

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Kallio, Petri; Pahkala, Katja; Heinonen, Olli J.; Tammelin, Tuija; Hirvensalo, Mirja; Telama, Risto; Juonala, Markus; Magnussen, Costan G.; Rovio, Suvi; Helajärvi, Harri; Hutri-Kähönen, Nina; Viikari, Jorma; Raitakari, Olli T.

Title: Physical Inactivity from Youth to Adulthood and Risk of Impaired Glucose Metabolism

Year: 2018

Version: Accepted version (Final draft)

Copyright: © 2018 by the American College of Sports Medicine

Rights: In Copyright

Rights url: <http://rightsstatements.org/page/InC/1.0/?language=en>

Please cite the original version:

Kallio, P., Pahkala, K., Heinonen, O. J., Tammelin, T., Hirvensalo, M., Telama, R., Juonala, M., Magnussen, C. G., Rovio, S., Helajärvi, H., Hutri-Kähönen, N., Viikari, J., & Raitakari, O. T. (2018). Physical Inactivity from Youth to Adulthood and Risk of Impaired Glucose Metabolism. *Medicine and Science in Sports and Exercise*, 50(6), 1192-1198.
<https://doi.org/10.1249/MSS.0000000000001555>

Physical Inactivity from Youth to Adulthood and Risk of Impaired Glucose Metabolism

Petri Kallio^{1,2,6}, Katja Pahkala^{1,2}, Olli J. Heinonen¹, Tuija Tammelin³, Mirja Hirvensalo⁴,
Risto Telama⁴, Markus Juonala⁵, Costan G. Magnussen^{2,7}, Suvi Rovio², Harri Helajärvi¹,
Nina Hutri-Kähönen⁸, Jorma Viikari⁵, and Olli T. Raitakari^{2,6}

¹Paavo Nurmi Centre & Department of Health and Physical Activity, University of Turku, Turku, Finland; ²Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; ³LIKES-Research Center for Sport and Health Sciences, Jyväskylä, Finland; ⁴Department of Sport Sciences, University of Jyväskylä, Finland;

⁵Department of Medicine, University of Turku and Division of Medicine, Turku University Hospital; ⁶Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, Finland; ⁷Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia; ⁸Department of Pediatrics, University of Tampere and Tampere University Hospital, Tampere, Finland

Accepted for Publication: 18 December 2017

Medicine & Science in Sports & Exercise®. Published ahead of Print contains articles in unedited manuscript form that have been peer reviewed and accepted for publication. This manuscript will undergo copyediting, page composition, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered that could affect the content.

Physical Inactivity from Youth to Adulthood and Risk of Impaired Glucose Metabolism

Petri Kallio^{1,2,6}, Katja Pahkala^{1,2}, Olli J. Heinonen¹, Tuija Tammelin³, Mirja Hirvensalo⁴,
Risto Telama⁴, Markus Juonala⁵, Costan G. Magnussen^{2,7}, Suvi Rovio², Harri Helajärvi¹,
Nina Hutri-Kähönen⁸, Jorma Viikari⁵, and Olli T. Raitakari^{2,6}

¹Paavo Nurmi Centre & Department of Health and Physical Activity, University of Turku, Turku, Finland; ²Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; ³LIKES-Research Center for Sport and Health Sciences, Jyväskylä, Finland; ⁴Department of Sport Sciences, University of Jyväskylä, Finland; ⁵Department of Medicine, University of Turku and Division of Medicine, Turku University Hospital; ⁶Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, Finland; ⁷Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia; ⁸Department of Pediatrics, University of Tampere and Tampere University Hospital, Tampere, Finland

Corresponding author:

Petri Kallio, MD

Paavo Nurmi Centre & Department of Health and Physical Activity, University of Turku, Turku, Finland

Kiinamylynkatu 10, 20520 Turku, Finland

petri.kallio@utu.fi

Tel +358(50)5391907

The Cardiovascular Risk in Young Finns Study was financially supported by the Suomen Akatemia (Academy of Finland) (grants 286284 [to T.L.]; 134309 [Eye]; 126925, 121584, 124282, and 129378 [Salve]; 117787 [Gendi]; 41071 [Skidi]; 275595 [to K.P.]); Social Insurance Institution of Finland; Kuopio, Tampere, and Turku University Hospital Medical Funds (grant X51001 to T.L.); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research; Finnish Cultural Foundation; Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; and Yrjö Jahnsson Foundation. This work was also partly funded by the National Heart Foundation of Australia Future Leader Fellowship (grant 100849 to C.G.M.) and the National Health and Medical Research Council Project (grant APP1098369). The authors made every attempt to present the results of the study clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The authors also acknowledge that the present study does not constitute endorsement by the American College of Sports Medicine. The authors declare that they have no competing interests. There are no conflict of interests to disclose for any of the authors.

ABSTRACT

Introduction: Physical activity (PA) is important in the prevention and treatment of impaired glucose metabolism. However, association of physical inactivity during the transition between childhood and adulthood with glucose metabolism is unknown. Therefore, we studied the association of persistent physical inactivity since childhood with glucose metabolism in adulthood. **Methods:** Data were drawn from the ongoing, Cardiovascular Risk in Young Finns Study with repeated follow-ups between 1980-2011 (baseline age 3-18 years, n=3596). Impaired glucose metabolism was defined as having impaired fasting glucose (6.1-6.9mmol/l) or type 2 diabetes in adulthood. Leisure-time PA habits were repeatedly collected with a standardized questionnaire and expressed as a PA index (PAI). Using PAI, four groups were formed (n=2000): 1) persistently low PA, 2) decreasingly active, 3) increasingly active and 4) persistently active subjects. Poisson regression model was used to examine the association between PA groups and impaired glucose metabolism. **Results:** The proportion of the sample with impaired glucose metabolism was 16.1% in individuals with persistently low PA, 14.5% in decreasingly active, 6.8% in increasingly active and 11.1% in persistently active. Compared to individuals with persistently low PA, age and sex adjusted risk for impaired glucose metabolism was lower in those who increased PA (RR=0.47 CI=0.29–0.76) and in those who were persistently active (RR=0.70 CI=0.51–0.97), but similar in those who decreased PA (RR=0.93 CI=0.66–1.36). **Conclusion:** Persistently physically inactive lifestyle from youth to adulthood is associated with increased risk of impaired glucose metabolism in adulthood. Importantly, a moderate increase in PA lowered the risk. The results highlight the importance of avoiding physically inactive lifestyle at all stages of life. **Key words:** Glucose metabolism, life-time physical inactivity, longitudinal data.

