000; **1**: 95–111.
19 Hill JO, Wyatt HR. Role of physical activity in preventing and treating obesity. *J Appl Physiol* 2005; **99**: 765–770.
20 Kaprio J, Pulkkinen L, Rose RJ. Genetic and environmental factors in health-related behaviors: studies on Finnish twins and twin families. *Twin Res* 2002; **5**: 366–371.
21 Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of leisure-time physical activity and mortality: the Finnish twin cohort. *JAMA* 1998; **279**: 440–444.
22 Sarna S, Kaprio J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. *Hum Hered* 1978; **28**: 241–254.
23 Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Future hospital care in a population-based series of twin pairs discordant for physical activity behavior. *Am J Public Health* 1999; **89**: 1869–1872.
24 Kaprio J, Kujala UM, Koskenvuo M, Sarna S. Physical activity and other risk factors in male twin-pairs discordant for coronary heart disease. *Atherosclerosis* 2000; **150**: 193–200.
25 Kujala UM, Kaprio J, Koskenvuo M. Diabetes in a population-based series of twin pairs discordant for leisure sedentariness. *Diabetologia* 2000; **43**: 259.
26 Winters-Hart CS, Brach JS, Storti KL, Trauth JM, Kriska AM. Validity of a questionnaire to assess historical physical activity in older women. *Med Sci Sports Exerc* 2004; **36**: 2082–2087.
27 Lakka TA, Salonen JT. The physical activity questionnaires of the Kuopio Ischemic Heart Disease Study (KIHD). A collection of physical activity questionnaires for health-related research. *Med Sci Sports Exerc* 1997; **29**: S46–S58.

28 Lakka TA, Salonen JT. Intra-person variability of various physical activity assessments in the Kuopio Ischaemic Heart Disease Risk Factor Study. *Int J Epidemiol* 1992; **21**: 467–472.
29 Silventoinen K, Sammalisto S, Perola M, Boomsma DI, Cornes BK, Davis C *et al*. Heritability of adult body height: a comparative study of twin cohorts in eight countries. *Twin Res* 2003; **6**: 399–408.
30 Chan DC, Watts GF, Barrett PH, Burke V. Waist circumference, waist-to-hip ratio and body mass index as predictors of adipose tissue compartments in men. *QJM* 2003; **96**: 441–447.
31 Lauderdale DS, Fabsitz R, Meyer JM, Sholinsky P, Ramakrishnan V, Goldberg J. Familial determinants of moderate and intense physical activity: a twin study. *Med Sci Sports Exerc* 1997; **29**: 1062–1068.
32 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** (Part C): 37–46.
33 Stubbe JH, Boomsma DI, Vink JM, Cornes BK, Martin NG, Skytthe A *et al*. Genetic influences on exercise participation in 37.051 twin pairs from seven countries. *PLoS ONE* 2006; **1**: E22.
34 Williamson DF, Madans J, Anda RF, Kleinman JC, Kahn HS, Byers T. Recreational physical activity and ten-year weight change in a US national cohort. *Int J Obes Relat Metab Disord* 1993; **17**: 279–286.
35 Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I. Association between leisure time physical activity and 10-year body mass change among working-aged men and women. *Int J Obes Relat Metab Disord* 1997; **21**: 288–296.
36 Schmitz KH, Jacobs Jr DR, Leon AS, Schreiner PJ, Sternfeld B. Physical activity and body weight: associations over ten years in the CARDIA study. coronary artery risk development in young adults. *Int J Obes Relat Metab Disord* 2000; **24**: 1475–1487.
37 Droyvold WB, Holmen J, Midthjell K, Lydersen S. BMI change and leisure time physical activity (LTPA): an 11-y follow-up study in apparently healthy men aged 20–69 y with normal weight at baseline. *Int J Obes Relat Metab Disord* 2004; **28**: 410–417.
38 Sternfeld B, Wang H, Quesenberry CP, Abrams B, Everson-Rose SA, Greendale GA *et al*. Physical activity and changes in weight and waist circumference in midlife women: findings from the study of women's health across the nation. *Am J Epidemiol* 2004; **160**: 912–922.
39 Saarni SE, Rissanen A, Sarna S, Koskenvuo M, Kaprio J. Weight cycling of athletes and subsequent weight gain in middleage. *Int J Obes (Lond)* 2006; **30**: 1639–1644.
40 Ross R, Janssen I, Dawson J, Kungl AM, Kuk JL, Wong SL *et al*. Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. *Obes Res* 2004; **12**: 789–798.
41 Han TS, van Leer EM, Seidell JC, Lean ME. Waist circumference action levels in the identification of cardiovascular risk factors: prevalence study in a random sample. *BMJ* 1995; **311**: 1401–1405.
42 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.
43 Rönnemaa T, Koskenvuo M, Marniemi J, Koivunen T, Sajantila A, Rissanen A *et al*. Glucose metabolism in identical twins discordant for obesity. The critical role of visceral fat. *J Clin Endocrinol Metab* 1997; **82**: 383–387.
44 Kesäniemi YK, Danforth E, Jensen MD, Kopelman PG, Lefebvre P, Reeder BA. Dose–response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc* 2001; **33**: S351–S358.
45 Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ* 2006; **174**: 801–809.
46 Lakka TA, Venäläinen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med* 1994; **330**: 1549–1554.
47 Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? *Med Sci Sports Exerc* 2001; **33**: S379–S399; discussion S419–20.
48 Wareham NJ, Rennie KL. The assessment of physical activity in individuals and populations: why try to be more precise about how physical activity is assessed? *Int J Obes Relat Metab Disord* 1998; **22** (Suppl 2): S30–S38.

IV

LEISURE-TIME PHYSICAL ACTIVITY AND TYPE 2 DIABETES DURING A 28 YEAR FOLLOW-UP IN TWINS

by

Waller K, Kaprio J, Lehtovirta M, Silventoinen K, Koskenvuo M, Kujala UM.
2010

Diabetologia 53(12), 2531-2537

Diabetologia (2010) 53:2531–2537
DOI 10.1007/s00125-010-1875-9

ARTICLE

Leisure-time physical activity and type 2 diabetes during a 28 year follow-up in twins

K. Waller · J. Kaprio · M. Lehtovirta · K. Silventoinen · M. Koskenvuo · U. M. Kujala

Received: 14 April 2010 / Accepted: 5 July 2010 / Published online: 13 August 2010

Abstract
Aims/hypothesis The study aimed to investigate whether baseline physical activity protects against the occurrence of type 2 diabetes during a 28 year follow-up, after controlling for childhood environment and genetic predisposition.
Methods At baseline in 1975 same-sex twin pairs born in Finland before 1958 were sent a questionnaire including questions on physical activity. The participants (20,487 individuals, including 8,182 complete twin pairs) were divided into quintiles by leisure-time physical activity metabolic equivalent (MET) index (MET h/day). Type 2 diabetes was determined from nationwide registers for the follow-up period (1 January 1976–31 December 2004). Individual and pairwise Cox proportional hazard models were used.
Results During follow-up, 1,082 type 2 diabetes cases were observed. Among all individuals, participants in MET quintiles (Q) III–V had significantly decreased risk for type 2 diabetes compared with sedentary individuals (QI). The pairwise analysis on pairs discordant for physical activity showed that participants in MET QII to V had significantly lower hazard ratios (0.61, 0.59, 0.61, 0.61) compared with sedentary participants. These findings from the pairwise analysis persisted after adjusting for BMI. In the pairwise analysis, the BMI-adjusted hazard ratio for type 2 diabetes was lower for physically active members of twin pairs (combined QII–V) than for inactive co-twins (HR 0.54; 95% CI 0.37–0.78). Similar results were obtained for both dizygotic and monozygotic pairs, as well as for the subgroup of twin pairs defined as free of co-morbidities in 1981 (HR 0.36; 95% CI 0.17–0.76).
Conclusions/interpretation Leisure-time physical activity protects from type 2 diabetes after taking familial and genetic effects into account.

Keywords Follow-up studies · Physical activity · Twin study · Type 2 diabetes mellitus

Abbreviations

DZ	Dizygotic
MET	Metabolic equivalent
MZ	Monozygotic
Q	Quintile

Electronic supplementary material The online version of this article (doi:10.1007/s00125-010-1875-9) contains supplementary material, which is available to authorised users.

