Does adiposity mediate the relationship between physical activity and biological risk factors in youth? – A cross-sectional study from the International Children's Accelerometry Database (ICAD)

Jakob Tarp¹, Anna Bugge¹, Lars Bo Andersen^{2,3}, Luis B. Sardinha⁴, Ulf Ekelund^{3,5}, Søren Brage⁵, Niels Christian Møller¹ On behalf of the International Children's Accelerometry Database (ICAD) Collaborators

¹Research Unit for Exercise Epidemiology, Centre of Research in Childhood Health, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

²Department of Teacher Education and Sport, Western Norway University of Applied Sciences, Sogndal, Norway

³Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway

⁴Exercise and Health Laboratory, CIPER, Faculdade de Motricidade Humana, Universidade de Lisboa, Cruz-Quebrada, Portugal

⁵Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK

Abstract

Background/Objectives—To model the association between accumulating sixty daily minutes of moderate-to-vigorous physical activity and a composite score of biological risk factors into a direct and an indirect effect, using abdominal obesity as the mediator.

Subjects/Methods—Cross-sectional data from the International Children's Accelerometry Database (ICAD) including six to eighteen years old children and adolescents (N=3412) from four countries providing at least three days of accelerometry-assessed physical activity. A standardized

Corresponding Author: Jakob Tarp, Address: University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark, Phone: + 4565504854, jtarp@health.sdu.dk.

Author contributions

J.T. conceived the study, performed the analysis, lead the analysis and writing of the manuscript. A.B. conceived the study, analyzed the data, and critically revised the manuscript. N.C.M. conceived the study, analyzed the data, critically revised the manuscript, and is an ICAD Collaborator. L.B.A. conceived the study, analyzed the data, critically revised the manuscript, and is an ICAD Collaborator. L.B.S. analyzed the data, critically revised the manuscript, and is an ICAD Collaborator. U.E. analyzed the data, critically revised the manuscript, and is an ICAD Collaborator. S.B. analyzed the data and critically revised the manuscript. All authors approved the final version of the manuscript. JT is the guarantor of this work

Availability of Data and Materials

Data from ICAD is available per request as a supported access resource. Analysed data is de-identified from the main ICAD database, available only for the approved analyses, and cannot be shared by the authors. Analyses included in this manuscript can be reproduced by requesting a new data release.

Conflict of interest

The authors declare no conflict of interest.

composite risk score was calculated from systolic blood pressure and fasting blood samples of insulin, glucose, triacylglycerol and inverse HDL-cholesterol. Abdominal obesity was assessed by the waist-circumference:height ratio. Two-stage regression analysis, allowing for exposure-mediator interaction, was used for the effect decomposition.

Results—Participants achieving sixty daily minutes of moderate-to-vigorous physical activity had a 0.31 (95% CI: -0.39, -0.23) standard deviations lower composite risk score than those achieving less than sixty minutes. Modelling the associations suggested that 0.24 standard deviations (95% CI: -0.32, -0.16) was attributed to the direct effect and -0.07 (95% CI: -0.11, -0.02) to the indirect effect indicating that 22 % of the total effect was mediated by central adiposity. Modelling thirty and ninety minutes of moderate-to-vigorous physical activity per day resulted in changes in the direct but not the indirect effect.

Conclusions—One hour of daily moderate-to-vigorous physical activity was associated with clinically relevant differences in metabolic control compared to engagement in less than this minimally recommended amount. The majority of the difference was explained by the direct effect of physical activity.

Keywords

Adolescents; cardiovascular disease risk; children; epidemiology; objective monitoring; mediation analysis

Introduction

Available evidence from prospective cohort studies suggests that higher levels of physical activity are, in a dose-response manner, protective against all-cause mortality¹ and incident cardiovascular disease (CVD) and type 2 diabetes². Similarly, in children and adolescents, physical activity is inversely associated with the biological risk factors (blood pressure, triacylglycerol, HDL-cholesterol and glycaemic control) comprised in the metabolic syndrome³ which strongly predicts CVD, type 2 diabetes and mortality in adults⁴.

Excess adipose tissue accumulation is one of the cornerstones in the aetiology of metabolic dysfunction⁴ and elevated BMI in youth has been shown to predict incident type 2 diabetes, the metabolic syndrome and advanced atherosclerosis in young adulthood similarly to elevated levels of three or more of the biological risk factors⁵. However, the risk of type 2 diabetes and CVD in young adulthood also appears to increase with advanced “clustering” of the risk factors in youth irrespective of the combination of its constituent parts^{5, 6}. Further, a recent meta-analysis suggested that 46 and 76 % of the effect of BMI on coronary heart disease and stroke, respectively, was mediated through blood pressure, cholesterol and glucose levels highlighting the importance of maintaining metabolic homeostasis⁷. Thus, identifying modifiable factors which can target biological risk factors in youth is relevant for primordial prevention of disease and for tailoring interventions for high-risk individuals.