INTRODUCTION

Impaired glucose metabolism – comprising impaired fasting glucose and type 2 diabetes - is an increasing, major health problem worldwide(1). According to the International Diabetes Federation, 415 million people have type 2 diabetes and there are 318 million adults with impaired glucose tolerance(2). Impaired glucose metabolism is caused by both genetic and environmental factors. Physical inactivity has been associated with impaired glucose metabolism, particularly in studies of adults. Mechanistically, physical activity (PA) increases glucose uptake also independently of insulin(3) and may improve insulin sensitivity and thus ameliorate glucose homeostasis by increasing oxidative capacity of skeletal muscles(4). Several studies, including prospective follow-ups(5, 6), a clinical randomized controlled trial(7), and a follow-up twin study(8), suggest that PA has an independent role in the prevention of type 2 diabetes. Also, a post hoc analysis of participants in the Finnish Diabetes Prevention Study suggested that an increase in PA may substantially reduce the incidence of type 2 diabetes in high-risk individuals(9). Although the benefits of PA on glucose metabolism are well established, it is, however, not known how lifelong physical inactivity is associated with glucose metabolism.

Therefore, using the unique longitudinal Cardiovascular Risk in Young Finns Study data from 1980 to 2011, the aim of this study was to investigate how persistent physical inactivity is associated with glucose metabolism in adulthood. Further, we studied how change in PA from youth to adulthood is associated with glucose metabolism.

METHODS

Study design and subjects

The data were drawn from the ongoing Cardiovascular Risk in Young Finns Study. The first cross-sectional survey was conducted in 1980. The original targeted cohort comprised 4,326 children and adolescents aged 3, 6, 9, 12, 15, and 18 years, of whom 3,596 (83.2% of the invited) participated in the baseline study. The cohort has been followed-up for 31 years in 3-9 year intervals (follow-up years 1983, 1986, 1989, 2001, 2007 and 2011). Altogether 2115 individuals (aged 34-49 years) participated in the most recent follow-up study in 2011. At all study phases, 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). Unavoidably, some of the individuals have been lost to follow-up. Those who dropped out were more often men and younger individuals than those who remained in the study. No differences were found in the PA levels between those who dropped out and those who remained in the study(11). All participants provided written informed consent, and the study was approved by the Turku University Hospital ethical committee.

The main focus of this study was to investigate the association of lifelong physical inactivity (follow-ups from 1980 to 2011, aged 9-49 years) with impaired glucose metabolism in adulthood (follow-ups from 2001 to 2011, aged 24-49 years). Individuals who had no glucose values available during 2001 – 2011 or lacked longitudinal PA data were thus excluded. PA data from age 3 and 6 years were not used since a different questionnaire was used at those ages than for over 9-year-old subjects. In total, 2726 subjects (1453 women, 1273 men) were included in this study. Additional data included this study, e.g. anthropometrics and laboratory analyses, were

collected in adulthood (2001, 2007 and 2011; aged 24-49 years). For these variables, the latest available values are used.

Impaired glucose metabolism

Impaired glucose metabolism comprises impaired fasting glucose and type 2 diabetes. Fasting glucose from 6.1 to 6.9 mmol/l is defined as impaired fasting glucose according to World Health Organization(12). Subjects fulfilling the impaired fasting glucose criteria, reporting to have been diagnosed with type 2 diabetes or reporting use of antidiabetic medication in any of the 2001, 2007 or 2011 follow-ups were classified as having impaired glucose metabolism (data on glycated hemoglobin was available only from the 2011 follow-up). Type 2 diabetes diagnoses were also checked from the National Social Insurance Institution Drug Reimbursement Registry. Individuals who had type 1 diabetes were excluded from the study. Also glucose values obtained from pregnant and nursing women were excluded. Of the participants with impaired glucose metabolism, 33% had type 2 diabetes.

Physical activity

Leisure-time PA, expressed as physical activity index (PA index), was self-reported with a standardized questionnaire (internal consistency coefficient: 0.72 to 0.82, the 2007 follow-up, and correlation of the PA index with cardiorespiratory fitness, $r=0.33$ to 0.53)(13,14). Between 1980 and 1989, the questions concerned the frequency and intensity of PA, participation in sports club training, participation in sport competitions and typical activity during leisure time. The items were coded from 1 (inactivity or very low activity) to 3 (frequent or vigorous activity) to form the PA index with scores ranging from 5 to 14. 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. The PA index (range from 5 to 15) was calculated similarly as in the earlier follow-ups(14).

Using the PA index, four physical activity groups were formed to investigate the association of physical inactivity and change in PA index with impaired glucose metabolism from youth to adulthood. Firstly, subjects 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 24-49 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=2000). Thirdly, the four groups were formed based on the quartiles: 1) persistently low PA (subjects in the lowest quartile both during youth and adulthood, n=244), 2) decreasingly active (subjects in the three highest quartiles in youth, but in the lowest quartile in adulthood, n=321), 3) increasingly active (subjects in the lowest quartile in youth, but in the three highest quartiles in adulthood, n=328), and 4) persistently active (subjects in the three highest quartiles both in youth and adulthood, n=1107). In females, this age specific cut-off point for the lowest quartile varied between 8.3 and 8.7, and in males, the corresponding cut-off points were between 8.0 and 8.3. To get a PA index value of 8, a subject e.g. did not participate in organized PA, but reported participating in vigorous PA once a week, for 20-40 minutes, and the activity caused moderate sweating *i.e.* 30 minutes of brisk walking.