K. Waller (✉) · U. M. Kujala
Department of Health Sciences, University of Jyväskylä,
PO Box 35, 40014 Jyväskylä, Finland
e-mail: katja.waller@jyu.fi

J. Kaprio · M. Lehtovirta · M. Koskenvuo
Department of Public Health, University of Helsinki,
Helsinki, Finland

J. Kaprio
Department of Mental Health and Alcohol Abuse Services,
National Institute for Health and Welfare,
Helsinki, Finland

J. Kaprio
Institute for Molecular Medicine, University of Helsinki,
Helsinki, Finland

K. Silventoinen
Population Research Unit, Department of Social Research,
University of Helsinki,
Helsinki, Finland

Introduction

Type 2 diabetes is an increasing worldwide health problem. More than half a million people in Finland (about 10% of the population) in 2008 [1] and about 170 million people worldwide in 2004 [2] were estimated to have type 2 diabetes. The worldwide figure is estimated to double by 2030 [2].

It has been shown that obesity is a major risk factor for type 2 diabetes [3, 4] and that lifestyle interventions, including diet modification and physical activity, are effective in preventing diabetes [5–7]. Prospective follow-up studies [8–12] and a randomised controlled trial [13] suggest that physical activity has an independent role in the prevention of type 2 diabetes. The evidence suggests that any physical activity may be better than none in the prevention of type 2 diabetes, but better results are achieved if individuals engage in moderate-intensity exercise, preferably daily [14].

It is known that physical fitness and the ability to achieve high levels of physical activity have a genetic component [15–17]. Type 2 diabetes has been clearly shown to be an environmental disease, but it also has a genetic component [18], based on family, twin and genome-wide association studies [19]. Twin pairs nearly always share the same childhood family environment. Dizygotic (DZ) pairs (like sibling pairs) share, on average, half of their segregating genes, while monozygotic (MZ) pairs are genetically identical at the sequence level. By studying outcomes in twin pairs discordant for an exposure, such as physical activity, the possible confounding role of genetic and early childhood experiences can be assessed.

The main aim of this study was to investigate whether physical activity predicts the development of type 2 diabetes during almost 30 years of follow-up, when controlled for genetic predisposition and childhood family environment (co-twin-control design). Another aim of the study was to see whether the effect of physical activity is independent of BMI.

Methods

Participants The Finnish Twin Cohort comprises virtually all the same-sex twin pairs born in Finland before 1958 and with both co-twins alive in 1967 [20]. In 1975, a baseline questionnaire (described below in detail) was sent to twin pairs with both members alive. The response rate was 89%. After excluding the participants with diagnosed diabetes at baseline, those of undefined zygosity and those who had moved abroad before 1976, the cohort consisted of 23,585 individuals with self-reported baseline data on education, social and occupational class, alcohol consumption, physical activity and BMI [19]. The final cohort for the present study included 20,487 individuals, with 8,182 complete twin pairs, who had complete physical activity information available for metabolic equivalent (MET) index calculations (see explanation below). Of the total sample, 9,842 were male and 10,645 female, and 6,399 were monozygotic twin individuals and 14,087 were dizygotic twin individuals. Determination of zygosity was based on an accurate and validated questionnaire method [21].

To remove the confounding factors due to disease, we studied a subgroup of 13,291 presumably healthy individuals. Participants with chronic diseases (such as angina pectoris, myocardial infarction, stroke, diabetes, cardiovascular disease, chronic obstructive pulmonary disease and malignant cancer) affecting weight and ability to engage in leisure physical activity prior to 1982 had been identified by a questionnaire in 1981 and by medical records as described in detail by Kujala et al. [22]. Type 2 diabetes [23] and some other diseases can remain subclinical and undiagnosed for some time after the onset of symptoms. Therefore, we set a 6 year period in order to ensure that any undiagnosed cases in 1975 would have been diagnosed by 1981. Thus, we obtained a true cohort of participants free of clinical co-morbidities.

The participants were informed about the purposes of the overall cohort study when given the baseline questionnaire in 1975. In responding to the questionnaire, participants also gave informed consent. The record linkages were also approved by the appropriate authorities responsible for the registers and the Ethics Committee of the Department of Public Health, University of Helsinki.

Baseline physical activity and covariate assessment The 1975 questionnaire included questions on medical history, education, occupation, physical activity and other health habits. Assessment of leisure-time physical activity volume (MET index) was based on a series of structured questions on leisure-time physical activity (monthly frequency, mean duration and mean intensity of sessions) and commuting physical activity. The index was calculated by first assigning a multiple of resting metabolic rate (MET value) to one of four categories defined according to the strenuousness of the activity [22]. After assigning the MET value, the product of the activity was calculated as follows: MET value × duration × frequency. The MET index was expressed as the sum score of leisure MET h/day (1 MET h/day corresponds to about 30 min walking every other day). The MET index thus established was then divided into quintiles. The same quintiles were used as in our earlier study on mortality [22]. For cut-off points see Table 1. For further analyses the index was dichotomised as

Table 1 Baseline characteristics of 20,487 individuals according to MET quintiles in 1975

Variable	MET QI <0.59 MET h/day	MET QII 0.59–1.29 MET h/day	MET QIII 1.30–2.49 MET h/day	MET QIV 2.50–4.49 MET h/day	MET QV≥4.5 MET h/day	*p* value[a]
Participants, *n* (%)	3,670 (18.2)	3,727 (18.1)	4,551 (22.4)	4,606 (22.5)	3,933 (18.8)	
Male, *n* (%)	1,531 (15.6)	1,825 (18.5)	2,043 (20.8)	2,216 (22.5)	2,227 (22.6)	
Female, *n* (%)	2,139 (20.1)	1,902 (17.9)	2,508 (23.6)	2,390 (22.5)	1,706 (16.0)	
Monozygotic, *n* (%)	1,137 (17.8)	1,136 (17.8)	1,395 (21.8)	1,461 (22.8)	1,270 (19.8)	
Dizygotic, *n* (%)	2,533 (18.0)	2,590 (18.4)	3,156 (22.4)	3,145 (22.3)	2,663 (18.9)	
Age in 1975, mean (±SD)	35.6 (±15.2)	34.1 (±13.0)	32.9 (±12.2)	33.2 (±13.0)	33.4 (±13.5)	<0.001
BMI in 1975, mean (±SD)	23.4 (±3.7)	23.3 (±3.4)	22.9 (±3.2)	22.9 (±3.2)	22.9 (±3.0)	<0.001
Pack years smoked, mean (±SD)	5.1 (±9.6)	4.8 (±8.9)	4.7 (±8.6)	4.4 (±8.4)	4.5 (±8.9)	<0.001
Alcohol (g/day), mean (±SD)	8.1 (±15.6)	8.5 (±13.6)	8.6 (±13.5)	8.6 (±13.4)	8.6 (±13.2)	<0.001
Current smokers, *n* (%)	1,335 (36.4)	1,207 (32.4)	1,561 (34.3)	1,445 (31.4)	1,096 (27.9)	<0.001
White collar/clerical workers, n (%)	841 (22.9)	1,235 (33.1)	1,587 (34.9)	1,681 (36.5)	1,366 (34.7)	<0.001
Heavy physical work, *n* (%)	2,240 (61.0)	2,057 (55.2)	2,289 (50.3)	2,298 (49.9)	2,114 (53.8)	<0.001

[a] *p* values are from cluster-corrected regression analyses adjusted for sex and age in 1975

sedentary <0.59 MET h/day (QI) and active ≥0.59 MET h/day (combined QII–V).

The MET index was validated in a previous study by our group [24] by comparing the MET index with a 12 month detailed physical activity questionnaire conducted by telephone interview. The intraclass correlation between the MET index and the detailed 12 month physical activity MET index was 0.68 ($p<0.001$) for leisure-time physical activity and 0.93 ($p<0.001$) for commuting.

Baseline self-reported weight and height were used to calculate BMI, which was used as a covariate in the study. In another study of Finnish twins the correlation between self-reported and measured BMI was very high [25].

Self-reported smoking status, use of alcohol, work-related physical activity and social class at baseline in 1975 were also used as covariates. Smoking status was coded into four categories, determined from responses to detailed smoking history questions: never smoked; former smoker; occasional smoker; and current daily smoker [26]. Alcohol use was coded as a dichotomous index of binge drinking and defined by whether the participant had drunk at least five drinks on a single occasion, at least monthly [27]. Alcohol was also used as a continuous variable expressed as grams consumed daily, as described in detail earlier [27]. Six categories were used to describe social class and the classification was based on self-reported job titles according to the criteria used by the Central Statistical Office of Finland [28]. Work-related physical activity was used as a categorical variable with a four-point ordinal scale [16].