Physical activity influences twenty-four hour (h) blood pressure⁸ and modest amounts of activity may improve glucose and lipid metabolism compared to an uninterrupted prolonged sedentary state⁹. Since physical activity is the largest modifiable component of total energy expenditure, it plays an important role in energy balance and hence weight gain which

occurs naturally during growth; indeed some, but not all, studies have suggested objectively measured moderate-to-vigorous physical activity (MVPA) is prospectively associated with accumulation of less adipose tissue in youth^{10–13}. Thus, benefits from physical activity may originate from at least two sources and previous studies in youth supports an independent protective effect on the risk factors^{14–17}. However, the relative contributions of these consequences of physical activity are not fully understood and previous studies have not described the associations in detail. We have previously reported a direct effect of MVPA on individual risk factors¹⁶ and now extend this work by 1) formally quantifying the indirect component, i.e. the effect on the risk factors attributed to the association between physical activity and adiposity, 2) allowing for potential exposure-mediator interaction, and 3) using a composite score of biological risk factors to maximize information on metabolic dysfunction¹⁴.

Methods

Study Design and Participants

This study is based on secondary data from the International Children's Accelerometer Database (ICAD), an international pooling of data from twenty studies in which accelerometry was used to assess physical activity in children three to eighteen years of age. The project has been detailed elsewhere¹⁸. All accelerometry data included in ICAD were centrally cleaned, reprocessed and harmonized. For these analyses, eligible studies (Copenhagen School Child Intervention Study (CoSCIS), National Health and Nutrition Examination Survey (NHANES) 03/04 and 05/06, and European Youth Heart Study (EYHS) Portugal, Estonia and Denmark) all provided data on fasting insulin, glucose, triacylglycerol, HDL-cholesterol and systolic blood pressure^{19–21}. From these studies, 8799 youth aged six to eighteen years provided a reliable accelerometer file (146 files were invalid). Of these, 4231 individuals accumulated at least three days of valid data, a fasting blood sample (no blood was drawn from children under the age of twelve in NHANES, excluding 1897) and a measure of waist-circumference. A further 819 participants were excluded due to missing data on covariates leaving 3412 participants (38 % of participants available from these studies in ICAD) for the present analysis. The analysed sample was older, accumulated two more minutes of daily MVPA, and had more favourable biological risk factor profiles as compared to non-analysed individuals. A comparison of characteristics is available in Supplementary Table 1. Descriptive characteristics of included participants stratified by study are shown in Table 1.

Exposure

Raw accelerometry files were reprocessed using commercially available software (KineSoft v3.3.20, Loughborough, UK). All files were analysed using a sixty-second epoch and non-wear was defined as sixty minutes (min) of consecutive zeroes, allowing for up to two min of non-zero interruptions¹⁸. Participants were included if they had a minimum of three days of 500 min of wear time in the h 07.00 to 24.00. In those studies in which physical activity was measured more than once, we used the first measurement only. We defined MVPA as 2296 counts/min as this cut-point has shown a classification specificity and sensitivity for four metabolic equivalents of 88 and 92 %, respectively, against indirect calorimetry in a

validation study of five to fifteen years old youth²². This cut-point is equivalent to the acceleration of the hip/waist during brisk walking, so would not include slow walking. MVPA was averaged across valid days.

Outcome

The main outcome was a standardized continuous risk score¹⁴ comprised of the aforementioned biological risk factors (using HOMA-IR as measure of glycaemic control calculated as; $(\text{insulin} \times \text{glucose})/22.5$) and created by standardizing each risk factor for age and sex in a linear regression analysis with the standardized residuals representing z-scores with a mean of 0 and a standard deviation (SD) of 1. HDL-cholesterol was multiplied by -1 prior to standardization. The residuals were subsequently averaged and the score standardized. In this composite score, a lower score represents a more favourable risk profile. Body height was added to the standardization of systolic blood pressure. Standardization was done for the complete analytical sample. Individual risk factors are presented as secondary outcomes.

Mediator

Waist-circumference:height ratio was used as a marker of abdominal obesity. Waist-circumference was measured midway between the lower rib margin and the iliac crest in the EYHS and CoSCIS studies and just above the iliac crest at the midaxillary line in the NHANES. A previous study found the mean differences between these measurement sites to be: 0.8 cm in six to eleven years old boys, 1.3 cm in six to eleven years old girls, 1.5 cm in twelve to nineteen years old boys and twelve to nineteen years old girls²³. A priori selected putative confounders of the exposure-outcome, exposure-mediator or mediator-outcome relations, which were available from ICAD, were used as covariates; these included age, sex, ethnicity (White or not), birthweight (continuous), mother's BMI (continuous), sexual maturity (Tanner stages) and mothers education (high/medium/low) from EYHS studies. Available from NHANES was age, sex, ethnicity (White, Black, Asian, and Hispanic) and household income (quartiles). Age and sex was available from CoSCIS.

