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Physical Inactivity from Youth to Adulthood and Adult Cardiometabolic Risk Profile

Petri Kallio, MD[1,2,3,4,*] petri.kallio@utu.fi, Katja Pahkala, Prof[1,2,4], Olli J. Heinonen, Prof, MD[1], Tuija H. Tammelin, PhD[5], Kristiina Pälve, PhD, MD[2,4,9], Mirja Hirvensalo, Prof[6], Markus Juonala,Prof, MD[7], Britt-Marie Loo, PhD[8], Costan G. Magnussen, PhD[2,4,10], Suvi Rovio, PhD[2,4], Harri Helajärvi, PhD, MD[1], Tomi P. Laitinen, Prof; MD[11], Eero Jokinen, Prof, MD[12], Päivi Tossavainen, PhD, MD[13], Nina Hutri-Kähönen, PhD, MD[14], Jorma Viikari, Prof, MD[7], and Olli T. Raitakari, Prof, MD[2,3,4]

[1]Paavo Nurmi Centre & Unit for Health and Physical Activity, University of Turku, Turku, Finland;

[2]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku;

[3]Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, Finland;

[4]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland;

[5]LIKES Research Centre for Physical Activity and Health, Jyväskylä, Finland;

[6]Faculty of sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland;

[7]Department of Medicine, University of Turku and Division of Medicine, Turku University Hospital, Turku, Finland;

[8]Joint Clinical Biochemistry Laboratory of University of Turku and Turku University Hospital, Turku, Finland;

[9]Heart Center, Turku University Hospital, Turku, Finland;

[10]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia;

[11]Department of Clinical Physiology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland;

[12]Department of Pediatric Cardiology, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland;

[13]Department of Pediatrics, PEDEGO Research Unit, Oulu University and University Hospital of Oulu, Oulu, Finland and

[14]Department of Pediatrics, Tampere University and Tampere University Hospital, Tampere, Finland

[*]Corresponding author at: Paavo Nurmi Centre & Unit for Health and Physical Activity, University of Turku, Turku, Finland Kiinamyllynkatu 10, 20520 Turku, Finland

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ABSTRACT

Adults with a low physical activity (PA) level are at increased risk for cardiometabolic diseases, but little is known on the association between physical inactivity since youth and cardiometabolic health in adulthood. We investigated the association of persistent physical inactivity from youth to adulthood with adult cardiometabolic risk factors. Data were drawn

from the ongoing Cardiovascular Risk in Young Finns Study with seven follow-ups between 1980-2011 (baseline age 3-18 years, n=1961). Physical activity data from a standardized questionnaire was expressed as a PA-index. Using the PA-index, four groups were formed: 1)persistently physically inactive (n=246), 2)decreasingly active (n=305), 3)increasingly active (n=328), and 4)persistently active individuals (n=1082). Adulthood cardiometabolic risk indicators included waist circumference, body mass index (BMI), blood pressure, and fasting lipids, insulin, and glucose. Clustered cardiometabolic risk was defined using established criteria for metabolic syndrome. Persistently physically inactive group was used as a reference. Compared to the persistently physically inactive group, those who were persistently active had lower risk for adult clustered cardiometabolic risk (RR=0.67;CI95%=0.53-0.84; Harmonized criteria), obesity (BMI>30 kg/m^2, RR=0.76;CI95%=0.59-0.98), high waist circumference (RR=0.82;CI95%=0.69-0.98), and high triglyceride (RR=0.60;CI95%=0.47-0.75), insulin (RR=0.58;CI95%=0.46-0.74) and glucose (RR=0.77;CI95%=0.62-0.96) concentrations as well as low high-density lipoprotein cholesterol (HDL-C) concentration (RR=0.78;CI95%=0.66-0.93). Comparable results were found when persistently physically inactive individuals were compared with those who increased PA. The results remained essentially similar after adjustment for education, diet, smoking, and BMI. Persistently physically inactive lifestyle since youth is associated with an unfavorable cardiometabolic risk profile in adulthood. Importantly, even minor increase in PA lowers the cardiometabolic risk.

Keywords: CARDIOVASCULAR, CVD, CHILDHOOD, INACTIVE LIFESTYLE, LONGITUDINAL

INTRODUCTION

According to the World Health Organization, cardiovascular diseases (CVDs) are the number one cause of death globally, representing 31% of all deaths[1]. Physical inactivity is an important modifiable risk factor for CVDs, and it is one of the leading risk factors for death worldwide with estimates suggesting physical inactivity to be as harmful as obesity and tobacco smoking[2]. Overall, it has been estimated that physical inactivity causes 5.2 million deaths, and 6-10% of major non-communicable diseases annually worldwide[2]. In the United States, an estimated $117 billion in annual health care costs, and about 10% of premature mortality are associated with inadequate physical activity[3]. Despite the increased knowledge of the benefits of PA on health, physically inactive lifestyle is common globally – it has been suggested that 31% of the world´s population is not meeting the minimum recommendations for PA[4].