To more clearly distinguish low active and active groups we additionally categorized PA using only the lowest and highest quartiles. Thus, the change from low to high physical activity and vice versa was also more pronounced. Accordingly, these groups were: 1) persistently low PA (participants in the lowest quartile during both youth and adulthood, n=244), 2) prominent PA decrease (subjects in the highest quartile in youth, but in the lowest quartile in adulthood, n=52), 3) prominent PA increase (subjects in the lowest quartile in youth, but in the highest quartile in adulthood, n=73), and 4) persistently high active (subjects in the highest quartile both in youth and adulthood, n=167).

Laboratory analyses

Venous blood samples were drawn after a 12-h fast. Standard enzymatic methods were used to assess plasma glucose and serum total cholesterol(15). Low-density lipoprotein cholesterol concentration was calculated using Friedewald formula(16). Glycated hemoglobin fraction in whole blood was measured by an Abbott Architect ci8200 analyzer (Abbott Laboratories and Hemoglobin A1c reagent, Fisher Diagnostics). Serum insulin concentration was analyzed using microparticle enzyme immunoassay kit (Abbott Laboratories, Chicago, IL, USA)(15). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the equation $[(\text{fasting insulin mU/mL} \times \text{fasting glucose mmol/L})/22.5]$ (17) and was used to estimate insulin resistance. The methods for total cholesterol, triglycerides, glucose and glycated hemoglobin analyses are accredited by the Finnish Accreditation Service according to ISO/IEC17025 standard(18).

Clinical examination

Weight was measured in light clothing without shoes using a digital scale with an accuracy of 0.1 kg. Height was measured by a wall-mounted stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) / [height (m)]². To use all available repeatedly measured BMI values in youth (age 12 to 18 years), we estimated a subject-specific curve for BMI by mixed model regression splines(19). The area under the curve (AUC) was evaluated to indicate a long-term burden of BMI(20). For interpretability, the AUC variables were standardized resulting in variables with a mean of 0 and SD 1. 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. Korotkoff's first sound was used as the sign of systolic blood pressure (SBP). Readings to the nearest even number of millimeters of mercury were performed at least three times on each participant. The mean of these three measurements was used.

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(21). The participants were asked to report the daily frequency and serving size of selected foods and dishes during the previous 12 months. The questionnaire included additional open questions to enable reporting of foods not listed. The daily specific food or food group consumption and nutrient intake was calculated using the latest version of the National Food Composition Database Fineli(22). A food-based diet score originally constructed to describe diet associated with lower risk of

diabetes(23) was used as an indicator of a healthy diet (range 0 to 27). Higher score indicates 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 socioeconomic status (SES) were collected with self-administered questionnaires. Those reporting daily smoking were considered as smokers. SES was determined based on the self-reported occupation: 1) manual; 2) lower, non-manual; or 3) upper, non-manual. In addition, we also used education (years) to indicate SES.

Statistical analyses

To characterize the individuals with and without impaired glucose metabolism, mean values and standard deviations (SD) for continuous variables and percentages for categorical variables were calculated. There was no interaction between PA index and sex using impaired glucose metabolism as the outcome (p for interaction=0.34). Therefore, combined analyses including both women and men were done. Risk ratios for impaired glucose metabolism were estimated using Poisson regression with robust error variance. The persistently low PA 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 diet, BMI, smoking and SES.

To estimate the possible association of long-term exposure of PA in youth (age 9 – 21 years) with adulthood glucose metabolism, area under the receiver-operating characteristic curve (AUC) was calculated for each participant using the results from repeated PA data. Participant-specific curves for PA were estimated by mixed model regression splines(19). Additionally we

also evaluated the effect of youth PA on adulthood glucose metabolism using mean PA index-values in youth (age 9-21 years).

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

RESULTS

In adulthood (mean age 36.7, range 24-49 years), the prevalence of impaired glucose metabolism was 11.4% (women: 7.9%, men: 15.4%; Table 1). Individuals with impaired glucose metabolism were more often obese (BMI >30 kg/m²) and had higher SBP than individuals without impaired glucose metabolism. Individuals with impaired glucose metabolism also had a lower PA index in adulthood (Table 1) and during the 31-year follow-up compared with their unaffected peers (adjusted for age and sex; $\beta=0.26$, SE 0.08, $p=0.001$; Figure 1). There was no association between PA index at age 9 to 21 years (AUC) ($\beta=0.002$, SE 0.005, $p=0.66$) or mean PA index in youth ($\beta=0.04$, SE 0.05, $p=0.43$) with impaired glucose metabolism later in adulthood (adjusted for age, sex and adult PA).

Of those with persistently low PA, 16.1% had impaired glucose metabolism in adulthood. Among the persistently active individuals, the prevalence of impaired glucose metabolism was 11.1%, 14.5% among those who decreased PA from youth to adulthood, and 6.8%, among those who increased PA. Compared with persistently low PA individuals, those who were increasingly active or were persistently active had a significantly lower risk of impaired glucose metabolism (Table 2, model A; adjusted for age and sex). Persistently low PA individuals and those who

were decreasingly active between youth and adulthood had a similar risk of impaired glucose metabolism.

To further study the independent association between physical inactivity and impaired glucose metabolism, the analyses were additionally adjusted for diet, BMI, smoking and SES. After adjustment for the healthy diet score, the results remained essentially unchanged (Table 2, model B). When also BMI was added to the analyses, lower risk of impaired glucose metabolism persisted only in those who were increasingly active compared with their persistently low PA peers (model C). The decreased risk of impaired glucose metabolism among subjects who were increasingly active compared with persistently low PA individuals remained after additional adjustments for smoking and SES (model D and E). In all analyses, those who were decreasingly active between youth and adulthood had a similar risk of impaired glucose metabolism as those with persistently low PA. The use of waist circumference instead of BMI did not affect the results (see Table, Supplemental Digital Content 1, Risk of impaired glucose metabolism across four physical activity groups, <http://links.lww.com/MSS/B193>). In line, the results were similar when education was used instead of occupation to indicate SES (see Table, Supplemental Digital Content 1, Risk of impaired glucose metabolism across four physical activity groups, <http://links.lww.com/MSS/B193>). When the more rigorous criteria were used to define the PA groups, the results remained essentially unchanged (see Table, Supplemental Digital Content 2, Risk of impaired glucose metabolism across four physical activity groups, <http://links.lww.com/MSS/B194>). Subjects in the prominent PA decrease group had a similar risk of impaired glucose metabolism as those with persistently low PA. Decreased risk was found in the prominent PA increase group compared with the persistently low PA group (see

Table, Supplemental Digital Content 2, Model 1; adjusted for age and sex. Risk of impaired glucose metabolism across four physical activity groups, <http://links.lww.com/MSS/B194>).