Mediation analysis (effect decomposition)

We used a two-stage regression approach to decompose the total effect on the respective outcome into a direct effect and an indirect effect thereby providing a quantitative estimate of the relative importance of these. An important aspect when conducting mediation analysis is to consider possible interactions between the exposure and the putative mediator^{24, 25}. Allowing for potential interaction, if such is present, provides not only correct effect decomposition, but determining the presence of exposure-mediator interaction is of importance in understanding aetiology with potential practical relevance for tailoring interventions. Mediation analysis allowing for exposure-mediator interaction has been defined within the counterfactual framework^{26–28}. For these effects to be identified in the presence of exposure-mediator interaction it is necessary to estimate the change from one fixed level of exposure to another (exact definitions given below). We therefore dichotomized mean MVPA/day for adherence to the WHO physical activity recommendation for five to seventeen years old youth of at least sixty min of MVPA/day (yes/no). Using the two-stage regression approach we first fit (Model 1) a linear regression

model for the outcome (Y) on achieving the respective activity exposure (a) controlling for waist-circumference:height ratio (mediator (m)), including a physical activity x waist-circumference:height ratio interaction term and controlling for confounding variables (c). Secondly, a linear regression model (Model 2) for the waist-circumference:height ratio on the respective activity exposure controlling for confounding variables is fitted.

$$E[Y|a, m, c] = \beta_0 + \beta_1 a + \beta_2 m + \beta_3 am + \beta_i c_i \quad 1)$$

$$E[M|a, c] = \theta_0 + \theta_1 a + \theta_i c_i \quad 2)$$

The coefficients from these regressions are then used to estimate the average direct and indirect effects in the population²⁸. As the focus of this analysis is to decompose the putative sources of the total association we estimate the natural direct and indirect effects^{27, 28}. Using the counterfactual framework, the direct effect can be interpreted as the contrast between achieving the activity target and not achieving the activity target, while for each individual fixing the mediator to the level it would have assumed if the activity target had not been achieved. In other words, the direct effect estimates the effect of the activity target on the composite risk score not acting through abdominal obesity. Similarly, the indirect effect can be interpreted as the contrast between fixing the mediator to the level it would have assumed had the activity target been achieved versus the level it would have assumed had the activity target not been achieved, while setting the activity target to not achieved. That is, the indirect effect is the effect of the activity target acting on the composite risk score by the activity target influencing abdominal obesity which, in turns, affects the composite risk score.

Statistical Analysis

Descriptive data are summarized as means with SD or medians with 25th and 75th percentiles dependent on distributional properties. All models were checked for normality and homoscedacity of residuals and inspected for a linear association between continuous dependent and independent variables. HOMA-IR, triacylglycerol and waist-circumference:height ratio were transformed by the natural logarithm prior to estimations. When using logarithmically transformed variables as outcomes these were multiplied by 100 so they can be interpreted as a difference in percentage²⁹. Results are presented as difference (standardized betas or percentage) in composite risk score, or individual risk factors, with 95% CI. The primary activity contrast was above or below 60 min of MPVA/day. To assess a possible graded association we further compared the following MVPA contrasts; 1) <30 versus 30 min, 2) < 30 versus 60 min, 3) <30 versus 90 min, and 4) <90 versus 90 min. Total, direct and indirect effects were estimated separately for each study and were subsequently pooled by weighting the estimates (meta-analysis). A bootstrap procedure using 1000 repetitions, with replacement, was used to derive the study specific 95% bias-corrected confidence intervals for the indirect effect as the 2.5th and the 97.5th percentiles. In meta-analysis the study weights are usually defined as $1 / (\text{standard error}^2)$.

Because the standard errors in this application are derived from a bootstrap procedure (in contrast to $SD/\sqrt{N}$), the standard errors of the total, direct and indirect effects will not necessarily be identical if using $1 / (\text{standard error}^2)$ as weights. This would result in failure of the decomposition to sum to the total effect in the meta-analysis, which is counterintuitive. Therefore, study weights were given as $(\text{study sample size}) / (\text{total sample size})$. Specifying the weights as such precluded using a random-effects meta-analysis (see supplementary Table 2 for study weights). The consequence of using a fixed rather than a random effects approach is that relatively more weight will be given to larger studies. The Q-statistic and I^2 were used to assess between-study heterogeneity. The proportion of the total effect which can be attributed to the indirect effect was calculated as $(\text{indirect effect} / \text{total effect}) \times 100$. To assess the robustness of results for meeting the sixty min MVPA target we performed the analysis stratified by sex and conducted the following sensitivity analyses; 1) omitting, in turn, one study from the meta-analysis, 2) reanalyse all data only controlling for age and sex, 3) treating the two age groups in EYHS studies as individual studies, 4) converting CoSCIS and EYHS waist-circumference measurements to NHANES equivalents using previously published equations^{23 5)}, using BMI as mediator, 6) using an empirically derived waist-circumference to height exponent (allometric scaling), 7) including accelerometer wear-time as covariate, 8) including all participants with at least one valid day ($n=3792$), 9) defining a valid day as ≥ 600 min, 10) including season of physical activity assessment as a covariate to account for seasonal variation in physical activity, 11) defining MVPA as counts/min >1999 and, 12) estimated the size of a dichotomous vector of unmeasured or residual confounding (U) necessary to completely explain away the difference between the activity contrast. The latter analysis was performed assuming a 20 and 50 % difference in prevalence of U simulating moderate and substantial confounding, respectively. Analyses were conducted using the PARAMED and METAN modules in Stata IC v.14.1 (StataCorp, College Station, Texas, USA).