Diabetes assessment Type 2 diabetes information for 1976–1996 was collected from death certificates, the National Hospital Discharge Register and the Medication Register of the Social Insurance Institution by linking this information to the personal identification assigned to all residents of Finland [19]. The Social Insurance Institution of Finland (KELA) is the agency responsible for the provision of basic social security [19, 29]. KELA reimburses whole or part of the cost of necessary medications to patients who are certified by a physician as having a diagnosed severe chronic disease [30]. Although the register is not sensitive to cases of mild disease, it has very high validity and the possibility of false-positive cases is unlikely [29]. The relevant medical records for 1976–1996 were reviewed and cases classified as type 2 diabetes, type 1 diabetes, gestational diabetes, secondary diabetes or other diagnoses as described by Kaprio et al. [31]. The date of onset of disease symptoms was determined and used in the analyses. The diabetes information for 1996–2004 was collected solely from the Medication Register and individuals were presumed to have type 2 diabetes, given their age [19]. For this period the date of being granted the right to reimbursable medication was used in the analysis as the date of disease onset. We have not yet extended the data collection for years 2005–2009, partly because the national programme of screening pre-diabetes and diabetes cases followed with preventive interventions (for example, dietary modification, physical activity) has been intensive during 2005–2009, which may cause a bias in our study design if included in our prospective long-term follow-up.

Data analysis Cox proportional hazard regression was used to estimate the hazard ratios, with 95% CI, for the incidence of type 2 diabetes by MET quintile. The inactive category (QI: <0.59 MET h/day) was used as the reference group. The follow-up for type 2 diabetes ended at the time of diagnosis and for the others at the time of death, emigration

from Finland or end of follow-up (31 December 2004). First, the Cox regression model was conducted as an individual analysis and second, the analyses were done as pairwise analyses, in which the data were stratified by pair and thus the risk estimates were within-pair estimates. For the individual analysis, the Cox regression model was adjusted for age and sex, and additionally for BMI. The pairwise analyses controlled by design for age and sex (co-twin-control design), but the models were also adjusted for BMI and were run separately for MZ and DZ pairs if the numbers permitted. The basic individual analysis was additionally adjusted for work-related physical activity, social class, alcohol use and smoking. In the individual-level analyses, lack of statistical independence of co-twins was taken into account by computing robust variance estimators for cluster-corrected data [32] to yield correct standard errors and p values. Data management and analysis were performed using the Stata statistical software, version 9.0.

Results

Table 1 shows the baseline characteristics of the participants according to the physical activity MET quintiles. The sedentary participants in QI were, as expected, the oldest, had highest BMI and smoked the most.

A total of 535,000 person-years were accumulated during the follow-up from 1976 to 2004. During this period, 1,082 new type 2 diabetes cases occurred among the 20,487 participants. The hazard ratios and 95% confidence intervals for type 2 diabetes between the different MET quintiles for all individuals are presented in Fig. 1a (see also Electronic supplementary material [ESM] Table 1).

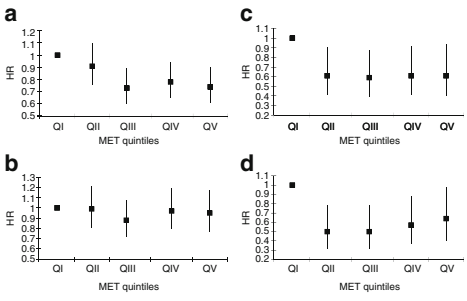

Fig. 1 HRs and 95% CIs for type 2 diabetes according to different MET quintiles for all participants: (**a**) individual analyses; (**b**) individual analyses adjusted for age, sex and BMI; (**c**) pairwise analyses; and (**d**) pairwise analyses adjusted for BMI. QI <0.59 MET h/day; QII 0.59–1.29 MET h/day; QIII 1.30–2.49 MET h/day; QIV 2.50–4.49 MET h/day; and QV: ≥4.50 MET h/day

The individual analyses showed that the participants in physical activity quintiles III–V had significantly lower age- and sex-adjusted hazard ratios during the follow-up compared with the sedentary individuals in QI. Analysis of healthy participants with no known medical constraints on physical activity (n=13,291 individuals) also showed similar hazard ratios (ESM Table 1). After adjusting the model for all individuals for work-related physical activity, social class, smoking and alcohol use (all separately), the hazard ratios remained similar. When the model was adjusted for BMI, the differences in the hazard ratios between the quintiles were no longer significant (Fig. 1b). There was no difference between individuals in risk by zygosity.

The pairwise analysis indicated (Fig. 1c) that the participants in physical activity quintiles II to V were significantly less likely to have type 2 diabetes (QII HR 0.61, 95% CI 0.41–0.90; QIII 0.59, 0.39–0.87; QIV 0.61 0.41–0.91; QV 0.61, 0.40–0.94) during the follow-up than their co-twins in the sedentary quintile (ESM Table 2). This analysis takes into account all pairs discordant for physical activity across all the quintiles. The hazard ratios (QII HR 0.50, 95% CI 0.32–0.78; QIII 0.50, 0.32–0.78; QIV 0.57, 0.37–0.88), except that for QV, were reduced even further when the model was adjusted for BMI (Fig. 1d). Similar results were found for both zygosities, with the MZ twins showing the lowest hazard ratios (ESM Table 2). Although numerically the lowest, the hazard ratios for the MZ pairs are not all statistically significant as the MZ also had the lowest number of informative discordant pairs. Again, the results of the subgroup analysis of the healthy participants with no known constraints on physical activity showed similar hazard ratios. The BMI-adjusted hazard ratios for type 2 diabetes remained statistically significant in all quintiles.

Of all the twin pairs, 1,919 pairs were discordant for physical activity when sedentariness (QI <0.59 MET h/day) was compared with any activity category (combined quintiles II–V) and 809 pairs were discordant for type 2 diabetes. Of these, 146 pairs were discordant for both baseline physical activity and follow-up type 2 diabetes. In 85 of the 146 pairs, the co-twin who was diagnosed with diabetes during the follow-up was sedentary at baseline, while the active co-twin remained healthy; in 61 pairs the converse was true. Among the MZ pairs the corresponding numbers were 21 and 10.

Further pairwise analyses showed that the BMI-adjusted hazard ratio (0.54; 95% CI 0.37–0.78) was lower in the members of the twin pairs who were physically active (combined Q II–V: ≥0.59 MET h/day) compared with their inactive (QI: <0.59 MET h/day) co-twins (Table 2). The results of the BMI-adjusted pairwise analyses were significant for all the analysed subgroups, except that for MZ

Table 2 Risk for type 2 diabetes during 1976–2004 in active members of twin pairs (≥0.59 MET h/day) compared with their sedentary co-twins (<0.59 MET h/day)[a]

Variable	Pairwise analyses			
	HR (95% CI)	*p* value	HR (95% CI) adjusted for BMI	*p* value
All	0.60 (0.43–0.84)	0.003	0.54 (0.37–0.78)	0.001
Men	0.51 (0.31–0.86)	0.011	0.49 (0.27–0.87)	0.014
Women	0.68 (0.44–1.05)	0.083	0.59 (0.36–0.96)	0.033
Monozygotic	0.5 (0.24–1.03)	0.061	0.49 (0.23–1.04)	0.064
Dizygotic	0.63 (0.44–0.92)	0.017	0.56 (0.37–0.86)	0.007
Healthy in 1981	0.4 (0.21–0.78)	0.007	0.36 (0.17–0.76)	0.007

[a] Sedentary participants (<0.59 MET h/day) are the reference group

pairs, which was marginally non-significant. However, the MZ pairs showed a similar or even lower hazard ratio than the other groups.

Discussion

Our 28 year prospective follow-up study in twins showed that leisure-time physical activity reduces the risk for type 2 diabetes when controlled for genetic predisposition and childhood home environment. This was seen in the pairwise analyses among both MZ and DZ pairs, including those using BMI-adjusted data. It can therefore be assumed that physical activity independently protects against type 2 diabetes, as many unmeasured confounding factors (both genetic and environmental) are controlled for by the twin design. These findings are consistent with those of earlier population-based studies [10–12]. However, our study had a longer follow-up and we were able to investigate the issue in genetically controlled participants.

On the one hand, high BMI may lead to inactivity and then to more type 2 diabetes; on the other hand inactivity may lead to higher BMI and then to type 2 diabetes. However, use of BMI as a covariate is problematic as both high muscle mass and high fat mass can contribute to high BMI. Our previous twin studies have shown that despite the lack of statistically significant differences in BMI between physically active and inactive members of twin pairs, physical activity reduces waist [24] and high-risk body fat (ectopic fat stores, liver fat and visceral fat) but maintains skeletal muscle mass and function [33], leading to lowered type 2 diabetes risk independent of BMI. It is also possible that the results from BMI-adjusted analyses are over-adjusted, as physical activity may reduce type 2 diabetes by independently reducing BMI.