A cardiometabolic risk profile is a constellation of metabolically interrelated risk factors; abdominal obesity, hypertension, dyslipidemia, hyperglycemia and hyperinsulinemia. Notably, adults with clustered cardiometabolic risk factors are at increased risk for type 2 diabetes and CVDs[5]. We have previously found in a cross-sectional setting that leisure-time PA already in childhood is beneficially associated with HDL-C and the ratio of HDL-C to total cholesterol, and reduced clustering of risk factors[6]. In line, cross-sectional and prospective data from childhood support that leisure-time PA is associated with various cardiometabolic risk factors, e.g. BMI, HDL-C and systolic blood pressure[7]. A prior report from the here applied longitudinal Cardiovascular Risk in Young Finns Study (YFS) group has shown that persistent PA is associated with lower prevalence of metabolic syndrome (MetS) in adults during a 9-year follow-up[8]. However, a need for further knowledge remains

regarding the longitudinal associations of PA, particularly from the perspective of persistent physical inactivity since youth, and adult cardiometabolic health. Moreover, it is not known how increase in PA from youth to adulthood is associated with the cardiometabolic risk profile as an adult. In line, the American Heart Association emphasizes that among children and adolescents the role of PA in the development of adult cardiometabolic risk and disease requires more research[9]. Therefore, using the unique 31-year longitudinal data derived from the YFS, the aim of this study was to investigate how persistent physical inactivity beginning in youth is associated with cardiometabolic risk profile in adulthood.

METHODS

Study design and individuals

The applied data were drawn from the ongoing longitudinal YFS, which first cross-sectional survey was conducted in 1980 when 3,596 children and adolescents aged 3, 6, 9, 12, 15, and 18 years participated in the baseline study. Since then the cohort has been followed-up for 31 years in 3-9 year intervals. Altogether 2115 individuals (aged 34-49 years) participated in the most recent follow-up study in 2011. At all follow-ups between 1980-2011, the examinations have included comprehensive data collection using questionnaires, physical measurements, and blood sampling. Detailed description of the study design has been published earlier[10]. Previously, no differences have been found in either men or women in the PA levels, total cholesterol, LDL-cholesterol (LDL-C), HDL-C, triglycerides, blood pressure, BMI or parental education years between those who were lost to follow up and those who remained in the study[10].

This study applied the longitudinal PA data collected at the YFS follow-ups from 1980 to 2011 (participants aged 9-49 years) to assess lifelong physical inactivity. Cardiometabolic risk profile in adulthood was assessed primarily by using data from the latest follow-up performed in 2011. If these data were not available, data assessed in the prior follow-up in 2007 were applied. In addition to applying the latest available data on adult cardiometabolic risk indicators (anthropometrics, systolic and diastolic blood pressure [SBP/DBP], total cholesterol, HDL-C, LDL-C, triglyceride, glucose and insulin concentrations), the latest available data on diet, smoking and socio-economic status (SES) were applied. Collectively, for these variables we thus primarily used data from the 2011 follow-up. Pregnant women were excluded. In total, 1961 individuals (1100 women, 861 men) were included in this study.

Physical activity

Leisure-time PA, expressed as a physical activity index (PA-index), was self-reported with a standardized questionnaire[11,12]. Between 1980 and 1989, the questions concerned frequency and intensity of PA, participation in sports club training, participation in sport competitions, and typical activity during leisure-time (in total 5 questions; a value ranging from 1 to 2 or 3 assigned to each response option). In 2001, 2007, and 2011 the PA questionnaire consisted of questions on frequency and intensity of PA, frequency of vigorous PA, hours spent in vigorous PA, average duration of a PA session and participation in organized PA, and the PA-index was calculated similarly as in the earlier follow-ups[12](Table S1 and S2).

Using the PA-index, four PA groups were formed to investigate the association of physical inactivity and change in PA from youth to adulthood with adult cardiometabolic risk factors. Firstly, individuals who had two or more PA index values from the follow-ups between 1980-

1989 (age 9-21 years; youth), and also from the follow-ups between 2001-2011 (age 24-50 years; adulthood) were included. Secondly, the mean of the PA-index during youth and adulthood were calculated, and based on these two values, individuals were divided into PA-index quartiles both in youth and adulthood (total n=1,961). Thirdly, four groups were formed based on the quartiles: 1) persistently physically inactive (individuals in the lowest quartile both during youth and adulthood, n=246), 2) decreasingly active (individuals in the three highest quartiles in youth, but in the lowest quartile in adulthood, n=305), 3) increasingly active (individuals in the lowest quartile in youth, but in the three highest quartiles in adulthood, n=328), and 4) persistently active (individuals in the three highest quartiles both in youth and adulthood, n=1082). The PA-index cut-off point for the lowest quartile varied between 8.0 and 8.7. To get a PA-index of 8, an individual e.g. did not participate in organized PA, but reported participating in PA once a week, for 20-40 minutes, and the activity caused moderate sweating (e.g. 30 minutes of brisk walking).

Secondarily to gain more detailed knowledge on the association of PA increase compared to being persistently physically inactive, we further split the increasingly active group into three: minor PA increasers (PA increase from the lowest quartile i.e. lowest 25th percentile in youth to 25th to 50th percentile in adulthood, n=142), moderate PA increasers (PA increase from the lowest 25th percentile in youth to 50th to 75th percentile in adulthood, n=115), major PA increasers (PA increase from the lowest 25th percentile in youth to >75th percentile in adulthood, n=71).