Results

The median number of valid participant days was four with 79 % of the sample achieving more than three days. Seven percent of the sample did not have data from a weekend day, while 73 % had data from two. Clinical characteristics and daily min of MVPA for the activity contrasts are shown in Table 2. Meeting the activity target of sixty min of MVPA/day, versus not meeting it, was associated with a -0.31 (-0.39, -0.23) SD lower composite risk score. This effect was composed of a direct effect of -0.24 (-0.32, -0.16) SD and an indirect effect of -0.07 (-0.11, -0.02) SD suggesting that 22 % of the effect was attributable to the mediator (Table 3). Tests of between-study heterogeneity were highly significant for total, direct and indirect effect (all p 's <0.01). The I^2 indicated that 78 to 91 % of the total variation was due to heterogeneity. Meeting the activity target of thirty min of MVPA/day, versus not meeting it, had a total effect on the risk score of -0.24 (-0.32, -0.16) SD, a direct effect of -0.17 (-0.25, -0.10) SD and an indirect effect of -0.07 (-0.10, -0.03) SD, i.e. 28 % of the total effect was attributable to the mediator. Similarly, meeting the ninety min of MVPA/day target versus not meeting the target resulted in a total effect on the risk score of -0.39 (-0.51, -0.27) SD, a direct effect of -0.33 (-0.44, -0.24) SD and an indirect effect of -0.06 (-0.13, 0.01) SD hence 15 % of the total effect was attributable to the mediator. The

confidence interval for the indirect effect included zero. When exploring the larger MVPA contrasts, results were similar with larger total effects explained primarily by larger direct effects.

We thereafter repeated the analyses using the individual risk factors as outcomes (Table 4), Meeting the activity target of sixty min of MVPA/day, versus not meeting it, resulted in a 15 % lower HOMA-IR score (-0.20, -0.10), a 1.9 mmHg lower systolic blood pressure (-2.64, -1.25), a 9 % lower triacylglycerol level (-0.12, -0.05), and a 0.05 mmol/l higher HDL-c level (0.02, 0.08). The percentage explained by the mediator varied from 12 to 31 %.

When stratifying by sex, results for boys were largely similar to the sex adjusted estimates with a total effect of meeting the PA target of sixty min of MVPA/day, versus not meeting it, on the risk score of -0.31 (-0.42, -0.21) SD, a direct effect of -0.22 (-0.32, -0.12) SD, and an indirect effect of -0.09 (-0.15, -0.04) SD. In girls, effects were smaller with a total effect of -0.19 (-0.37, -0.00) SD, a direct effect of -0.18 (-0.47, 0.11) SD and an indirect effect of 0.03 (-0.25, 0.32) SD. All effects in girls had confidence intervals overlapping zero. However in the NHANES studies very few girls (twenty four in total) achieved sixty min of MVPA/day resulting in imprecise estimates for these studies.

Removing the exposure-mediator interaction had little impact on estimates. The total effect with no interaction was -0.31 (-0.39, -0.23) SD, a direct effect of -0.24 (-0.31, -0.17) SD, and an indirect effect of -0.07 (0.11, -0.03) SD. None of our sensitivity analyses substantially changed results (Supplementary Figure 1-3). Excluding one study at a time resulted in little variation of the total effect (Supplementary Figure 1-3), but the composition changed substantially with estimates explained by the mediator varying from 15 to 35 %. To reduce our estimates of the direct effect to zero, the influence of U on the risk score would have to be -0.62 and -1.55 SD under the moderate and substantial confounding scenarios, respectively. For the indirect effect, the required influence of U was estimated as 0.34 and 0.14 SD under moderate and substantial confounding scenarios, respectively.

Discussion

The result of this effect decomposition model indicates that the majority of the association between meeting the sixty min MVPA/day target and metabolic control can be attributed to the direct effect of MVPA, rather than to an indirect effect by abdominal adiposity. The data demonstrated an inverse, graded relationship for the direct, although not the indirect effect.

A recent publication from the Cardiovascular Risk in Young Finns Study reported that a one SD increase in four different composite risk scores in youth predicted incident type 2 diabetes and advanced atherosclerosis between fifteen to twenty-five years later. The magnitude was substantial with an increased risk between 30 to 78 % for type 2 diabetes and 12 to 61 % for advanced atherosclerosis, depending on the definition of the composite score³⁰. Thus, our estimate of a 0.31 SD lower risk score for meeting, compared with not meeting, the sixty min MVPA target is clinically relevant. Further, meeting the sixty min MVPA target was associated with a 1.9 mmHg lower systolic blood pressure of which less than one fifth of the effect was through abdominal adiposity. Assuming such a difference is

maintained over time, estimated reductions in stroke and ischemic heart disease in middle age are likely not trivial 31.