To further investigate the independent role of PA on impaired glucose metabolism, the analyses reported in Table 2 were additionally adjusted for insulin (see Table, Supplemental Digital Content 3, Risk of impaired glucose metabolism across four physical activity groups, <http://links.lww.com/MSS/B195>), HOMA-IR (see Table, Supplemental Digital Content 4, Risk of impaired glucose metabolism across four physical activity groups, <http://links.lww.com/MSS/B196>) and BMI (AUC) between ages 12 and 18 years (see Table, Supplemental Digital Content 5, Risk of impaired glucose metabolism across four physical activity groups, <http://links.lww.com/MSS/B197>). After these adjustments the results were essentially unchanged.

DISCUSSION

In this 31-year follow-up since youth, individuals who had persistently low PA also had the highest prevalence of impaired glucose metabolism later in life. In addition, when compared to persistently physically active or increasingly active groups, being in the persistently low PA group was associated with a greater risk of impaired glucose metabolism in adulthood. Similar risk in those who were decreasingly active to those with persistently low PA shows that the benefits of PA on glucose metabolism are not preserved within time. In line, PA exposure during youth was not associated with impaired glucose metabolism in adulthood. We also found that even a moderate increase in PA was associated with a lower risk of impaired glucose

metabolism. This study is the first to report the association of persistently low PA lifestyle since youth with impaired glucose metabolism in mid-adulthood.

Our results are in line with prior data reporting benefits of PA on glucose metabolism and in prevention of type 2 diabetes(5–9, 23). Based on a number of studies conducted in adult populations, continued physical inactivity may lead to progression of impaired glucose metabolism(24). There is also emerging epidemiological evidence – from both cross-sectional and prospective observational studies – indicating that time spent in sedentary behaviors is an independent risk factor for several health outcomes, including impaired glucose metabolism(25). Furthermore, similar results have been observed using objectively measured PA; already light-intensity PA assessed with accelerometers was favorably associated with glucose metabolism(26). There is also evidence that any amount of PA may reduce the risk of type 2 diabetes(8). Our finding that being persistently physically inactive over the life-course is associated with greater risk of impaired glucose metabolism stresses the need for continued identification and intervention of individuals who lead a physically inactive lifestyle. Simultaneously, beneficial lifestyle changes have proven effective in preventing or delaying the onset of type 2 diabetes in individuals at increased risk(26, 27). Regarding PA behavior, our cohort data has shown that physically active lifestyle starts to develop very early in childhood and that the stability of PA is moderate or high along the life course from youth to adulthood(14).

In addition to the detrimental effects of persistent physical inactivity, our study pointed out that decreasing PA may have similar results as having persistently low PA: those who decreased PA

from youth to adulthood did not preserve the benefits of PA on glucose metabolism. Prior data show that already 2 weeks physical inactivity attenuates peripheral insulin sensitivity(29). A short-term experimental study has also shown significantly reduced whole-body insulin action already after one day of prolonged sitting(30). On the other hand, our study clearly shows that a moderate increase in PA from youth to adulthood is associated with greatly reduced risk of impaired glucose metabolism. This finding highlights the important role of increasing PA among sedentary children and adolescents. In line with these data, prior results have shown that even light-to-moderate(31) PA has a beneficial association with cardiometabolic health(32). In summary, previous studies support the findings of our study that being persistently physically inactive increases the risk of impaired glucose metabolism and even a moderate increase in PA is associated with decreased risk of the condition.

The underlying biological mechanisms observed between physical inactivity and impaired glucose metabolism are not yet fully elucidated, but there is a strong suggestion that physical inactivity is a necessary component of insulin resistance(29). High-fat diet -induced, or obesity-associated insulin resistance, do not normally occur in skeletal muscle, when a sufficient level of PA is imposed(29). An experimental study has also shown that decline in insulin action was not fully prevented through reduction of energy intake during prolonged sitting(30). Other potential factors specific to low muscle activity playing role in the metabolic response to prolonged sitting may involve greater circulating levels of counterregulatory hormones (e.g. glucagon, epinephrine, cortisol) or hemodynamic changes (decreased muscle blood flow) and capillary recruitment(30). Animal studies have suggested that loss of muscle contractions induced through prolonged sitting has been shown to suppress lipoprotein lipase activity which has served as the

prototype for insights about how exercise and physical inactivity may impact disease outcomes(33). On the other hand, PA increases skeletal muscle glucose uptake even independent of insulin(3). Furthermore, adjustments particularly with BMI weakened the associations between physical inactivity and glucose metabolism, indicating that these factors are interrelated. Independent effects of PA on glucose metabolism have previously been reported from our(34) and also other cohort studies(34–36, 37). In summary, complex mechanisms are likely responsible for reduced insulin action as a result of physically inactive lifestyle.

Limitations

PA was assessed using questionnaires prone to several challenges, inherent to subjective methodologies, which may hamper detection of existing associations. In our study, the questionnaire was unable to gather all dimensions of PA and lack of data on e.g. PA during school/working hours may have led to underestimation of total PA and might have diluted the observed associations of PA with glucose metabolism. On the other hand standardized questionnaires enabled unique 31-year follow up. In this study setting, we could not take into account sedentary behavior as one form of physically inactive lifestyle and the possible confounding effect of pubertal maturation on glucose metabolism was not explored. As another limitation we used fasting plasma glucose as one component to determine impaired glucose metabolism, although oral glucose tolerance test would be a more sensitive marker of peripheral insulin resistance(39). However, the study design is unique extending from childhood to adulthood over 30 years with repeated PA data from an extremely well characterized cohort of 2773 participants. As an additional strength of the study we also had access to the national

registry data on type 2 diabetes diagnosis to complement the plasma glucose measurements and medication data.