Clinical examination

Weight was measured in light clothing without shoes using a digital scale with an accuracy of 0.1 kg. Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm. BMI

was calculated as weight (kg)/[height (m)]^2. Obesity was defined as BMI >30 kg/m^2. Waist circumference was measured at midway between iliac crest and the lowest rib at the mid-axillary line using a non-stretchable, plastic-covered cloth measuring tape with an accuracy of 0.1 cm. Blood pressure was measured with a random zero sphygmomanometer.

Laboratory analyses

Venous blood samples were drawn after a 12 h fast[13]. Standard enzymatic methods were used for serum total cholesterol, triglycerides and glucose. HDL-C concentration was measured after dextran sulfate precipitation, and LDL-C concentration was calculated using Friedewald formula[14]. All the above assays were performed on an AU400 instrument (Olympus, Japan), and the same methods were used in 2007 and 2011. Insulin was measured by microparticle enzyme immunoassay as previously described[15].

Clustered risk and high risk cut-off points

Clustered risk in adulthood was primarily defined using the Harmonized criteria to form MetS[16]. The criteria for having MetS include: waist ≥102 cm in men and ≥88 cm in women, fasting plasma glucose ≥5.6 mmol/l (≥100 mg/dl) or diabetes treatment, serum triglycerides ≥1.7 mmol/l (≥150 mg/dl) and HDL-C levels <1.0 mmol/l (<40 mg/dl) in men and <1.3 mmol/l (<50 mg/dl) in women and blood pressure ≥130/ ≥85 mmHg or treatment for hypertension. A diagnosis requires ≥3 of the 5 components.

Secondarily for sensitivity analysis purposes we also defined MetS using the criteria set by the International Diabetes Federation (IDF)[17], National Cholesterol Education Program Adult

Treatment Panel III[18], and European Group for the Study of Insulin[19] (See these MetS criteria in supplemental material).

To define high-risk, we used the cut-off points applied in the Harmonized MetS criteria for waist circumference, plasma glucose, HDL-C, and blood pressure. For risk factors not included in the Harmonized MetS criteria, the following cut-off points for high risk were applied: BMI>30kg/m^2, total cholesterol>5.17 mmol/l (200 mg/dl), LDL-C>3.36 mmol/l (130 mg/dl), and insulin >80th percentile (in our study 13.05 mU/l).

Diet, smoking and socioeconomic status

Food consumption data were collected using a 131-item food frequency questionnaire, developed and validated by the Finnish National Institute for Health and Welfare[20]. The participants were asked to report the daily frequency and serving size of selected foods and dishes during the previous 12 months. The daily specific food or food group consumption and nutrient intake was calculated using the latest version of the National Food Composition Database Fineli[21]. A food-based diet score, originally constructed to describe diet associated with lower risk of diabetes[22], was used as an indicator of a healthy diet (range 0 to 27). Higher score indicates a healthier diet, including e.g. low intake of red and processed meats, sweets, sugared beverages and fried potatoes, and high intake of whole grains, vegetables, fruits, fish and nuts/seeds.

Data on smoking and SES were collected with self-administered questionnaires[23]. Those reporting daily smoking were considered as smokers. SES was determined based on self-reported years of education[24].

Statistical analyses

To characterize the PA groups (Table 1), mean values and standard deviations (SD) for continuous variables and percentages for categorical variables were calculated, and linear regression analysis was applied for the continuous outcome variables while Cochran-Mantel-Haenszel -method was used for the categorized variables. In the primary analyses for continuous cardiometabolic risk factors, ANCOVA (Analyses of covariance) was applied to compare the PA groups. The association (risk ratios; RR) between PA group and dichotomous cardiometabolic risk factors as well as MetS was assessed using Zou's modified Poisson approach[25]. The adult cardiometabolic risk factor, SES, dietary and smoking data were obtained primarily in 2011, or secondarily in 2007. The persistently physically inactive group was used as the reference group to which the other groups were compared. The analyses were adjusted for age and sex, and additionally for SES (years of education; continuous variable), diet, smoking, and BMI.

Statistical analyses were performed using SAS version 9.4 and statistical significance was inferred at a two-tailed p-value <0.05.

RESULTS

Comparison of background characteristics showed that adulthood SES, being a daily smoker and a score indicative of a healthy diet differed between the PA groups (Table 1).

Continuous cardiometabolic risk factors

Compared to persistently physically inactive individuals, those who were persistently active from youth to adulthood had lower waist circumference, and triglyceride, glucose and insulin concentrations as well as higher HDL-C concentration in adulthood (Table 2, model 1). Similar results were found when individuals who increased PA from youth to adulthood were

compared to those who were persistently physically inactive, with the exception of them also having lower BMI (Table 2, model 1). Persistently physically inactive individuals and those who were decreasingly active between youth and adulthood had a similar cardiometabolic risk factor profile in adulthood (Table 2, model 1).

To further study the independent association between persistent physical inactivity since youth and adulthood cardiometabolic risk factors, the analyses were additionally adjusted for adulthood education (years; indicator of SES), diet, and being a daily smoker. After these adjustments, the associations weakened and for waist circumference, the difference between persistently physically inactive and persistently active individuals was no longer statistically significant (Table 2, model 2). When also adulthood BMI as a potential mediator was included in the analyses, the individuals who increased PA or were persistently physically inactive had similar triglyceride and insulin concentrations (Table 2, model 3).