The observed direct association between MVPA and the composite risk score not through abdominal adiposity was inverse and graded. In opposite, we found no indication of a graded relationship with the composite score for the association through abdominal adiposity when contrasting meeting versus not meeting the thirty, sixty and ninety min MVPA targets and in absolute terms the contribution of abdominal adiposity to the association was modest. This is not surprising given the unclear role of physical activity for the prevention of excess adipose tissue accumulation in youth^{12, 13}. Importantly, with increasing activity contrasts (below thirty min vs. above sixty and above ninety min) the absolute magnitude of the indirect effect increased, although not in relation to the total effect as indicated by the percent attributable to the indirect effect. This suggests that large activity contrasts are needed to reduce adipose tissue to a degree where this reduction may improve metabolic control whereas, in comparison, even meeting the thirty min MVPA target conferred a three times higher reduction in the composite score compared with those not meeting this amount of MVPA. Therefore, indices of adiposity may not be the most sensitive marker of improved metabolic control following a physical activity intervention. Further, increases in physical activity at the population level are likely to be important even if adiposity is not affected. We observed very little effect of allowing for the interaction between physical activity and abdominal adiposity and the interaction terms were not statistically significant (results not shown) indicating that the relationship between meeting these physical activity contrasts and abdominal adiposity is additive only. This observation may be interpreted as the effect of e.g. accumulating sixty min of daily MPVA on metabolic control is similar across levels of abdominal adiposity, potentially relevant for intervention studies in high-risk populations.

An effect of physical activity on metabolic control irrespective of weight loss is biologically plausible. Physical activity improves insulin sensitivity up to seventy-two h in adults³² and stimulates glucose uptake in the muscle through a non-insulin dependent impact on the GLUT4 protein allocation. Insulin resistance, together with abdominal obesity, may be the common factor behind hypertension, dyslipidaemia and chronic low grade inflammation⁴. An independent effect of physical activity on metabolic risk factors in youth is in concert with previous publications^{14–17, 33}. We extend these observations by formal effect decomposition modelling and allowing for interaction between physical activity and abdominal adiposity to describe the associations in more detail. Our results corroborate previous studies suggesting a direct effect of MVPA on metabolic control since these associations are usually only slightly attenuated following adjustment for adiposity indices in the model¹⁷. Plausibility of a direct effect is further supported by the following observations; 1) An improvement in metabolic control without concurrent loss of adipose tissue was reported in an uncontrolled study of twenty-one overweight girls after twelve weeks of aerobic training³⁴, 2) one-legged training studies demonstrate site-specific adaptations in glucose metabolism³⁵ which, by design, are independent of abdominal fat mass, and, 3) in adults, physical activity is associated with a reduced risk of mortality in all strata of adiposity³⁶. In a cross-sectional study in young Brazilian adults, Horta et al. (2015)³⁷ found that the indirect effect of MVPA through waist-circumference explained 44 % of the total effect of MVPA on arterial stiffness. Such a high indirect effect may be due

to differences in age in comparison with the present study or that arterial stiffness represents years of accumulated exposure, while the other biological risk factors respond more rapidly to recent changes in behaviour.

The present study should be interpreted in the light of several limitations. 1) The total effect and the effect decomposition is based on the assumptions of no residual or unmeasured exposure-outcome, exposure-mediator or mediator-outcome confounding as well as no mediator-outcome confounder affected by the exposure. In our analysis, we controlled for important biological variables such as birthweight and maturation as well as mothers BMI and markers of socioeconomic status and ethnicity in all but the CoSCIS study. Importantly, in models only adjusted for age and sex results were virtually unchanged. Further, when we, under simplistic assumptions, simulated an unmeasured confounder (e.g. diet, a genetic factor or smoking) the impact of such would have to be substantial to completely explain the total effect under the moderate confounding scenario, but only minor to explain the indirect effect under the substantial confounding scenario. However, the decomposition should be interpreted in the light of the lack of control of diet quality and quantity which could potentially confound all paths in the analysis. 2) The study is cross-sectional so we cannot infer direction of causality or even claim that adiposity is in fact a mediator as it could also be conceptualized as a confounder. Our position is that the fundamental laws of thermodynamics speak to a not purely confounding role, irrespective of the intrinsically complicated nature of weight management. Under the assumptions of our decomposition, the major constituent of the association was direct; suggesting physical activity positively influences metabolic control irrespective of either mediating or confounding from adiposity. However, it is conceivable that the association between physical activity and adiposity is bidirectional³⁸. To investigate this issue, we re-arranged the exposure-mediator order and modelled associations with being overweight/obese (according to IOTF age-and gender specific BMI cut-points as no international waist-circumference cut-points exists) versus not being so, using physical activity in its continuous form and allowing for exposure-mediator interaction. While being overweight/obese, as compared to not being so, was associated with a nearly one standard deviation higher composite risk score (total effect with 95% CI: 0.81 (0.72, 0.86)), the data suggests only 2 % of this association (indirect effect with 95% CI: 0.02 (0.002, 0.03)) is attributable to the association between being overweight/obese and lower physical activity levels. This lends support to our hypothesized pathway where it is physical activity which prevents excess body weight, but non-identical levels of measurement error in physical activity and adiposity assessment questions a direct comparison of the indirect effects. 3) We were unable to account for the sampling procedure in the NHANES studies or the composite data structure in EYHS and CoSCIS. The later tend to artificially deflate variance estimates. 4) We were unable to weight our meta-analytic estimates based on precision (standard error) and maintain meaningful effect decomposition. When we omitted one study at a time, the total effect was robust while the decomposition was more sensitive. However, the between study heterogeneity was substantial, the cause of which should be an area of further study. 5) Waist-circumference:height ratio is not a direct measure of abdominal adiposity, which may introduce measurement error in our mediator biasing our indirect effect towards the null³⁹. However, the correlation between waist-circumference and fat mass assessed by dual-energy X-ray absorptiometry in children is