Summary and conclusion

Physical inactivity during the transition between childhood and adulthood is associated with higher risk of impaired glucose metabolism. Moreover, a decrease in PA from youth to adulthood poses a similar risk of impaired glucose metabolism than having persistently low PA. Most importantly, those who became increasingly active had a greatly reduced risk. The results highlight the importance of avoiding physically inactive lifestyle at all stages of life.

Acknowledgments

The authors thank Noora Kartiosuo and Irina Lisinen from the Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, for statistical advice with these data.

Funding. The Cardiovascular Risk in Young Finns Study was financially supported by the Suomen Akatemia (Academy of Finland) (grants 286284 [to T.L.]; 134309 [Eye]; 126925, 121584, 124282, and 129378 [Salve]; 117787 [Gendi]; 41071 [Skidi]; 275595 [to K.P.]); Social Insurance Institution of Finland; Kuopio, Tampere, and Turku University Hospital Medical Funds (grant X51001 to T.L.); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research; Finnish Cultural Foundation; Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; and Yrjö Jahnsson Foundation. This work was also partly funded by the National Heart Foundation of Australia Future Leader Fellowship (grant 100849 to C.G.M.) and the National Health and Medical Research Council Project (grant APP1098369).

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., M.H. and R.T. 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. V.M. contributed to the critical revision of the manuscript for important intellectual content. C.G.M. contributed to the study design and critical revision of the manuscript for important intellectual content. S.R., H.H. 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 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. The authors also acknowledge that the present study does not constitute endorsement by the American College of Sports Medicine.

Conflict of Interest

The authors declare that they have no competing interests. There are no conflict of interests to disclose for any of the authors.

REFERENCES

1. Diabetes DOF. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013 Jan;36 Suppl 1:S67-74.
2. IDF. *DIABETES ATLAS 7th Edition*. 2015.
3. Shepherd PR, Kahn BB. Glucose Transporters and Insulin Action — Implications for Insulin Resistance and Diabetes Mellitus. *N Engl J Med*. 1999;341:248–57.
4. Gill JMR, Malkova D. Physical activity, fitness and cardiovascular disease risk in adults: interactions with insulin resistance and obesity. *Clin Sci*. 2006;110(4):409–25.
5. Manson JE, Stampfer MJ, Colditz GA, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet*. 1991 Sep;338(8770):774–8.
6. Helmrach SP, Ragland DR, Leung RW, Paffenbarger RS. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1991 Jul 18;325(3):147–52.
7. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997 Apr;20(4):537–44.
8. Waller K, Kaprio J, Lehtovirta M, Silventoinen K, Koskenvuo M, Kujala UM. Leisure-time physical activity and type 2 diabetes during a 28 year follow-up in twins. *Diabetologia*. 2010;53(12):2531–7.
9. Laaksonen DE, Lindstrom J, Lakka TA, et al. Physical Activity in the Prevention of Type 2 Diabetes: The Finnish Diabetes Prevention Study. *Diabetes*. 2004 Dec 22;54(1):158–65.
10. Raitakari OT, Juonala M, Rönnemaa T, et al. Cohort profile: The cardiovascular risk in young Finns study. *Int J Epidemiol*. 2008;37(6):1220–6.

11. Kari JT, Pehkonen J, Hirvensalo M, et al. Income and Physical Activity among Adults: Evidence from Self-Reported and Pedometer-Based Physical Activity Measurements. *PLoS One*. 2015 Jan;10(8):e0135651.
12. WHO. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia. *Who2*. 2006;50.
13. Telama R, Yang X, Viikari J, Välimäki I, Wanne O, Raitakari O. Physical activity from childhood to adulthood: a 21-year tracking study. *Am J Prev Med*. 2005 Apr;28(3):267–73.
14. Telama R, Yang X, Leskinen E, et al. Tracking of physical activity from early childhood through youth into adulthood. *Med Sci Sports Exerc*. 2014;46(5):955–62.
15. Sabin MA, Burgner D, Atkinson RL, et al. Longitudinal investigation of adenovirus 36 seropositivity and human obesity: the Cardiovascular Risk in Young Finns Study. *Int J Obes (Lond)*. 2015;(February):1644–50.
16. Vinet L, Zhedanov A. A “missing” family of classical orthogonal polynomials. *J Phys A Math Theor*. 2011 Feb 25;44(8):85201.
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985 Jul;28(7):412–9.
18. Nuotio J, Oikonen M, Magnussen CG, et al. Cardiovascular risk factors in 2011 and secular trends since 2007: The Cardiovascular Risk in Young Finns Study. *Scand J Public Health*. 2014;(June):563–71.
19. Welham S, Cullis B, Kenward M, Thompson R. The Analysis of Longitudinal Data Using Mixed Model L-Splines. *Biometrics*. 2006;62(2):392–401.

20. Lai C-C, Sun D CR et al. Impact of Long-Term Burden of Excessive Adiposity and Elevated Blood Pressure From Childhood on Adulthood Left Ventricular Remodeling Patterns: The Bogalusa Heart Study. *J Am Coll Cardiol.* 2014;64(15):1580–7.
21. Paalanen L, Männistö S, Virtanen MJ, et al. Validity of a food frequency questionnaire varied by age and body mass index. *J Clin Epidemiol.* 2006 Sep;59(9):994–1001.
22. Finnish Food composition Database. 7. 2007. Helsinki, Finland: The National Public Health Institute NU. Fineli. 2007.
23. Nettleton JA, Hivert MF, Lemaitre RN, et al. Meta-analysis investigating associations between healthy diet and fasting glucose and insulin levels and modification by loci associated with glucose homeostasis in data from 15 cohorts. *Am J Epidemiol.* 2013;177(2):103–15.
24. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol.* 2012;2(2):1143–211.
25. Dunstan DW, Howard B, Healy GN, Owen N. Too much sitting - A health hazard. *Diabetes Res Clin Pract.* 2012;97(3):368–76.
26. Healy GN, Dunstan DW, Salmon J, et al. Objectively Measured Light-Intensity Associated With 2-h Plasma Glucose. *Diabetes Care.* 2007;30:1384–9.
27. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of Type 2 Diabetes Mellitus By Changes in Lifestyle Among Subjects With Impaired Glucose Tolerance. *N Engl J Med.* 2001;344(18):1343–50.
28. Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ Br Med J.* 2007;334(7588):299.