Physical activity increase from youth to adulthood – secondary analyses

To study in more detail the association of PA increase with the continuous adult cardiometabolic risk factors, we compared in secondary analyses the persistently physically inactive individuals to those who had a minor, moderate or major PA increase from youth to adulthood. The analyses revealed e.g. that also a minor increase in PA from youth to adulthood associated beneficially with part of the adulthood cardiometabolic risk factors (i.e., waist circumference, HDL-cholesterol, triglycerides) compared to being persistently physically inactive (Table S3).

High-risk cardiometabolic risk factors

When the cardiometabolic risk factors were treated as high-risk, those who were persistently or increasingly active between youth and adulthood had a lower risk for obesity (for persistently active RR=0.76;CI95%=0.59-0.98), high waist circumference (RR=0.82;CI95%=0.69-0.98), and high triglyceride (RR=0.60;CI95%=0.47-0.75) and insulin (RR=0.58;CI95%=0.46-0.74) concentrations, as well as low HDL-C concentration (RR=0.78;CI95%=0.66-0.93) in adulthood compared with persistently physically inactive individuals (Table 3, model 1). In addition, persistently active individuals had a lower risk for high glucose concentration compared to the persistently physically inactive peers (RR=0.77;CI95%=0.62-0.96) (Table 3, model 1). No difference was found when the persistently physically inactive group was compared with the decreasingly active individuals except for higher risk for high blood pressure among those who were decreasingly active from youth to adulthood (Table 3, model 1).

When the analyses were further adjusted for SES, diet, and being a daily smoker in adulthood, the persistently physically inactive group continued to have an increased risk for high triglyceride and insulin concentrations when compared to the persistently active individuals while the risk for obesity, high waist circumference, low HDL-cholesterol, and high glucose concentration became similar between the groups (Table 3, model 2). Also the increased risk for high triglycerides in the persistently inactive individuals compared to those who were increasingly active was non-significant after the adjustments. After further addition of BMI to the analyses, the persistently inactive individuals continued to have an increased risk of having high triglyceride concentration compared to the persistently active peers while the risk for high insulin concentration became similar (Table 3, model 3). The risk for low HDL-cholesterol and high insulin concentrations was also similar between the persistently and increasingly active individuals after adding BMI to the analyses.

Physical activity increase from youth to adulthood – secondary analyses

When the high-risk cardiometabolic risk factors were applied, the risk for obesity and low HDL-C concentration decreased in a step-wise manner as PA increased in comparison to individuals who were physically inactive from youth to adulthood. A minor increase in PA was associated only with lower risk for high insulin concentration in adulthood compared to being persistently physically inactive (Table S4).

Clustered cardiometabolic risk

We also compared the PA groups according to clustered risk defined by MetS (Table 4). Compared to persistently physically inactive individuals, those who were persistently active and those who were increasingly active had a lower risk for MetS in adulthood, regardless of the definition (Table 4, model 1; for Harmonized criteria, persistently active RR=0.67;CI95%=0.53-0.84). To further study the association between physical inactivity from youth to adulthood and adult MetS, the analyses were additionally adjusted for SES, diet and smoking (Table 4, model 2). After the adjustments, the results remained unchanged with the exception that the persistently inactive individuals and those who increased physical activity had a similar risk for MetS defined according to the IDF. Persistently physically inactive individuals and those who were decreasingly active between youth and adulthood had similar risk for MetS in adulthood.

Supplemental Table 5 provides data on the absolute values and prevalence of the cardiometabolic risk indicators according to PA group.

DISCUSSION

Our longitudinal data show that persistently physically inactive lifestyle since youth is associated with unfavorable cardiometabolic risk profile in adulthood. In general, individuals who were decreasingly active from youth to adulthood had a similar cardiometabolic risk profile compared to those who were persistently physically inactive, suggesting that the health benefits of youth PA are not preserved if the physically active lifestyle is not sustained into adulthood. From a clinical relevance point of view, the detrimental link between persistent physical inactivity and clustered cardiometabolic risk is particularly notable due to the related subsequent increased disease risk. These 31-year follow-up data since youth importantly add a novel insight to the previous data on role of physical inactivity on cardiometabolic risk factors and prevention of CVDs.

Data from the YFS have previously shown in a six-year follow-up that persistently inactive children and young adults have an unfavorable coronary risk factor profile compared to those persistently active[26]. We have also reported that maintaining PA from youth to adulthood may have an important role in reducing the risk of obesity in adulthood[27]. In addition to cardiometabolic risk factors, we have shown that leisure-time PA in adolescence and young adulthood is favorably associated with carotid artery elasticity later in life[28]. From the perspective of physically inactive lifestyle, we recently reported that persistent physical inactivity beginning from youth is associated with impaired glucose metabolism in adulthood[29]. The present study elaborates prior findings from the YFS by applying a follow-up of 31 years and focusing on the perspective of persistent physical inactivity, and by reporting that the detrimental association between persistent physical inactivity since early life is broader and extends to a wider cardiometabolic risk profile. In addition to the continuous and high-risk cardiometabolic risk factors, we showed the detrimental association of physical inactivity since youth and adult clustered cardiometabolic risk defined as MetS. In

line, prior data link PA level with risk of having MetS[8,30]. The results showing the wide detrimental associations of physical inactivity from youth to adulthood with cardiometabolic risk factors, and particularly their clustering, in adulthood also highlight the clinical relevance of avoiding this behavior. Collectively, these data suggest that maintaining PA from youth may benefit future cardiometabolic health.