high ($r > 0.88$) and associations with health outcomes are nearly identical between the two measures⁴⁰ giving us confidence in the use of waist-circumference as indicator of abdominal adiposity. 6) Accelerometry is an imperfect measure of physical activity which will have resulted in an underestimation of the total effect and may also have influenced the relative contributions of direct and indirect effects. Further, lack of consensus concerning measurement protocols and data-reduction decisions limits the ability to make direct comparisons between independent manuscripts. 7) Excess adipose tissue accumulation represents only one of many mediators of health benefits from physical activity. E.g. physical activity may also improve cardiorespiratory fitness which is highly associated with metabolic risk factors¹⁷. Our direct effects would include associations owing to physically active youth having a higher cardiorespiratory fitness, and future studies could consider attempts to further decompose physical activity associations with health outcomes. In summary, habitual levels of MVPA was associated, in an inverse, graded relationship, with a strong direct effect on a composite risk score of established CVD risk factors in youth, while the indirect effect through adiposity was smaller in comparison. Thus our results extend previous reports of an independent effect of physical activity by doing a formal decomposition and allowing for exposure-mediator interaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank all participants and funders of the original studies that contributed data to ICAD. We also gratefully acknowledge the contribution of Professor Chris Riddoch, Professor Ken Judge, Professor Ashley Cooper and Dr Pippa Griew to the development of ICAD.

The ICAD Collaborators include: Prof LB Andersen, University of Southern Denmark, Odense, Denmark (Copenhagen School Child Intervention Study (CoSCIS)); Prof S Anderssen, Norwegian School for Sport Science, Oslo, Norway (European Youth Heart Study (EYHS), Norway); Dr AJ Atkin, MRC Epidemiology Unit & Centre for Diet and Activity Research, University of Cambridge, UK; Prof G Cardon, Department of Movement and Sports Sciences, Ghent University, Belgium (Belgium Pre-School Study); Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), Hyattsville, MD USA (National Health and Nutrition Examination Survey (NHANES)); Dr R Davey, Centre for Research and Action in Public Health, University of Canberra, Australia (Children's Health and Activity Monitoring for Schools (CHAMPS)); Prof U Ekelund, Norwegian School of Sport Sciences, Oslo, Norway & MRC Epidemiology Unit, University of Cambridge, UK; Dr DW Esliger, School of Sports, Exercise and Health Sciences, Loughborough University, UK; Dr P Hallal, Postgraduate Program in Epidemiology, Federal University of Pelotas, Brazil (1993 Pelotas Birth Cohort); Dr BH Hansen, Norwegian School of Sport Sciences, Oslo, Norway; Prof KF Janz, Department of Health and Human Physiology, Department of Epidemiology, University of Iowa, Iowa City, US (Iowa Bone Development Study); Prof S Kriemler, Epidemiology, Biostatistics and Prevention Institute, University of Zürich, Switzerland (Kinder-Sportstudie (KISS)); Dr N Möller, University of Southern Denmark, Odense, Denmark (European Youth Heart Study (EYHS), Denmark); Ms L Molloy, School of Social and Community Medicine, University of Bristol, UK (Avon Longitudinal Study of Parents and Children (ALSPAC)); Dr A Page, Centre for Exercise, Nutrition and Health Sciences, University of Bristol, UK (Personal and Environmental Associations with Children's Health (PEACH)); Prof R Pate, Department of Exercise Science, University of South Carolina, Columbia, US (Physical Activity in Pre-school Children (CHAMPS-US) and Project Trial of Activity for Adolescent Girls (Project TAAG)); Dr JJ Puder, Service of Endocrinology, Diabetes and Metabolism, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland (Ballabeina Study); Prof J Reilly, Physical Activity for Health Group, School of Psychological Sciences and Health, University of Strathclyde, Glasgow, UK (Movement and Activity Glasgow Intervention in Children (MAGIC)); Prof J Salmon, School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia (Children Living in Active Neighbourhoods (CLAN)); Prof LB Sardinha, Exercise and Health Laboratory, Faculty of Human Movement, Universidade de Lisboa, Lisbon, Portugal (European Youth Heart Study (EYHS), Portugal); Dr LB Sherar, School of Sports, Exercise and Health Sciences, Loughborough University, UK; Dr A Timperio, Centre for Physical Activity and Nutrition Research, Deakin University Melbourne, Australia