As chronic exposure of pancreatic beta cells to elevated glucose and fatty acid levels may impair their function and lead to type 2 diabetes [34, 35], both endurance and resistance exercise training has been proven to have effects on various mechanisms that enhance the insulin sensitivity of skeletal muscles [36] and thus diminish glycaemic stress. More specifically, physical activity or exercise training has been shown to reduce visceral fat [33], improve skeletal muscle insulin sensitivity [37, 38] and increase the oxidative capacity of skeletal muscle, which correlates with insulin sensitivity [39], and also leads to increased/modified fat oxidation, which is most likely to prevent lipid-mediated insulin resistance [40].

The evidence to date on the dose-response relationship regarding the amount of physical activity needed to prevent type 2 diabetes remains conflicting [14]. In our study any amount of physical activity seemed to reduce the risk for type 2 diabetes, as seen in the pairwise analyses. As little physical activity as 0.6–1.3 MET h/day or 4.2–9.1 MET h/week, produced significant results compared with sedentariness. Four MET h/week are equivalent to 1 h moderate-intensity exercise weekly and 9 MET h/week are equivalent to about 2 h moderate-intensity exercise weekly, which still is less than the generally advised 150 min moderate intensity exercise per week [14]. The hazard ratios in the pairwise analyses were similar across all the physical activity quintiles (II–V), indicating that total inactivity in particular is a predictor of future type 2 diabetes. However, it may be that during our long-term follow-up those individuals who at baseline exercised most have decreased their exercise levels. The dose-response relation between physical activity and occurrence of type 2 diabetes, and particularly the role of the intensity of activity, still remain unanswered.

Strengths and limitations The main strengths of the present study are a very long follow-up period, the twin study design and a large sample size. The twin design enabled us to control for both genetic predisposition and childhood family environment. The large sample included a very large proportion of all the same-sex twin pairs born in Finland before 1958 and therefore can be expected to be a good representation of the Finnish general population of that generation. Another important strength of the study is the use of hospital discharge and death registers and information on reimbursable medication for type 2 diabetes assessment, which provide data on outcomes on all participants. There were very few, if any, false-positive cases of type 2 diabetes among our data [29].

However, the registers also have a limitation as diagnoses of type 2 diabetes tend to be delayed, which then means delay in granting of the right to reimbursable medication; this would bias results if the delay was different by physical activity category. Biochemical assessment of all participants for follow-up status would have been ideal. In practice, repeated measures of glucose metabolism from all participants is not possible, as this may also lead to participation bias based on presence of diabetes or related symptoms. Self-reported data on physical activity habits and BMI also have known limitations. However, these physical activity questions correlated well with the results of a detailed interview [24] and predicted mortality [22] consistently with other studies that have used different measures of physical activity. As stated earlier, correlation between self-reported and measured BMI is very high [25]. Another limitation in our study relates to the use of baseline BMI as a covariate. This does not control for the changes in BMI over time that are possible during such a long follow-up. More detailed measures of body composition in 1975 would have been desirable but were not available.

Conclusion

Our longitudinal twin pair study established that leisure-time physical activity protects from type 2 diabetes after taking genetic effects into account. On the basis of our co-twin-control design even small amounts of physical activity compared with sedentariness play a significant role in reducing or postponing the occurrence of type 2 diabetes.

Acknowledgements The Finnish Twin Cohort Study is supported by the Academy of Finland Centre of Excellence in Complex Disease Genetics. The Social Insurance Institution of Finland provided the register data free of charge and its support for analyses through the TwinKELA project is gratefully acknowledged.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Reunanen A, Virta L, Klaukka T (2008) Tyypin 2 diabeetikkoja on jo yli puoli miljoonaa (Already over half a million type 2 diabetics). Suomen Lääkärilehti (Finnish Medical Journal) 21:1952–1955 (in Finnish)
2. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053
3. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1994) Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 17:961–969
4. Carey VJ, Walters EE, Colditz GA et al (1997) Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol 145:614–619
5. Tuomilehto J, Lindstrom J, Eriksson JG et al (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344:1343–1350
6. Knowler WC, Barrett-Connor E, Fowler SE et al (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393–403
7. Ramachandran A, Snehalatha C, Mary S et al (2006) The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 49:289–297
8. Manson JE, Rimm EB, Stampfer MJ et al (1991) Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 338:774–778
9. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr (1991) Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 325:147–152
10. Hu FB, Sigal RJ, Rich-Edwards JW et al (1999) Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. JAMA 282:1433–1439
11. Folsom AR, Kushi LH, Hong CP (2000) Physical activity and incident diabetes mellitus in postmenopausal women. Am J Public Health 90:134–138
12. Hu G, Qiao Q, Silventoinen K et al (2003) Occupational, commuting, and leisure-time physical activity in relation to risk for Type 2 diabetes in middle-aged Finnish men and women. Diabetologia 46:322–329
13. Pan XR, Li GW, Hu YH et al (1997) Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 20:537–544
14. Physical Activity Guidelines Advisory Committee (2008) Physical activity guidelines advisory committee report, 2008
15. Bouchard C, Dionne FT, Simoneau JA, Boulay MR (1992) Genetics of aerobic and anaerobic performances. Exerc Sport Sci Rev 20:27–58
16. Kujala UM, Kaprio J, Koskenvuo M (2002) Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. Am J Epidemiol 156:985–993
17. Stubbe JH, Boomsma DI, de Geus EJ (2005) Sports participation during adolescence: a shift from environmental to genetic factors. Med Sci Sports Exerc 37:563–570
18. Malecki MT, Klupa T (2005) Type 2 diabetes mellitus: from genes to disease. Pharmacol Rep 57(Suppl):20–32
19. Lehtovirta M, Pietilainen KH, Levalahti E et al (2010) Evidence that BMI and type 2 diabetes share only a minor fraction of genetic variance: a follow-up study of 23, 585 monozygotic and dizygotic twins from the Finnish Twin Cohort Study. Diabetologia 53:1314–1321
20. Kaprio J, Koskenvuo M (2002) Genetic and environmental factors in complex diseases: the older Finnish Twin Cohort. Twin Res 5:358–365
21. Sarna S, Kaprio J, Sistonen P, Koskenvuo M (1978) Diagnosis of twin zygosity by mailed questionnaire. Hum Hered 28:241–254
22. Kujala UM, Kaprio J, Sarna S, Koskenvuo M (1998) Relationship of leisure-time physical activity and mortality: the Finnish twin cohort. JAMA 279:440–444
23. Glumer C, Jorgensen T, Borch-Johnsen K, Inter99 study (2003) Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. Diabetes Care 26:2335–2340
24. Waller K, Kaprio J, Kujala UM (2008) Associations between long-term physical activity, waist circumference and weight gain: a 30-year longitudinal twin study. Int J Obes 32:353–361

25. Mustelin L, Silventoinen K, Pietilainen K, Rissanen A, Kaprio J (2009) Physical activity reduces the influence of genetic effects on BMI and waist circumference: a study in young adult twins. Int J Obes (Lond) 33:29–36
26. Kaprio J, Koskenvuo M (1988) A prospective study of psychological and socioeconomic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and non-smokers. J Clin Epidemiol 41:139–150
27. Kaprio J, Koskenvuo M, Langinvainio H, Romanov K, Sarna S, Rose RJ (1987) Genetic influences on use and abuse of alcohol: a study of 5638 adult Finnish twin brothers. Alcohol Clin Exp Res 11:349–356
28. Central Statistical Office of Finland (1972) Alphabetical list of occupations and classification of social class. Central Statistical Office of Finland, Helsinki
29. Kujala UM, Sarna S, Kaprio J (2003) Use of medications and dietary supplements in later years among male former top-level athletes. Arch Intern Med 163:1064–1068
30. The Social Insurance Institution of Finland (2006) Medicines. Available from www.kela.fi/in/internet/english.nsf/NET/131003131216MH?openDocument, accessed 17 October 2006
31. Kaprio J, Tuomilehto J, Koskenvuo M et al (1992) Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 35:1060–1067
32. Williams RL (2000) A note on robust variance estimation for cluster-correlated data. Biometrics 56:645–646
33. Leskinen T, Sipila S, Alen M et al (2009) Leisure-time physical activity and high-risk fat: a longitudinal population-based twin study. Int J Obes (Lond) 33:1211–1218
34. Poitout V, Robertson RP (2002) Minireview: secondary beta-cell failure in type 2 diabetes—a convergence of glucotoxicity and lipotoxicity. Endocrinology 143:339–342
35. Florez JC (2008) Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? Diabetologia 51:1100–1110
36. Tresierras MA, Balady GJ (2009) Resistance training in the treatment of diabetes and obesity: mechanisms and outcomes. J Cardiopulm Rehabil Prev 29:67–75
37. Zierath JR (2002) Invited review: exercise training-induced changes in insulin signaling in skeletal muscle. J Appl Physiol 93:773–781
38. Wang Y, Simar D, Fiatarone Singh MA (2009) Adaptations to exercise training within skeletal muscle in adults with type 2 diabetes or impaired glucose tolerance: a systematic review. Diabetes Metab Res Rev 25:13–40
39. Bruce CR, Kriketos AD, Cooney GJ, Hawley JA (2004) Disassociation of muscle triglyceride content and insulin sensitivity after exercise training in patients with Type 2 diabetes. Diabetologia 47:23–30
40. Slentz CA, Houmard JA, Kraus WE (2009) Exercise, abdominal obesity, skeletal muscle, and metabolic risk: evidence for a dose response. Obesity 17:S27–S33

STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH

1 KIRJONEN, JUHANI, On the description of a human movement and its psychophysical correlates under psychomotor loads. 48 p. 1971.
2 KIRJONEN, JUHANI JA RUSKO, HEIKKI, Liikkeen kinemaattisista ominaispiirteistä, niiden psykofyysisistä selitysyhteyksistä ja näiden muutoksista psykomotorisen kuormituksen ja kestävyysharjoittelun vaikutuksesta. - On the kinematic charac-teristics and psychophysical correlates of a human movement and their changes during psychomotor loading and endurace conditioning. 156 p. 1971.
3 SARVIHARJU, PEKKA J., Effects of psycho-physical loading and progressive endurance conditioning on selected biochemical correlates of adaptive responses in man. 95 p. 1973.
4 KIVIAHO, PEKKA, Sport organizations and the structure of society. 54 p. 1973.
5 KOMI, PAAVO V., NELSON, RICHARD C. AND PULLI, MATTI, Biomechanics of skijumping. 53 p. 1974.
6 METELI, Työolot, terveys ja liikuntakäyttäytyminen metallitehtaissa. Kartoittavan kyselyn aineistot ja toteuttaminen. 178 p. 1974.
7 TIAINEN, JORMA M., Increasing physical education students' creative thinking. 53 p. 1976.
8 RUSKO, HEIKKI, Physical performance characteristics in Finnish athletes. 40 p. 1976.
9 KIISKINEN, ANJA, Adaptation of connective tissues to physical training in young mice. 43 p. 1976.
10 VUOLLE, PAULI, Urheilu elämänsisältönä. Menestyneiden urheilijoiden elämänura kilpailuvuosina - Top sport as content of life. 227 p. 1977.
11 SUOMINEN, HARRI, Effects of physical training in middle-aged and elderly people with special regard to skeletal muscle, connective tissue, and functional aging. 40 p. 1978.
12 VIITASALO, JUKKA, Neuromuscular performance in voluntary and reflex contraction with special reference to muscle structure and fatigue. 59 p. 1980.
13 LUHTANEN, PEKKA, On the mechanics of human movement with special reference to walking, running and jumping. 58 p. 1980.
14 LAAKSO, LAURI, Lapsuuden ja nuoruuden kasvuympäristö aikuisiän liikuntaharrastusten selittäjänä: retrospektiivinen tutkimus. - Socialization environment in childhood and youth as determinant of adult-age sport involvement: a retrospective study. 295 p. 1981.
15 BOSCO, CARMELO, Stretch-schortening cycle inskeletal muscle function with special reference to elastic energy and potentiation of myoelectrical activity. 64 p. 1982.
16 OLIN, KALEVI, Päätöksentekijöiden viiteryhmät kaupunkien liikuntapolitiikassa. - Reference groups of decision-makers in the sport politics of cities. 155 p. 1982.
17 KANNAS, LASSE, Tupakointia koskeva terveyskasvatus peruskoulussa. - Health education on smoking in the Finnish comprehensive school. 251 p. 1983.
18 Contribution of sociology to the study of sport. Festschrift Book in Honour of Professor Kalevi Heinilä. Ed. by OLIN, K. 243 p. 1984.
19 ALÉN, MARKKU, Effects of self-administered, high-dose testosterone and anabolic steroids on serum hormones, lipids, enzymes and on spermatogenesis in power athletes. 75 p. 1985.
20 HÄKKINEN, KEIJO, Training and detraining adaptations in electromyographic, muscle fibre and force production characteristics of human leg extensor muscles with special reference to prolonged heavy resistance and explosive type strength training. 106 p. 1986.
21 LAHTINEN, ULLA, Begåvningshandikappad ungdom i utveckling. En uppföljningstudie av funktionsförmåga och fysisk aktivitet hos begåvningshandikappade ungdomar i olika livsmiljöer. 300 p. 1986.
22 SILVENNOINEN, MARTTI, Koululainen liikunnanharrastajana: liikuntaharrastusten ja liikuntamotiivien sekä näiden yhteyksien muuttuminen iän mukana peruskoululaisilla ja lukiolaisilla. - Schoolchildren and physically active interests: The changes in interests in and motives for physical exercise related to age in Finnish comprehensive and upper secondary schools. 226 p. 1987.
23 POHJOLAINEN, PERTTI, Toimintakykyisyys, terveydentila ja elämäntyyli 71-75-vuotiailla miehillä. - Functional capacity, health status and life-style among 71-75 year-old men. 249 p. Summary 13 p. 1987.
24 MERO, ANTTI, Electromyographic acticity, force and anaerobic energy production in sprint running; with special reference to different constant speeds ranging from submaximal to supramaximal. 112 p. Tiivistelmä 5 p. 1987.
25 PARKATTI, TERTTU, Self-rated and clinically measured functional capacity among women and men in two age groups in metal industry. 131 p. Tiivistelmä 2 p. 1990.
26 HOLOPAINEN, SINIKKA, Koululaisten liikuntataidot. - The motor skills of schoolboys and girls. 217 p. Summary 6 p. 1990.
27 NUMMINEN, PIRKKO, The role of imagery in physical education. 131 p. Tiivistelmä 10 p. 1991.
28 TALVITIE, ULLA, Aktiivisuuden ja omatoimivuuden kehittäminen fysioterapian tavoitteena. Kehittävän työntutkimuksen sovellus lääkintävoimistelijan työhön. - The development of activity and self-motivation as the aim of physiotherapy. The application of developmental work research in physiotherapy. 212 p. Summary 8 p. 1991.
29 KAHILA, SINIKKA, Opetusmenetelmän merkitys prososiaalisessa oppimisessa - auttamis-

käyttäytymisen edistäminen yhteistyöskentelyn avulla koululiikunnassa. - The role of teaching method in prosocial learning - developing helping behavior by means of the cooperative teaching method in physical education. 132 p. Summary 2 p. 1993.

30 LIIMATAINEN-LAMBERG, ANNA-ESTER, Changes in student smoking habits at the vocational institutions and senior secondary schools and health education. 195 p. Yhteenveto 5 p. 1993.

31 KESKINEN, KARI LASSE, Stroking characteristics of front crawl swimming. 77 p. Yhteenveto 2 p. 1993.

32 RANTANEN, TAINA, Maximal isometric strength in older adults. Cross-national comparisons, background factors and association with Mobility. 87 p. Yhteenveto 4 p. 1994.

33 LUSA, SIRPA, Job demands and assessment of the physical work capacity of fire fighters. 91 p. Yhteenveto 4 p. 1994.

34 CHENG, SULIN, Bone mineral density and quality in older people. A study in relation to exercise and fracture occurrence, and the assessment of mechanical properties. 81 p. Tiivistelmä 1 p. 1994.

35 KOSKI, PASI, Liikuntaseura toimintaympäristössään. - Sports club in its organizational environment. 220 p. Summary 6 p. 1994.

36 JUPPI, JOEL, Suomen julkinen liikuntapolitiikka valtionhallinnon näkökulmasta vuosina 1917-1994. - Public sport policy in Finland from the viewpoint of state administration in 1917-1994. 358 p. Summary 7 p. 1995.

37 KYRÖLÄINEN, HEIKKI, Neuromuscular performance among power- and endurance-trained athletes. 82 p. Tiivistelmä 3 p. 1995.

38 NYANDINDI, URSULINE S., Evaluation of a school oral health education programme in Tanzania: An ecological perspective. 88 p. Tiivistelmä 2 p. 1995.

39 HEIKINARO-JOHANSSON, PILVIKKI, Including students with special needs in physical education. 81 p. Yhteenveto 4 p. 1995.

40 SARLIN, EEVA-LIISA, Minäkokemuksen merkitys liikuntamotivaatiotekijänä. - The significance of self perception in the motivational orientation of physical education. 157 p. Summary 4 p. 1995.