29. Krogh-Madsen R, Thyfault JP, Broholm C, et al. A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity. *J Appl Physiol*. 2010;108(5):1034–40.
30. Stephens BR, Granados K, Zderic TW, Hamilton MT, Braun B. Effects of 1 day of inactivity on insulin action in healthy men and women: Interaction with energy intake. *Metabolism*. 2011;60(7):941–9.
31. Lee I-M, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical Activity and Coronary Heart Disease in Women. *JAMA*. 2001 Mar 21;285(11):1447.
32. Ng B, Haddad E, Gp K, Ga W, Rj S. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: A meta-analysis of controlled clinical trials. *Jama*. 2001;286(10):1218–27.
33. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes*. 2007;56(November):2655–67.
34. Mansikkaniemi K, Juonala M, Taimela S, et al. Cross-sectional associations between physical activity and selected coronary heart disease risk factors in young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med* 2012 Nov;44(7):733–44.
35. Rizzo NS, Ruiz JR, Oja L, Veidebaum T, Sjöström M. Associations between physical activity, body fat, and insulin resistance (homeostasis model assessment) in adolescents: the European Youth Heart Study. *Am J Clin Nutr*. 2008 Mar;87(3):586–92.
36. Jeon CY, Lokken RP, Hu FB, Van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: A systematic review. Vol. 30, *Diabetes Care*. American Diabetes Association; 2007. p. 744–52.
37. Kavouras SA, Panagiotakos DB, Pitsavos C, et al. Physical activity, obesity status, and

- glycemic control: The ATTICA study. *Med Sci Sports Exerc.* 2007;39(4):606–11.
38. Pahkala K, Heinonen OJ, Simell O, et al. Association of physical activity with vascular endothelial function and intima-media thickness. *Circulation.* 2011 Nov 1;124(18):1956–63.
39. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: Implications for care. *Diabetes Care.* 2007;30(3):753–9.

ACCEPTED

Supplemental digital content:

SDC, Table 1.doc

SDC, Table 2.doc

SDC, Table 3.doc

SDC, Table 4.doc

SDC, Table 5.doc

Figure legends:

Figure 1. Age and sex standardized mean physical activity index (PA index) in individuals with impaired glucose metabolism (IGM) and unaffected peers during the 31-year follow-up. Participants with IGM had significantly lower PA index compared to unaffected peers ($B=0.26$, $SE\ 0.08$, $p=0.001$). Continuous line indicates those who have IGM and dotted line those without IGM.

Figure 1

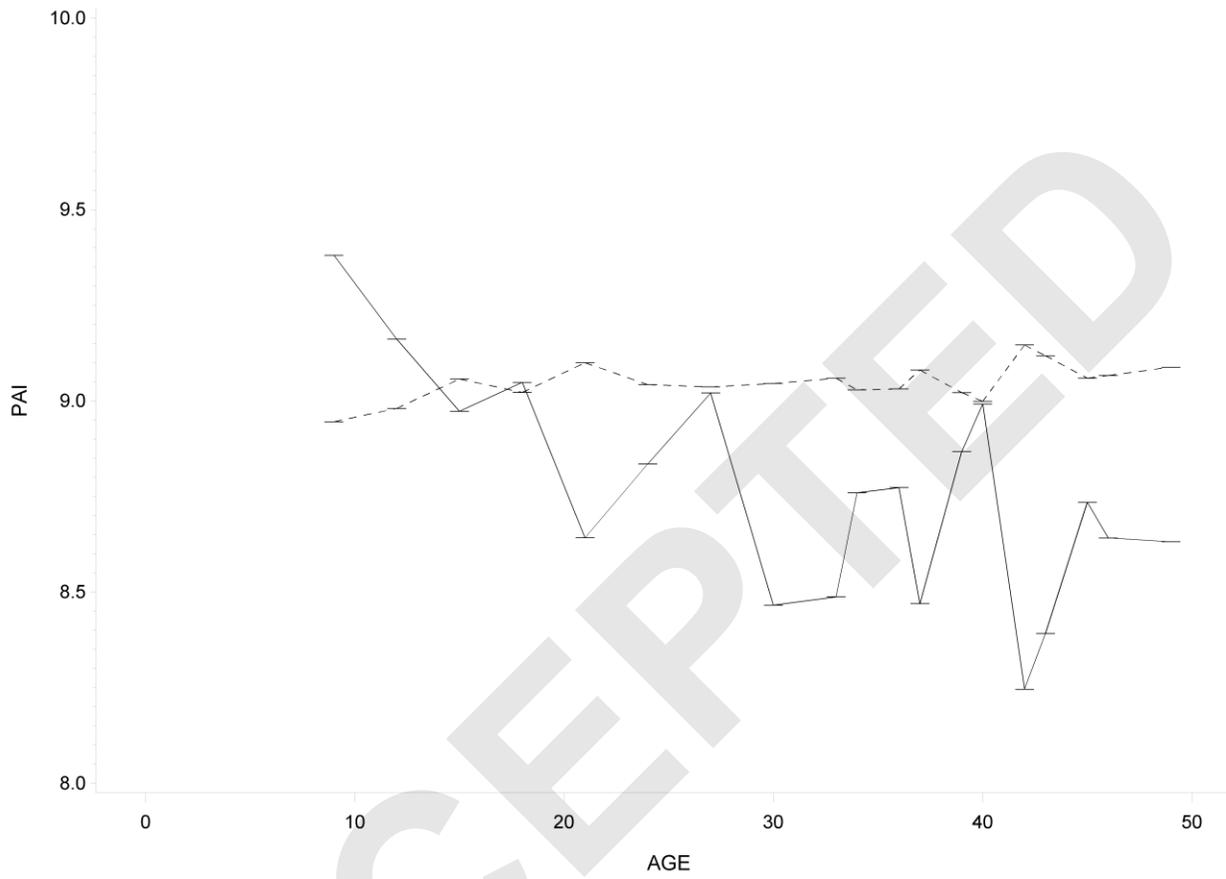


Table 1. Characteristics of the study participants in adulthood (age 24 – 49 years) according to the impaired glucose metabolism status. The data are obtained at the time the latest glucose value was measured.