(Healthy Eating and Play Study (HEAPS)); Dr EMF van Sluijs, MRC Epidemiology Unit & Centre for Diet and Activity Research, University of Cambridge, UK (Sport, Physical activity and Eating behaviour: Environmental Determinants in Young people (SPEEDY)).

Funding

JT was funded by TrygFonden (Grant Number: 11683), the University of Southern Denmark, and received financial support from “Christian og Ottilia Brorsons Rejselegat” while contributing to this work. The pooling of the data was funded through a grant from the National Prevention Research Initiative (Grant Number: G0701877) (<http://www.mrc.ac.uk/research/initiatives/national-prevention-research-initiative-npri/>).

The funding partners relevant to this award are: British Heart Foundation; Cancer Research UK; Department of Health; Diabetes UK; Economic and Social Research Council; Medical Research Council; Research and Development Office for the Northern Ireland Health and Social Services; Chief Scientist Office; Scottish Executive Health Department; The Stroke Association; Welsh Assembly Government and World Cancer Research Fund. This work was additionally supported by the Medical Research Council [MC_UU_12015/3; MC_UU_12015/7], The Research Council of Norway (249932/F20), Bristol University, Loughborough University and Norwegian School of Sport Sciences. The study sponsors were not involved in the design of the study; the collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

Abbreviations used in this article

CVD	cardiovascular disease
CoSCIS	Copenhagen School Child Intervention Study
EYHS	European Youth Hearth Study
h	hours
ICAD	International Children’s Accelerometer Database
min	minutes
MVPA	moderate-to-vigorous physical activity
NHANES	National Health and Nutrition Examination Survey

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Table 1

Study characteristics

Study	CoSCIS	EYHS DENMARK	EYHS ESTONIA	EYHS PORTUGAL	NHANES 2003/4	NHANES 2005/6
Country and year of data acquisition	Denmark, 01–05	Denmark, 97–98 and 03/04	Estonia, 98–99	Portugal, 99–00	US, 03–04	US, 05–06
Age (years)	6–11	8–17	8–17	9–16	12–18	12–18
Participants	358 (47)	1022 (55)	535 (55)	499 (50)	523 (45)	475 (50)
Height (cm)	Mean (SD)	149 (15)	152 (17)	147 (15)	165 (10)	164 (10)
Weight (kg)	Median(IQR)	24.0 (22.1–26.7)	42.6 (29.9–56.0)	39.0 (31.1–53.9)	60.8 (50.6–72.6)	58.9 (49.3–71.3)
Waist circumference (cm)	Median(IQR)	55.0 (52.3–58.0)	61.4 (56.2–67.6)	63.9 (58.5–69.5)	76.8 (69.4–87.0)	75.7 (69.7–86.6)
WC/H-ratio	Median(IQR)	0.45 (0.43–0.46)	0.41 (0.39–0.43)	0.43 (0.41–0.46)	0.46 (0.42–0.53)	0.46 (0.42–0.52)
composite-score	Mean (SD)	–0.13 (0.85)	0.05 (0.88)	–0.44 (0.92)	0.01 (1.14)	0.12 (1.12)
MVPA/day (min)	Median(IQR)	55 (41–82)	55 (35–83)	46 (27–72)	34 (20–54)	28 (17–44)
Physical activity-categories	%	13/43/26/18	19/38/24/19	28/37/22/13	43/36/15/6	53/33/9/4
Ethnicity (white)	%	NA	98	99	21	25
Birthweight (g)	Mean (SD)	3406 (586)	3543 (603)	3418 (505)	NA	NA
Mothers' BMI (kg m ⁻²)	Median(IQR)	22.8 (20.9–25.6)	23.1 (20.9–26.5)	25.3 (22.8–28.2)	NA	NA
Sexual maturity	%	60/10/2/13/16	44/9/9/19/19	18/47/2/8/24	NA	NA
Household income quartiles	%	NA	NA	NA	22/17/32/28	19/22/28/32
Mothers Education	%	31/36/33	29/33/38	89/6/5	NA	NA

¹ Abbreviations: CoSCIS, Copenhagen School Child Intervention Study; EYHS, European Youth Heart Study; NHANES, National Health and Nutrition Examination Survey; MVPA, moderate-to-vigorous physical activity; BMI, body mass index; IQR, inter-quartile range; SD, standard deviation.