We have previously shown that increased PA between youth and adulthood lowers the risk of adult impaired glucose metabolism,[29] and that even a moderate increase from being physically inactive is related to decreased progression of aortic intima-media thickness in adolescence[31]. In this study, the evident benefits of increasing PA are reflected on several markers of cardiometabolic health. Of individual risk factors, increase in PA was associated with e.g. 3.9 cm smaller waist circumference and 1.3 kg/m^2 lower BMI in adulthood compared to being persistently physically inactive. In line, prior study among sedentary healthy men showed that endurance training improved glucose metabolism and body composition[32]. Further, in sedentary patients with type 2 diabetes and MetS, exercise intervention was effective in improving cardiovascular risk profile[33]. A large prospective study of adults (>300.000 participants) found that increasing leisure-time PA after being inactive in adolescence reduced the risk for all-cause and cause-specific mortality[34]. Taken together, our study and the previously reported longitudinal data indicate that an increase in PA is beneficially associated with cardiometabolic risk profile.

The underlying biological mechanisms between physical inactivity and cardiometabolic risk profile remain poorly understood. However, various mechanistic pathways likely interact with each other[35]. The beneficial effects of PA on CVD risk are likely mediated by favorable effects on several risk factors, as judged by independent relations to markers of lipoprotein

metabolism, glucose metabolism, and inflammation[36]. It has also been suggested that genetic pleiotropy partly explains the observed associations between PA and morbidity[37]. A recent review suggests that a part of the protective effect of PA on CVD is due to conventional risk factors, e.g. abnormal serum cholesterol concentration, but still half of the protection afforded by PA remains unexplained[35]. Physical inactivity also engages signals for specific molecular responses contributing to poor lipid metabolism by suppression of skeletal muscle lipoprotein lipase activity[38]. Further, physical inactivity is an important contributor to insulin resistance[39] and PA increases skeletal muscle glucose uptake even independently of insulin[40]. In this study, the long-term PA habits were associated with diet, smoking behavior and SES, and the adjustments for these factors somewhat diluted the associations of physical inactivity with cardiometabolic risk profile, lending support to that these factors were possibly partly underlying the observed associations. In summary, several mechanistic pathways likely underlie the association between physical inactivity and cardiometabolic risk profile.

Strengths and limitations. A limitation of the study is that PA was measured using questionnaires. Apart from providing subjective data, the applied two questionnaires were non-identical, and unable to detect all dimensions or total volume of overall PA. For example, PA during school and/or working hours may have led to underestimation of total PA. In general, questionnaires are not the golden standard to measure PA, and current studies typically use accelerometres to collect more objective PA data. However, the standardized questionnaires enabled a unique 31-year follow-up of PA from youth to adulthood. We also acknowledge that the use of percentile based cut-off points to define the PA groups is arbitrary and due to the applied PA assessment method, it does not allow direct comparison to PA recommendations. The study used questionnaires also to assess diet and smoking, a simplistic variable was used to describe smoking habits, and we cannot rule out the

possibility of residual confounding or cardiometabolic health status affecting PA (reverse causation). Furthermore, the study included multiple statistical tests, which may lead to random findings. The YFS is an in depth characterized cohort; the participants have been closely followed with well-established methods since youth to adulthood. An additional strength is also the use of national registry data on medication.

Conclusion. A sustained physically inactive lifestyle, or becoming physically inactive, from youth to adulthood is associated with an unfavorable adult cardiometabolic risk profile. Importantly, those who increased their PA during the 31-year follow-up had a reduced risk for the cardiometabolic risk factors. These results highlight the importance of not leading a physically inactive lifestyle at all stages of life.

The following are the supplementary data related to this article.

Supplement Table 1. The assessment of physical activity and creation of the physical activity index (PAI) in 1980-1989.

Supplement Table 2. The assessment of physical activity and creation of the physical activity index (PAI) in 1992-2011.

Supplement table 3 – Age, sex, education, diet and smoking adjusted mean differences in cardiometabolic risk factors for the physical activity increase groups when the persistently physically inactive group is the reference. For variables with skewed distribution, i.e. triglycerides, glucose and insulin, logarithmically transformed values were used in the analyses, and reported here. In addition, adjusted mean differences in absolute values for these variables are shown in parenthesis.

Supplement table 4 – Risk ratios (RR) for high-risk cardiometabolic risk factors for the physical activity increase groups when the persistently physically inactive group is the reference (age, sex, education, smoking and diet adjusted). Criteria for the definitions of high-risk are shown in the footnote.

Supplement table 5 - Characteristics of the cardiometabolic risk factors in adulthood (age 30 – 49 years) according to the physical activity group. Adult values are mean/median (SD/quartile range) or prevalence (%).