		<i>IGM(WHO)+</i>	<i>IGM(WHO)-</i>	<i>p-value</i>
IGM, n (%)		310 (11)	2416 (89)	
Sex, n (%)	Men	196 (15.4)	1077 (84.6)	
	Women	114 (7.9)	1339 (92.1)	
BMI, kg/m ² ; mean (SD)	+ = 308	30.5 (6.2)	25.8 (4.6)	<.0001
	- = 2394			
BMI >30 kg/m ² ; n (%)	+ = 308	144 (46.8)	383 (16.0)	<.0001
	- = 2394			
Waist, cm; mean (SD)	+ = 308	103.1 (15.4)	89.0 (13.3)	<.0001
	- = 2400			
SBP, mmHg; mean (SD)	+ = 307	126.7 (14.8)	118.7 (13.9)	<.0001
	- = 2390			
PA index (range 5 – 15); mean (SD)	+ = 269	8.6 (1.8)	9.2 (2.0)	0.0004
	- = 2214			
Diet score (range 0 – 27); mean (SD)	+ = 207	13.2 (4.3)	13.7 (4.0)	0.88
	- = 1739			
Smoker; n (%)	+ = 255	49 (19.2)	247 (14.5)	0.07
	- = 1709			
SES (range 1 -3); mean (SD)	+ = 220	2.1 (0.8)	2.2 (0.7)	0.03
	- = 1549			
Total chol, mmol/l; mean (SD)	+ = 310	5.3 (1.0)	5.1 (0.9)	0.77

	- = 2416			
LDL-chol, mmol/l (SD)	+ = 296	3.3 (0.9)	3.2 (0.8)	0.39
	- = 2372			
Glucose, mmol/l (SD)	+ = 310	6.5 (1.5)	5.2 (0.4)	<.0001
	- = 2416			
Insulin, mU/l (SD)	+ = 308	18.9 (21.8)	8.3 (7.9)	<.0001
	- = 2410			
HOMA-IR, (insulin x glucose)/22.5 (SD)	+ = 308	6.2 (13.5)	1.9 (1.8)	<.0001
	- = 2410			

IGM = Impaired glucose metabolism; IGM(WHO) + = Participants with IGM; IGM(WHO) - = Participants without IGM; BMI = Body Mass Index; SD = Standard Deviation; SBP = Systolic Blood Pressure; PAI = Physical Activity Index; SES = Socioeconomic status; Chol = Cholesterol; LDL-chol = Low-Density Lipoprotein cholesterol; HOMA-IR = Homeostasis model assessment of insulin resistance model.

Table 2: Risk of impaired glucose metabolism across physical activity groups.

Persistently low PA: participants in the lowest quartile both during youth and adulthood (n=244); Decreasingly active: participants in the three highest quartiles in youth, but in the lowest quartile in adulthood (n=321); Increasingly active: participants in the lowest quartile in youth, but in the three highest quartiles in adulthood (n=328); and Persistently active: participants in the three highest quartiles both in youth and adulthood (n=1107).

		Model				
		1 (n=1985)	2 (n=1651)	3 (n=1402)	4 (n=1353)	5 (n=1233)
<i>Persistently low PA</i>	RR	Ref	Ref	Ref	Ref	Ref
	CI 95%					
Decreasingly active	RR	0.93	0.89	0.83	0.80	0.80
	CI 95%	0.63 – 1.36	0.57 – 1.39	0.52 – 1.32	0.50 – 1.29	0.51 – 1.20
Increasingly active	RR	0.47	0.36	0.44	0.45	0.44
	CI 95%	0.29 – 0.76	0.20 – 0.65	0.24 – 0.80	0.24 – 0.83	0.22 – 0.88
Persistently active	RR	0.70	0.67	0.74	0.72	0.78
	CI 95%	0.51 – 0.97	0.46 – 0.99	0.50 – 1.11	0.48 – 1.08	0.51 – 1.20

Adjusted variables in the models (**data from the last available follow-up has been used; years 2001, 2007 or 2011**): 1=Age and sex, 2=Age, sex and diet, 3=Age, sex, diet and BMI, 4=Age, sex, diet, BMI and smoking, 5=Age, sex, diet, BMI, smoking and SES.

Supplemental Table S1. Risk of impaired glucose metabolism across four physical activity groups.

<i>Model</i>	<i>5a</i> (<i>n</i> =1235)	<i>5b</i> (<i>n</i> =1342)
<i>RR</i>	Ref	Ref
<i>CI 95%</i>		
<i>RR</i>	0.77	0.84
<i>CI 95%</i>	0.46 – 1.27	0.52 – 1.36
<i>RR</i>	0.42	0.44
<i>CI 95%</i>	0.21 – 0.84	0.23 – 83
<i>RR</i>	0.75	0.77
<i>CI 95%</i>	0.50 – 1.15	0.51 – 1.16

Adjusted variables in the models: 5a= Age, sex, diet, waist, smoking and SES, 5b= 5= Age, sex, diet, BMI, smoking and education

Supplemental table S2: Risk of impaired glucose metabolism across four physical activity groups.