² Waist-circumference was measured midway between the lower rib margin and the iliac crest in the EYHS and CoSCIS studies and just above the iliac crest at the midaxillary line in the NHANES studies. Mothers' BMI is based on self-reported height and weight. Household income quartiles in ascending order is based on distribution in complete NHANES data sets. WC:H-ratio, waist-circumference:height ratio; NA, not applicable; SD, standard deviation; IQR, 25th–75th percentile.

Table 2
Daily min of moderate-to-vigorous physical activity and clinical characteristics for the physical activity contrasts

	0–30 min of MVPA per day (n=1076)	30 – <60 min of MVPA per day (n=1274)	60 – <90 min of MVPA per day (n=668)	90 min of MVPA per day (n=394)
MVPA (min per day)	17.8 (10.3–24.2)	43.6 (36.8–51.3)	72.8 (66.0–81.0)	107.8 (97.6–128.0)
HOMA-IR	1.9 (1.2–2.8)	1.5 (1.0–2.3)	1.3 (0.8–1.9)	1.1 (0.7–1.7)
Systolic BP (mm Hg)	106.0 (100.0–113.3)	104.7 (97.7–111.0)	102.0 (96.3–108.5)	100.7 (94.3–108.0)
Triacylglycerol (mmol l ⁻¹)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.6 (0.5–0.9)	0.6 (0.5–0.8)
HDL-c (mmol l ⁻¹)	1.4 (1.2–1.6)	1.5 (1.3–1.7)	1.4 (1.3–1.7)	1.5 (1.3–1.7)

¹ Abbreviations: MVPA, moderate-to-vigorous physical activity; BP, blood pressure; HDL-c, high density lipoprotein-cholesterol.

² Data is median (25th–75th percentile).

Table 3
Total, direct and indirect effects of physical activity on the composite risk score

Physical activity contrast	Sample (n)	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)	Percent of total effect attributable to indirect effect
< versus 60 min MVPA per day	3412	-0.307 (-0.389, -0.225)	-0.239 (-0.317, -0.161)	-0.068 (-0.112, -0.023)	22%
< versus 30 min MVPA per day	3412	-0.240 (-0.320, -0.160)	-0.174 (-0.248, -0.100)	-0.066 (-0.102, -0.030)	28%
< versus 90 min MVPA per day	3412	-0.391 (-0.508, -0.273)	-0.331 (-0.438, -0.224)	-0.060 (-0.132, 0.013)	15%
< 30 versus 60 min MVPA per day	2138	-0.400 (-0.506, -0.293)	-0.304 (-0.403, -0.205)	-0.096 (-0.154, -0.037)	24%
< 30 versus 90 min MVPA per day	1470	-0.578 (-0.733, -0.423)	-0.455 (-0.601, -0.031)	-0.123 (-0.233, -0.013)	21%

¹ Abbreviations: CI, confidence interval; MVPA, moderate-to-vigorous physical activity; HDL-c, high density lipoprotein-cholesterol.

² The composite risk score is comprised of standardized values of HOMA-IR, systolic blood pressure, triacylglycerol and inverse HDL-c. HOMA-IR and triacylglycerol were transformed by the natural logarithm before standardization. Exposures are the various physical activity contrasts coded as 0 for below the speCified threshold and 1 for above. Estimates are weighted means with 95% CI from fixed effects meta-analysis with study weights given as $(\text{study sample size})/(\text{total sample size})$.

Table 4
Total, direct and indirect effects of physical activity on individual metabolic risk factors using below versus above 60 min of MVPA per day as activity contrast

Risk factor	Sample (n)	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)	Percent of total effect attributable to indirect effect
HOMA-IR (%)	3412	-0.150 (-0.203, -0.098) [-0.243]	-0.104 (-0.153, -0.055) [-0.169]	-0.046 (-0.076, -0.016) [-0.074]	31%
Systolic blood pressure (mm Hg)	3412	-1.895 (-2.644, -1.146) [-0.205]	-1.620 (-2.345, -0.895) [-0.176]	-0.275 (-0.548, -0.002) [-0.029]	15%
Triacylglycerol (%)	3412	-0.085 (-0.119, -0.051) [-0.157]	-0.075 (-0.110, -0.040) [-0.131]	-0.010 (-0.022, 0.001) [-0.026]	12%
HDL-c (mmol l ⁻¹)	3412	0.048 (0.021, 0.075) [0.118]	0.034 (0.007, 0.061) [0.072]	0.014 (0.004, 0.025) [0.046]	29%

¹ Abbreviations: CI, confidence interval; MVPA, moderate-to-vigorous physical activity; HDL-c, high density lipoprotein-cholesterol.

² HOMA-IR and triacylglycerol are logarithmically transformed and multiplied by 100 so can be interpreted as a difference in percentage. The contrast is an exposure below (coded as 0) vs above (coded as 1) 60 min of MVPA per day. Estimates are unstandardized weighted means with 95% CI from fixed effects meta-analysis with study weights given as (study sample size)/(total sample size). Values in brackets are standardized betas.