Supplementary material

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important intellectual content. O.T.R. coordinates and contributed to the design of the Cardiovascular Risk in Young Finns Study, to obtaining funding, editing of the manuscript and to the critical revision of the manuscript for important intellectual content

P.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors made every attempt to present the results of the study clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Authors' contributions

P.K. researched data and wrote the manuscript. K.P. and O.H. contributed to the study concept, design, critical revision of the manuscript for important intellectual content and edited the manuscript. T.T., K.P., M.H., E.-M.L. and C.G.M. contributed to the study design and critical revision of the manuscript for important intellectual content. M.J. contributed to the design of the Cardiovascular Risk in Young Finns Study and critical revision of the manuscript for important intellectual content. S.R., H.H., T.L., E.J., P.T. and N.H.-K. contributed to the critical revision of the manuscript for important intellectual content. J.V. contributed to obtaining funding, the design of the Cardiovascular Risk in Young Finns Study and the critical revision of the manuscript for important intellectual content. O.T.R. coordinates and contributed to the design of the Cardiovascular Risk in Young Finns Study, to obtaining funding, editing of the manuscript and to the critical revision of the manuscript for important intellectual content

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Table 1 - Characteristics of the study participants in adulthood (age 30 – 49 years) according to physical activity group. The latest available data obtained primarily in 2011, or secondarily in 2007 are applied. The values are mean (SD) or prevalence, %.

	PERSISTENTLY PHYSICALLY INACTIVE (N=246)	DECREASINGLY ACTIVE (N=305)	INCREASINGLY ACTIVE (N=328)	PERSISTENTLY ACTIVE (N=1082)	P-VALUE
AGE (YEARS)	41.7 (5.1)	41.2 (5.2)	40.7 (5.2)	41.4 (5.1)	0.089
SEX (% MALES)	44.7	45.6	40.0	44.4	0.45

EDUCATION (YEARS)	14.8 (3.5)	14.8 (3.5)	15.6 (3.5)	15.8 (3.6)	<0.0001
DAILY SMOKER (%)	28.5	23.0	12.8	10.3	<0.0001
DIETSCORE (RANGE 0–27)[a]	12.0 (4.2)	12.5 (4.0)	14.2 (4.2)	14.0 (4.1)	<0.0001

[a]Higher dietscore indicates healthier diet

Table 2 – Persistent physical inactivity and continuous cardiometabolic risk factors

The table reports adjusted mean differences in cardiometabolic risk factors between the physical activity groups when the persistently physically inactive group is the reference. For variables with skewed distribution, i.e. triglycerides, glucose and insulin, logarithmically transformed values were used in the analyses, and reported here. In addition, adjusted mean differences in absolute values for these variables are shown.

	PERSISTENTLY PHYSICALLY INACTIVE		**DECREASINGLY ACTIVE**	**INCREASINGLY ACTIVE**	**PERSISTENTLY ACTIVE**
		Model	mean diff 95% CI	mean diff 95% CI	mean diff 95% CI
BMI (kg/m^2) (n=1931)	26.9	1	0.18 -0.77-1.14	-1.29 -2.24 - -0.35	-0.67 -1.45-0.12
	26.8	2	0.28 -0.71-1.27	-1.15 -2.15 - -0.16	-0.55 -1.38-0.28
		3	NA	NA	NA
WAIST (cm) (n=1932)	93.0	1	0.01 -2.52-2.54	-3.90 -6.40- -1.40	-2.52 -4.60- -0.43
	92.4	2	0.21 -2.41-2.83	-3.39 -6.01 - -0.77	-2.00 -4.20-0.20
		3	NA	NA	NA
SBP (mmHg) (n=1932)	119.6	1	1.82 -0.91-4.55	0.94 -1.76-3.63	0.36 -1.88-2.61
	118.3	2	1.56 -1.21-4.33	0.96 -1.81-3.73	0.60 -1.73-2.93
	118.0	3	1.37 -1.32-4.05	1.76 -0.93-4.46	0.98 -1.27-3.24
DBP (mmHg) (n=1932)	75.2	1	0.42 -1.64-2.48	0.09 -1.95-2.12	-0.29 -1.99-1.40
	75.0	2	0.46 -1.62-2.54	0.05 -2.03-2.13	-0.26 -2.00-1.49
	74.7	3	0.28 -1.69-2.25	0.82 -1.16-2.79	-0.10 -1.55-1.76
Total cholesterol (mmol/l) (n=1928)	5.20	1	0.09 -0.09-0.28	-0.07 -0.25-0.11	-0.12 -0.27-0.03
	5.17	2	0.10 -0.08-0.29	-0.06 -0.24-0.13	-0.09 -0.25-0.06
	5.16	3	0.10 -0.09-0.28	-0.03 -0.22-0.16	-0.08 -0.24-0.07
LDL cholesterol	3.29	1	0.06	-0.09	-0.10