	Model				
	1 (n=533)	2 (n=434)	3 (n=371)	4 (n=355)	5 (n=328)
<i>Persistently low PA</i>	RR	Ref	Ref	Ref	Ref
	CI 95%				
Prominent decrease	RR	0.78	0.64	0.62	0.43
	CI 95%	0.32 – 1.91	0.20 – 2.05	0.20 – 1.96	0.10 – 1.81
Prominent increase	RR	0.12	0.15	0.23	0.22
	CI 95%	0.17 – 0.85	0.02 – 1.09	0.03 – 1.67	0.03 – 1.66
Persistently high active	RR	0.59	0.59	0.67	0.66
	CI 95%	0.35 – 0.98	0.33 – 1.06	0.36 – 1.24	0.34 – 1.29

Adjusted variables in the models: 1=Age and sex, 2=Age, sex and diet, 3= Age, sex, diet and BMI, 4=Age, sex, diet, BMI and smoking, 5= Age, sex, diet, BMI, smoking and SES.

Supplemental table S3: Risk of impaired glucose metabolism across four physical activity groups.

Persistently low PA: participants in the lowest quartile both during youth and adulthood (n=244);

Decreasingly active: participants in the three highest quartiles in youth, but in the lowest quartile in adulthood (n=321);

Increasingly active: participants in the lowest quartile in youth, but in the three highest quartiles in adulthood (n=328);

and Persistently active: participants in the three highest quartiles both in youth and adulthood (n=1107).

		Model				
		1	2	3	4	5
		(n=1691)	(n=1397)	(n=1391)	(n=1342)	(n=1224)
<i>Persistently low PA</i>	RR	Ref	Ref	Ref	Ref	Ref
	CI 95%					
Decreasingly active	RR	0.91	0.80	0.80	0.67	0.64
	CI 95%	0.60 – 1.36	0.51 – 1.25	0.50 – 1.30	0.40 – 1.11	0.37 – 1.11
Increasingly active	RR	0.54	0.36	0.43	0.42	0.44
	CI 95%	0.32 – 0.89	0.20 – 0.66	0.24 – 0.79	0.23 – 0.77	0.22 – 0.86
Persistently active	RR	0.76	0.65	0.73	0.73	0.80
	CI 95%	0.54 – 1.09	0.44 – 0.96	0.49 – 1.09	0.48 – 1.09	0.52 – 1.23

Adjusted variables in the models (data from the last available follow-up has been used; years 2001, 2007 or 2011): 1=Age, sex and insulin 2=Age, sex, insulin and diet, 3=Age, sex, insulin, diet and BMI, 4=Age, sex, insulin, diet, BMI and smoking, 5=Age, sex, insulin, diet, BMI, smoking and SES.

Supplemental table S4: Risk of impaired glucose metabolism across four physical activity groups.

Persistently low PA: participants in the lowest quartile both during youth and adulthood (n=244);

Decreasingly active: participants in the three highest quartiles in youth, but in the lowest quartile in adulthood (n=321);

Increasingly active: participants in the lowest quartile in youth, but in the three highest quartiles in adulthood (n=328);

and Persistently active: participants in the three highest quartiles both in youth and adulthood (n=1107).

		Model				
		1	2	3	4	5
		(n=1691)	(n=1397)	(n=1391)	(n=1342)	(n=1224)
<i>Persistently low PA</i>	RR	Ref	Ref	Ref	Ref	Ref
	CI 95%					
Decreasingly active	RR	0.91	0.73	0.74	0.64	0.61
	CI 95%	0.61 – 1.37	0.46 – 1.16	0.45 – 1.20	0.38 – 1.08	0.34 – 1.09
Increasingly active	RR	0.53	0.36	0.41	0.41	0.44
	CI 95%	0.32 – 0.87	0.20 – 0.64	0.23 – 0.75	0.22 – 0.75	0.22 – 0.87
Persistently active	RR	0.75	0.65	0.73	0.73	0.80
	CI 95%	0.53 – 1.07	0.44 – 0.95	0.49 – 1.09	0.49 – 1.09	0.52 – 1.22

Adjusted variables in the models (data from the last available follow up has been used; years 2001, 2007 or 2011): 1=Age, sex and HOMA-IR 2=Age, sex, HOMA-IR and diet, 3=Age, sex, HOMA-IR, diet and BMI, 4=Age, sex, HOMA-IR, diet, BMI and smoking, 5=Age, sex, HOMA-IR, diet, BMI, smoking and SES.

Supplemental table S5: Risk of impaired glucose metabolism across physical activity groups.

Persistently low PA: participants in the lowest quartile both during youth and adulthood (n=244);

Decreasingly active: participants in the three highest quartiles in youth, but in the lowest quartile

in adulthood (n=321); Increasingly active: participants in the lowest quartile in youth, but in the

three highest quartiles in adulthood (n=328); and Persistently active: participants in the three

highest quartiles both in youth and adulthood (n=1107).

		Model				
		1 (n=1985)	2 (n=1651)	3 (n=1402)	4 (n=1353)	5 (n=1233)
<i>Persistently low PA</i>	RR	Ref	Ref	Ref	Ref	Ref
	CI 95%					
Decreasingly active	RR	0.84	0.81	0.89	0.88	0.89
	CI 95%	0.57 – 1.22	0.52 – 1.27	0.57 – 1.41	0.55 – 1.40	0.54 – 1.47
Increasingly active	RR	0.46	0.36	0.44	0.46	0.47
	CI 95%	0.28 – 0.74	0.20 – 0.65	0.24 – 0.79	0.25 – 0.83	0.23 – 0.93
Persistently active	RR	0.67	0.66	0.77	0.76	0.83
	CI 95%	0.49 – 0.93	0.45 – 0.96	0.52 – 1.14	0.51 – 1.13	0.55 – 1.26

Adjusted variables in the models (data from the last available follow up has been used; years

2001, 2007 or 2011), BMI (AUC) between ages 12 and 18 years: 1=Age and sex, BMI (AUC)

12-18, 2=Age, sex, BMI (AUC) 12-18 and diet, 3=Age, sex, BMI (AUC) 12-18, diet and BMI,

4=Age, sex, BMI (AUC) 12-18, diet, BMI and smoking, 5=Age, sex, BMI (AUC) 12-18, diet,

BMI, smoking and SES.