41 LINTUNEN, TARU, Self-perceptions, fitness, and exercise in early adolescence: a four-year follow-up study. 87 p. Yhteenveto 5 p.1995.

42 SIPILÄ, SARIANNA, Physical training and skeletal muscle in elderly women. A study of muscle mass, composition, fiber characteristics and isometric strength. 62 p. Tiivistelmä 3 p. 1996.

43 ILMANEN, KALERVO, Kunnat liikkeellä. Kunnallinen liikuntahallinto suomalaisen yhteiskunnan muutoksessa 1919-1994. - Municipalities in motion. Municipal sport administration in the changing Finnish society 1919-1994. 285 p. Summary 3 p. 1996.

44 NUMMELA, ARI, A new laboratory test method for estimating anaerobic performance characteristics with special reference to sprint running. 80 p. Yhteenveto 4 p. 1996.

45 VARSTALA, VÄINÖ, Opettajan toiminta ja oppilaiden liikunta-aktiivisuus koulun liikuntatunnilla. - Teacher behaviour and students' motor engagement time in school physical education classes. 138 p. Summary 4 p. 1996.

46 POSKIPARTA, MARITA, Terveysneuvonta, oppimaan oppimista. Videotallenteet hoitajien terveysneuvonnan ilmentäjinä ja vuorovaikutustaitojen kehittämismenetelmänä. - Health counselling, learning to learn. Videotapes expressing and developing nurses´ communication skills. 159 p. Summary 6 p. 1997.

47 SIMONEN, RIITTA, Determinants of adult psychomotor speed. A study of monozygotic twins. - Psykomotorisen nopeuden determinantit identtisillä kaksosilla. 49 p. Yhteenveto 2 p. 1997.

48 NEVALA-PURANEN, NINA, Physical work and ergonomics in dairy farming. Effects of occupationally oriented medical rehabilitaton and environmental measures. 80 p. (132 p.) 1997.

49 HEINONEN, ARI, Exercise as an Osteogenic Stimulus. 69 p. (160 p.) Tiivistelmä 1 p. 1997.

50 VUOLLE, PAULI (Ed.) Sport in social context by Kalevi Heinilä. Commemorative book in Honour of Professor Kalevi Heinilä. 200 p. 1997.

51 TUOMI, JOUNI, Suomalainen hoitotiede-keskustelu. - The genesis of nursing and caring science in Finland. 218 p. Summary 7 p. 1997.

52 TOLVANEN, KAIJA, Terveyttä edistävän organisaation kehittäminen oppivaksi organisaatioksi. Kehitysnäytökset ja kehittämistehtävät terveyskeskuksen muutoksen virittäjänä. - Application of a learning organisation model to improve services in a community health centre. Development examples and development tasks are the key to converting a health care. 197 p. Summary 3 p. 1998.

53 OKSA, JUHA, Cooling and neuromuscular performance in man. 61 p. (121 p.) Yhteenveto 2 p. 1998.

54 GIBBONS, LAURA, Back function testing and paraspinal muscle magnetic resonance image parameters: their associations and determinants. A study on male, monozygotic twins. 67 p (128 p.) Yhteenveto 1p. 1998.

55 NIEMINEN, PIPSA, Four dances subcultures. A study of non-professional dancers´ socialization, participation motives, attitudes and stereotypes. - Neljä tanssin alakulttuuria. Tutkimus tanssinharrastajien tanssiin sosiaalistumisesta, osallistumismotiiveista, asenteista ja stereotypioista. 165 p. Yhteenveto 4 p. 1998.

56 LAUKKANEN, PIA, Iäkkäiden henkilöiden selviytyminen päivittäisistä toiminnoista. - Carrying

100 Ranta, Sari, Vanhenemismuutosten eteneminen. 75-vuotiaiden henkilöiden antropometristen ominaisuuksien, fyysisen toimintakyvyn ja kognitiivisen kyvykkyyden muutokset viiden ja kymmenen vuoden seuranta-aikana. - The progress of aging processes. A 5- and 10-year follow-up study of the changes in anthropometrical characteristics and physical and cognitive capacities among 75-year-old persons. 186 p. Summary 2 p. 2004.

101 Sihvonen, Sanna, Postural balance and aging. Cross-sectional comparative studies and a balance training intervention. - Ikääntyminen ja tasapaino. Eri ikäisten tasapaino ja tasapainoharjoittelun vaikuttavuus ikääntyneillä palvelukodissa asuvilla naisilla. 65 p. (106 p.) Yhteenveto 2 p. 2004.

102 Rissanen, Aaro, Back muscles and intensive rehabilitation of patients with chronic low back pain. Effects on back muscle structure and function and patient disability. - Selkälihakset ja pitkäaikaista selkäkipua sairastavien potilaiden intensiivinen kuntoutus. Vaikutukset selkälihasten rakenteeseen ja toimintaan sekä potilaiden vajaakuntoisuuteen. 90 p. (124 p.) Yhteenveto 2 p. 2004.

103 Kallinen, Mauri, Cardiovascular benefits and potential hazards of physical exercise in elderly people. - Liikunnan hyödylliset ja mahdolliset haitalliset vaikutukset ikääntyneiden verenkiertoelimistöön. 97 p. (135 p). Yhteenveto 2 p. 2004.

104 Sääkslahti, Arja, Liikuntaintervention vaikutus 3–7-vuotiaiden lasten fyysiseen aktiivisuuteen ja motorisiin taitoihin sekä fyysisen aktiivisuuden yhteys sydän- ja verisuonitautien riskitekijöihin. - Effects of physical activity Intervention on physical activity and motor skills and relationships between physical activity and coronary heart disease risk factors in 3–7-year-old children. 153 p. Summary 3 p. 2005.

105 Hämäläinen, Piia, Oral health status as a predictor of changes in general health among elderly people. 76 p. (120 p.) Summary 2 p. 2005.

106 Liinamo, Arja, Suomalaisnuorten seksuaalikasvatus ja seksuaaliterveystiedot oppilaan ja koulun näkökulmasta. Arviointia terveyden edistämisen viitekehyksessä. - Sexual education and sexual health knowledge among Finnish adolescents at pupil and school level. Evaluation from the point of view of health promotion. 111 p. (176 p.) Summary 5 p. 2005.

107 Ishikawa, Masaki, *In vivo* muscle mechanics during human locomotion. Fascicle-tendinous tissue interaction during stretch-shortening cycle exercises. - Venytysrefleksin muutokset liikkeessä ja väsymyksessä. 89 p. (228 p.) Yhteenveto 1 p. 2005.

108 Kärki, Anne, Physiotherapy for the functioning of breast cancer patients. Studies of the effectiveness of physiotherapy methods and exercise, of the content and timing of post-operative education and of the experienced functioning and disability . - Rintasyöpäleikattujen toimintakyky ja siihen vaikuttaminen fysioterapiassa ja harjoittelussa. 70 p. (138 p.) Yhteenveto 3 p. 2005.

109 Rajaniemi, Vesa, Liikuntapaikkarakentaminen ja maankäytön suunnittelu. Tutkimus eri väestöryhmät tasapuolisesti huomioon ottavasta liikuntapaikkasuunnittelusta ja sen kytkemisestä maankäyttö- ja rakennuslain mukaiseen kaavoitukseen. - Sports area construction and land use planning – Study of sports area planning that considers all the population groups even-handedly and integrates sports area planning with land use planning under the land use and building act. 171 p. Summary 6 p. 2005.

110 Wang, Qingju, Bone growth in pubertal girls. Cross-sectional and lingitudinal investigation of the association of sex hormones, physical activity, body composition and muscle strength with bone mass and geometry. 75 p. (117 p.) Tiivistelmä 1 p. 2005.

111 Ropponen, Annina, The role of heredity, other constitutional structural and behavioral factors in back function tests.- Perimä, muut synnynnäiset rakenteelliset tekijät ja käyttäytymistekijät selän toimintakyky-testeissä. 78 P. (125 p.) Tiivistelmä 1 p. 2006.

112 Arkela-kautiainen, marja, Functioning and quality of life as perspectives of health in patients with juvenile idiopathic arthritis in early adulthood. Measurement and long-term outcome. - Toimintakyky ja elämänlaatu terveyden näkökulmina lastenreumaa sairastaneilla nuorilla aikuisilla. Mittaaminen ja pitkäaikaistulokset. 95 p. (134 p.) Tiivistelmä 2 p. 2006.

113 Rautio, Nina, Seuruu- ja vertailututkimus sosioekonomisen aseman yhteydestä toimintakykyyn iäkkäillä henkilöillä. - A follow-up and cross-country comparison study on socio-economic position and its relationship to functional capacity in elderly people. 114 p. (187 p.) Summary 3 p. 2006.