(mmol/l) (n=1910)			-0.10-0.22	-0.24-0.07	-0.23-0.04
	3.26	2	0.07 -0.09-0.24	-0.08 -0.24-0.09	-0.08 -0.22-0.06
	3.25	3	0.07 -0.10-0.23	-0.05 -0.22-0.11	-0.06 -0.20-0.07
HDL cholesterol (mmol/l) (n=1926)	1.26	1	0.05 -0.01-0.11	0.11 0.05-0.17	0.08 0.03-0.13
	1.27	2	0.04 -0.03-0.10	0.10 0.04-0.17	0.06 0.01-0.12
	1.28	3	0.04 -0.01-0.10	0.08 0.02-0.14	0.05 -0.0005-0.10
Triglycerides (mmol/l) (n=1928) *Logarithmically transformed values*	0.24	1	-0.005 -0.10 – 0.09	-0.14 -0.24 - -0.04	-0.16 -0.24 - -0.08
	0.21	2	0.003 -0.10 – 0.10	-0.12 -0.23 - -0.02	-0.13 -0.21 - -0.04
	0.19	3	-0.009 -0.10 – 0.08	-0.08 -0.17 – 0.02	-0.10 -0.18 - -0.03
Triglycerides (mmol/l) (n=1928) *Absolute values*	1.48	1	0.04	-0.12	-0.20
	1.43	2	0.07	-0.19	-0.15
	1.41	3	0.05	-0.12	-0.11
Glucose (mmol/l) (n=1928) *Logarithmically transformed values*	1.69	1	-0.006 -0.03 – 0.02	-0.03 -0.05 - -0.009	-0.02 -0.04 - -0.006
	1.69	2	-0.01 -0.03 – 0.01	-0.03 -0.05 - -0.009	-0.02 -0.04 - -0.003
	1.68	3	-0.01 -0.03 - 0.008	-0.02 -0.04 - -0.002	-0.02 -0.04 - -0.0002
Glucose (mmol/l) (n=1928) *Absolute values*	5.49	1	-0.06	-0.21	-0.18
	5.48	2	-0.09	-0.22	-0.18
	5.47	3	-0.11	-0.18	-0.15
Insulin (mU/l) (n=1927) *Logarithmically transformed values*	2.11	1	-0.01 -0.17 – 0.15	-0.26 -0.42 - -0.11	-0.23 -0.36 - -0.10
	2.09	2	-0.001 -0.16 – 0.15	-0.21 -0.38 - -0.06	-0.21 -0.34 - -0.08
	2.05	3	-0.03 -0.16 – 0.10	-0.12 -0.25 – 0.01	-0.16 -0.27 - -0.05
Insulin (mU/l) (n=1927) *Absolute values*	11.4	1	-0.53	-2.98	-2.69
	11.4	2	-0.63	-3.05	-2.71
	10.9	3	-0.91	-1.94	-2.17

Model 1: Age, sex adjusted mean differences in cardiometabolic risk factors between the physical activity groups. Persistently physically inactive group is the reference.

Model 2: Age, sex, education, diet and smoking adjusted mean differences in cardiometabolic risk factors between the physical activity groups. Persistently physically inactive group is the reference.

Model 3: Age, sex, education, diet, smoking, and body mass index adjusted mean differences in cardiometabolic risk factors between the physical activity groups. Persistently physically inactive group is the reference.

BMI, Body Mass Index; DBP, Diastolic Blood Pressure; HDL High-Density Lipoprotein; LDL, Low-Density Lipoprotein; Mean diff, Mean Difference; SBP, Systolic Blood Pressure; Waist, Waist Circumference; NA, not applicable.

Table 3 – Persistent physical inactivity and high risk cardiometabolic risk factors

The table reports risk ratios (RR) for high-risk cardiometabolic risk factors between the physical activity groups. Persistently physically inactive group is the reference. Criteria for the definitions of high-risk are shown in the footnote.

		PERSISTENTLY PHYSICALLY INACTIVE	**DECREASINGLY ACTIVE**	**INCREASINGLY ACTIVE**	**PERSISTENTLY ACTIVE**
	Model	RR	RR 95% CI	RR 95% CI	RR 95% CI
OBESITY (n=1931)	1	1	1.14 0.86 – 1.51	0.49 0.34 – 0.71	0.76 0.59 – 0.98
	2	1	1.18 0.87 – 1.59	0.53 0.36 – 0.79	0.79 0.60 – 1.04
			NA	NA	NA
HIGH WAIST (n=1932)	1	1	1.05 0.86 – 1.29	0.75 0.60 – 0.94	0.82 0.69 – 0.98
	2	1	1.05 0.85 – 1.29	0.75 0.59 – 0.95	0.84 0.69 – 1.01
			NA	NA	NA
HIGH BLOOD PRESSURE (n=1931)	1	1	1.40 1.10 – 1.78	1.13 0.88 – 1.46	1.06 0.86 – 1.31
	2	1	1.40 1.09 – 1.78	1.07 0.82 – 1.40	1.06 0.84 – 1.33
	3	1	1.38 1.09 – 1.74	1.18 0.91 – 1.53	1.11 0.90 – 1.38
HIGHT TOTAL CHOLESTEROL (n=1928)	1	1	1.21 0.80 – 1.82	0.81 0.52 – 1.28	0.82 0.57 – 1.16
	2	1	1.31 0.85 – 2.04	0.88 0.53 – 1.46	0.91 0.61 – 1.35
	3	1	1.29 0.83 – 2.00	0.90 0.54 – 1.49	0.91 0.62 – 1.35
HIGH LDL CHOLESTEROL (n=1910)	1	1	1.16 0.79 – 1.71	0.98 0.65 – 1.46	0.83 0.60 – 1.17
	2	1	1.26 0.84 – 1.90	1.06 0.68 – 1.65	0.92 0.63 – 1.33
	3	1	1.23 0.81 – 1.85	1.10 0.71 – 1.70	0.92 0.64 – 1.33
LOW HDL CHOLESTEROL (n=1904)	1	1	0.84 0.68 – 1.04	0.67 0.53 – 0.85	0.78 0.66 – 0.93
	2	1	0.89 0.71 – 1.12	0.72 0.56 – 0.92	0.86 0.71 – 1.04
	3	1	0.90 0.72 – 1.13	0.82 0.64 – 1.04	0.93 0.77 – 1.12