114 Tiikkainen, Pirjo, Vanhuusiän yksinäisyys. Seuruutukimus emotionaalista ja sosiaalista yksinäisyyttä määrittävistä tekijöistä. - Loneliness in old age – a follow-up study of determinants of emotional and social loneliness. 76 p. (128 p.) Summary 2 p. 2006.

115 Ahtiainen, Juha, Neuromuscular, hormonal and molecular responses to heavy resistance training in strength trained men; with special reference to various resistance exercise protocols, serum hormones and gene expression of androgen receptor and insulin-like growth factor-I. - Neuromuskulaariset,

hormonaaliset ja molekulaariset vasteet voimaharjoittelussa voimaurheilijoilla. 119 p. (204 p.) Yhteenveto 2 p. 2006.

116 Pajala, Satu, Postural balance and susceptibility to falls in older women. Genetic and environmental influences in single and dual task situations. - Iäkkäiden naisten tasapainokyky yksinkertaisissa sekä huomion jakamista vaativissa tilanteissa ja kaatumisriskiperimän merkitys yksilöiden välisten erojen selittäjinä. 78 p. (120 p.) Yhteenveto 3 p. 2006.

117 Tiainen, Kristina, Genetics of skeletal muscle characteristics and maximal walking speed among older female twins. - Lihasvoiman ja kävelynopeuden periytyvyys iäkkäillä naiskaksosilla. 77 p. (123 p.) Yhteenveto 2 p. 2006.

118 Sjögren, Tuulikki, Effectiveness of a workplace physical exercise intervention on the functioning, work ability, and subjective well-being of office workers – a cluster randomised controlled cross-over trial with one-year follow-up. - Työpaikalla tapahtuvan fyysisen harjoitteluintervention vaikuttavuus toimistotyöntekijöiden toimintakykyyn, työkykyyn ja yleiseen subjektiiviseen elämänlaatuun – ryhmätasolla satunnaistettu vaihtovuorokoe ja vuoden seuranta. 100 p. (139 p.) Tiivistelmä 3 p. 2006.

119 Lyyra, Tiina-Mari, Predictors of mortality in old age. Contribution of self-rated health, physical functions, life satisfaction and social support on survival among older people. - Kuolleisuuden ennustetekijät iäkkäässä väestössä. Itsearvioidun terveyden, fyysisten toimintojen, elämään tyytyväisyyden ja sosiaalisen tuen yhteys iäkkäiden ihmisten eloonjäämiseen. 72 p. (106 p.) Tiivistelmä 2 p. 2006.

120 Soini, Markus, Motivaatioilmaston yhteys yhdeksäsluokkalaisten fyysiseen aktiivisuuteen ja viihtymiseen koulun liikuntatunneilla. - The relationship of motivational climate to physical activity intensity and enjoyment within ninth grade pupils in school physical education lessons. 91 p. 2006.

121 Vuorimaa, Timo, Neuromuscular, hormonal and oxidative stress responses to endurance running exercises in well trained runners. - Neuromuskulaariset, hormonaaliset ja hapettumisstressiin liittyvät vasteet kestävyysjuoksuharjoituksiin hyvin harjoitelleilla juoksijoilla. 93 p. (152 p.) Yhteenveto 3 p. 2007.

122 Mononen, Kaisu, The effects of augmented feedback on motor skill learning in shooting. A feedback training intervention among inexperienced rifle shooters. - Ulkoisen palautteen vaikutus motoriseen oppimiseen ammunnassa: Harjoittelututkimus kokemattomilla kivääriampujilla. 63 p. Yhteenveto 4 p. 2007.

123 Sallinen, Janne, Dietary Intake and Strength Training Adaptation in 50–70 -year old Men and Women. With special reference to muscle mass, strength, serum anabolic hormone concentrations, blood pressure, blood lipids and lipoproteins and glycemic control. - Ravinnon merkitys voimaharjoittelussa 50–70 -vuotiailla miehillä ja naisilla 103 p. (204 p.) Yhteenveto 3 p. 2007.

124 Kasila Kirsti, Schoolchildren's oral health counselling within the organisational context of public oral health care. Applying and developing theoretical and empirical perspectives. 96 p. (139 p.) Tiivistelmä 3 p. 2007.

125 Pyöriä, Outi, Reliable clinical assessment of stroke patients' postural control and development of physiotherapy in stroke rehabilitation. - Aivoverenkiertohäiriöpotilaiden toimintakyvyn luotettava kliininen mittaaminen ja fysioterapian kehittäminen Itä-Savon sairaanhoitopiirin alueella. 94 p. (143 p.) Yhteenveto 6 p. 2007.

126 Valkeinen, Heli, Physical fitness, pain and fatigue in postmenopausal women with fibromyalgia. Effects of strength training. - Fyysinen kunto, kipu- ja väsymysoireet ja säännöllisen voimaharjoittelun vaikutukset menopaussi-iän ohittaneilla fibromyalgiaa sairastavilla naisilla. 101 p. (132 p.) Yhteenveto 2 p. 2007.

127 Hämäläinen, Kirsi, Urheilija ja valmentaja urheilun maailmassa. Eetokset, ihanteet ja kasvatus urheilijoiden tarinoissa. - An athlete and a coach in the world of sports. Ethos, ideals and education in athletes' narratives. 176 p. Tiivistelmä 2 p. 2008.

128 Aittasalo, Minna, Promoting physical activity of working aged adults with selected personal approaches in primary health care. Feasibility, effectiveness and an example of nationwide dissemination. - Työikäisten liikunnan edistäminen avoterveydenhuollossa – työtapojen toteuttamiskelpoisuus ja vaikuttavuus sekä esimerkki yhden työtavan levittämisestä käytäntöön. 105 p. (161 p.) Yhteenveto 3 p. 2008.

129 Portegijs, Erja, Asymmetrical lower-limb muscle strength deficit in older people. - Alaraajojen lihasvoiman puoliero iäkkäillä ihmisillä. 105 p. (155 p.) Yhteenveto 3 p. 2008.

130 Laitinen-Väänänen, Sirpa, The construction of supervision and physiotherapy expertise: A qualitative study of physiotherapy students' learning sessions in clinical education. - Opiskelijan ohjauksen ja fysioterapian asiantuntijuuden rakentuminen: Laadullinen tutkimus fysioterapiaopiskelijan oppimistilanteista työharjoittelussa. 69 p. (118 p.) Yhteenveto 3 p. 2008.

131 Iivonen, Susanna, Early Steps -liikunta-ohjelman yhteydet 4–5-vuotiaiden päiväkotilasten motoristen perustaitojen kehitykseen. - The associations between an Early Steps physical education curriculum and the fundamental motor skills development of 4–5-year-old preschool children. 157 p. Summary 4 p. 2008.

132 Ortega-Alonso, Alfredo, Genetic effects on mobility, obesity and their association in older female twins. 87 p. 2009.

133 Hulmi, Juha, Molecular and hormonal responses and adaptation to resistance exercise and protein nutrition in young and older men. - Voimaharjoittelun fysiologiset ja molekyylibiologiset vaikutukset lihaskasvunsäätelyssä lisäproteiinia nautittaessa tai ilman. 109 p. (214 p.) Yhteenveto 2 p. 2009.

134 Martinmäki, Kaisu, Transient changes in heart rate variability in response to orthostatic task, endurance exercise and training. With special reference to autonomic blockades and time-frequency analysis. - Sykevaihtelun muutokset ortostaattisessa testissä, kestävyysliikunnassa ja kestävyysharjoittelussa käyttäen hyväksi autonomisen säätelyn salpauskokeita ja aika-taajuusanalyysiä . 99 p. (151 p.) Yhteenveto 2 p. 2009.

135 Sedliak, Milan, Neuromuscular and hormonal adaptations to resistance training. Special effects of time of day of training. 84 p. (175 p.) 2009.

136 Nikander, Riku, Exercise loading and bone structure. 97 p. (141 p.) Yhteenveto 1 p. 2009.

137 Korhonen, Marko T., Effects of aging and training on sprint performance, muscle structure and contractile function in athletes. - Ikääntymisen ja harjoittelun vaikutukset nopeussuorituskykyyn, lihasten rakenteeseen ja voimantuotto-ominaisuuksiin urheilijoilla. 123 p. (211 p.) Tiivistelmä 5 p. 2009.

138 Javanainen-Levonen, Tarja, Terveydenhoitajat liikunnanedistäjinä lastenneuvolatyössä. - Public Health Nurses as Physical Activity Promoters in Finnish Child Health Clinics. 104 p. (148 p.) Summary 6 p. 2009.