HIGH TRIGLYCERIDES (n=1928)	1	1	0.88 0.68 – 1.15	0.69 0.51 – 0.93	0.60 0.47 – 0.75
	2	1	0.88 0.67 – 1.17	0.73 0.53 – 1.01	0.64 0.50 – 0.82
	3	1	0.86 0.65 – 1.13	0.82 0.60 – 1.11	0.67 0.53 – 0.86
HIGH GLUCOSE (n=1928)	1	1	0.91 0.70 – 1.19	0.76 0.57 – 1.01	0.77 0.62 – 0.96
	2	1	0.90 0.68 – 1.18	0.80 0.59 – 1.07	0.81 0.64 – 1.03
	3	1	0.88 0.67 – 1.15	0.85 0.63 – 1.14	0.85 0.68 – 1.07
HIGH INSULIN (n=1927)	1	1	0.91 0.69 – 1.20	0.61 0.45 – 0.84	0.58 0.46 – 0.74
	2	1	0.95 0.71 – 1.26	0.63 0.46 – 0.90	0.60 0.47 – 0.78
	3	1	1.06 0.77 – 1.45	0.91 0.65 – 1.27	0.76 0.56 – 1.03

Model 1: Age, sex adjusted risk ratios in cardiometabolic risk factors between the physical activity groups. Persistently physically inactive group is the reference.

Model 2: Age, sex, education, diet and smoking adjusted risk ratios in cardiometabolic risk factors between the physical activity groups. Persistently physically inactive group is the reference.

Model 3: Age, sex, education, diet, smoking, and body mass index adjusted risk ratios in cardiometabolic risk factors between the physical activity groups. Persistently physically inactive group is the reference.

CI; confidence interval; Obesity, BMI>30 kg/m^2; High waist, Waist circumference ≥88cm in women and ≥102 in men; High Blood Pressure, ≥130/≥85 mmHg or treatment for hypertension; High total cholesterol, >6.2 mmol/l; High LDL cholesterol, low-density lipoprotein >4.14 mmol/l; Low HDL cholesterol, high-density lipoprotein <1.03 mmol/l in men and <1.29 mmol/l in women or treatment; High triglycerides, >1.7 mmol/l or treatment; High glucose, ≥5.6 mmol/l, High insulin, >80th percentile (in our study 13.05 mU/l); NA, not applicable.

Table 4 - Persistent physical inactivity and clustered cardiometabolic risk

The table reports risk ratios (RR) for clustered cardiometabolic risk (metabolic syndrome) between the physical activity groups. Persistently physically inactive group is the reference.

		HARMONIZED		**IDF**		**NCEP**		**EGIR**	
		MODEL 1 (N=1922)	MODEL 2 (N=1813)	MODEL 1 (N=1899)	MODEL 2 (N=1797)	MODEL 1 (N=1920)	MODEL 2 (N=1811)	MODEL 1 (N=1918)	MODEL 2 (N=1809)

PERSISTENTLY PHYSICALLY INACTIVE	RR	1	1	1	1	1	1	1	1
DECREASINGLY ACTIVE	RR 95 % CI	0.91 0.70-1.19	0.91 0.68-1.21	0.94 0.73-1.21	0.94 0.72-1.22	0.97 0.75-1.25	0.97 0.74-1.28	0.75 0.56-1.01	0.74 0.54-1.02
INCREASINGLY ACITVE	RR 95 % CI	0.62 0.45-0.84	0.64 0.45-0.89	0.73 0.56-0.97	0.78 0.58-1.04	0.65 0.48-0.88	0.66 0.48-0.92	0.52 0.37-0.73	0.53 0.37-0.77
PERSISTENTLY ACTIVE	RR 95 % CI	0.67 0.53-0.84	0.71 0.55-0.91	0.71 0.57-0.88	0.76 0.60-0.96	0.63 0.50-0.79	0.67 0.52-0.86	0.48 0.37-0.61	0.49 0.37-0.65

Model 1: age and sex adjusted.

Model 2: age, sex, education, diet and smoking adjusted.

CI, confidence interval; EGIR, Metabolic syndrome definition by the European Group for the Study of Insulin Resistance; HARMONIZED, Metabolic syndrome by the harmonized definition; IDF, Metabolic syndrome definition by the International Diabetes Federation; NCEP, Metabolic syndrome definition by the National Cholesterol Education Program Adult treatment Panel III.