139 Klemola, Ulla, Opettajaksi opiskelevien vuorovaikutustaitojen kehittäminen liikunnan aineenopettajakoulutuksessa.- Developing student teachers´ social interaction skills in physical education teacher education. 92 p. (138 p.) Summary 4 p. 2009.

140 Niemi, Reetta, Onks tavallinen koe vai sellanen, missä pitää miettii? Ympäristölähtöisen terveyskasvatuspedagogiikan kehittäminen narratiivisena toimintatutkimuksena. - Is this a normal test or do we have to think? Developing environmentally oriented health education pedagogy through narrative action research . 215 p. 2009.

141 von Bonsdorff, Mikaela, Physical activity as a predictor of disability and social and health service use in older people. - Fyysinen aktiivisuus toiminnanvajauden ja sosiaali- ja terveyspalvelujen käytön ennustajana iäkkäillä henkilöillä 101 p. (134 p.) Yhteenveto 2 p. 2009.

142 Palomäki, Sanna, Opettajaksi opiskelevien pedagoginen ajattelu ja ammatillinen kehittyminen liikunnanopettajakoulutuksessa. - Pre-service teachers' pedagogical thinking and professional development in physical education teacher education. 118 p. (163 p.) Summary 3 p. 2009.

143 Vehmas, Hanna, Liikuntamatkalla Suomessa. Vapaa-ajan valintoja jälkimodernissa yhteiskunnassa. - Sport tourism in Finland – leisure choices in the post-modern society. 205 p. Summary 10 p. 2010.

144 Kokko, Sami, Health promoting sports club. Youth sports clubs' health promotion profiles, guidance, and associated coaching practice, in Finland. 147 p. (230 p.) Yhteenveto 5 p. 2010.

145 Kääriä, Sanna, Low back disorders in the long term among employees in the engineering industry. A study with 5-, 10- and 28-year follow-ups. - Metalliteollisuuden työntekijöiden alaselän sairaudet ikääntyessä: METELI–tutkimuksen 5–, 10– ja 28–vuotisseurantatutkimus. 76 p. (102 p.) Yhteenveto 2 p. 2010.

146 Santtila, Matti, Effects of added endurance or strength training on cardiovascular and neuromuscular performance of conscripts during the 8-week basic training period. - Lisätyn voima- ja kestävyysharjoittelun vaikutukset varusmiesten hengitys- ja verenkiertoelimistön sekä hermo-lihas järjestelmän suorituskykyyn kahdeksan viikon peruskoulutuskauden aikana. 85 p. (129 p.) Yhteenveto 2 p. 2010.

147 Mänty, Minna, Early signs of mobility decline and physical activity counseling as a preventive intervention in older people. - Liikkumiskyvyn heikkenemistä ennakoivat merkit ja liikuntaneuvonta liikkumisvaikeuksien ehkäisyssä iäkkäillä henkilöillä. 103 p. (149 p.) Yhteenveto 2 p. 2010.

148 Rantalainen, Timo, Neuromuscular function and bone geometry and strength in aging. - Neuromuskulaarinen suorituskyky luun geometrian ja voiman selittäjänä ikääntymisen yhteydessä. 87 p. (120 p.) Yhteenveto 1 p. 2010.

149 Kuitunen, Sami, Muscle and joint stiffness regulation during normal and fatiguing stretch-shortening cycle exercise . - Lihas- ja niveljäykkyyden säätely normaalin sekä väsyttävän venymis-lyhenemissykli – tyyppisen harjoituksen aikana . 76 p. (142 p.) Yhteenveto 1 p. 2010.

150 Piitulainen, Harri, Functional adaptation of sarcolemma to physical stress. - Lihassolukalvon toiminnallinen mukautu minen fyysiseen kuormitukseen. 103 p. (178 p.) Yhteenveto 2 p. 2010.

151 Viljanen, Anne, Genetic and environmental effects on hearing acuity and the association between hearing acuity, mobility and falls in older women. - Kuulon tarkkuuden periy-tyvyys ja yhteys liikkumiskykyyn sekä kaatumisiin iäkkäillä naisilla. 85 p. (116 p.) Yhteenveto 2 p. 2010.

152 Kulmala, Jenni, Visual acuity in relation to functional performance, falls and mortality in old age. - Heikentyneen näöntarkkuuden vaikutus toimintakykyyn, kaatumisiin ja kuolleisuuteen iäkkäillä henkilöillä. 98 p. (140 p.) Yhteenveto 3 p. 2010.

153 Nivala, Sirkka, Kokemuksellinen vanheneminen sotainvalideilla. Suomalaisten sotainvalidien kokemus elämänkulustaan ja ikääntymisestään. - Disabled war veterans and experiential ageing. Finnish disabled war veterans and their experience of the course of their lives and growing older. 178 p. Summary 4 p. 2010.

154 Rinne, Marjo, Effects of physical activity, specific exercise and traumatic brain injury on motor abilities. Theoretical and pragmatic assessment. 86 p. (134 p.) Tiivistelmä 2 p. 2010.

155 Mikkola, Tuija, Genetic and environmental contributions to bone structural strength in postmenopausal women. - Perimän ja ympäristötekijöiden vaikutus luun lujuuteen vaihdevuosi-iän ohittaneilla naisilla. 77 p. (130 p.) Yhteenveto 2 p. 2010.

156 Salo, Petri, Assessing physical capacity, disability, and health-related quality of life in neck pain. 93 p. (132 p.) Yhteenveto 2 p. 2010.

157 Ronkainen, Paula, Towards powerful old age. Association between hormone replacement therapy and skeletal muscle. - Vaihdevuosioireisiin käytettävän HRT:n yhteys luurankolihaksiston rakenteeseen ja toimintaan. 118 p. (170 p.) Yhteenveto 2 p. 2010.

158 Kilpikoski, Sinikka, The McKenzie method in assessing, classifying and treating non-specific low back pain in adults with special reference to the centralization phenomenon. - McKenzien mekaaninen diagnostisointi- ja terapiamenetelmä tutkittaessa, luokitel-taessa ja hoidettaessa aikuisten epäspesifiä alaselkäkipua. 90 p. (130 p.) Yhteenveto 2 p. 2010.

159 Mutikainen, Sara, Genetic and environmental effects on resting electrocardiography and the association between electrocardiography and physical activity, walking endurance and mortality in older people. - Lepo-EKG –muuttujien periy-tyvyys sekä yhteydet fyysiseen aktiivisuuteen, kävelykestävyyteen ja kuolleisuuteen iäkkäillä henkilöillä. 84 p. (131 p.) Yhteenveto 3 p. 2010.

160 Völgyi, Eszter, Bone, fat and muscle gain in pubertal girls. Effects of physical activity. 76 p. (138 p.) Tiivistelmä 1 p. 2010.

161 Sillanpää, Elina, Adaptations in body composition, metabolic health and physical fitness during strength or endurance training or their combination in healthy middle-aged and older adults. 113 p. (179 p.) Yhteenveto 3 p. 2011.

162 Karavirta, Laura, Cardiorespiratory, neuromuscular and cardiac autonomic adaptations to combined endurance and strength training in ageing men and women. - Yhdistetyn kestävyys- ja voima-harjoittelun vaikutukset hengitys- ja veren-kiertoelimistön sekä hermo-lihasjärjestel-män toimintaan ja sydämen autonomiseen säätelyyn ikääntyvillä miehillä ja naisilla. 108 p. (178 p.) Yhteenveto 2 p. 2011.

163 Hynynen, Esa, Heart rate variability in chronic and acute stress with special reference to nocturnal sleep and acute challenges after awakening. - Sykevariaatio-mittaukset kroonisen ja akuutin stressin seurannassa käyttäen hyväksi yöunen ja akuuttien tehtävien aikaisia vasteita. 74 p. (109 p.) Yhteenveto 3 p. 2011.

164 Pavelka, Béla, Open Water as a Sportscape. Analysis of canoeing in Finland for developing sport infrastructure and services. 116 p. 2011.

165 Pesonen, Jyri, Opettajat oppijoina. Toiminta tutkimus liikunnanopettajien pätevöittämis-koulutuksen käynnistämisestä ja kehittämisesestä. - Teachers as learners – An action research on starting the development of qualifying training for teachers of physical education. 204 p. Summary 4 p. 2011.

166 Borremans, Erwin, Asperger syndrome and physical exercise. A study about senso-motor profiles, physical fitness, and the effectiveness of an exercise training program in a group of adolescents with Asperger syndrome. 111 p. (181 p.). Yhteenveto 3 p. 2011.