Title: Physical activity and sedentary time associations with metabolic health across weight statuses in children and adolescents

Authors: Nicholas Kuzik[1], Valerie Carson[1], Lars Bo Andersen[2,3], Luís B. Sardinha[4], Anders Grøntved[5] , Bjørge Herman Hansen[2], Ulf Ekelund[2,6] and on behalf of the International Children's Accelerometry Database (ICAD) Collaborators[7].

[1]Faculty of Physical Education and Recreation, University of Alberta, Edmonton, Canada
[2]Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway
[3]Department of Teacher Education and Sport, Sogn and Fjordane University College, Sogndal, Norway
[4]Exercise and Health Laboratory, CIPER, Faculdade de Motricidade Humana, Universidade de Lisboa, Cruz-Quebrada, Portugal
[5]Centre of Research in Childhood Health, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
[6]Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom
[7] 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); 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)); Prof A Cooper, Centre for Exercise, Nutrition and Health Sciences, University of Bristol, UK (Personal and Environmental Associations with Children's Health (PEACH)); 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 K Froberg, University of Southern Denmark, Odense, Denmark (European Youth Heart Study (EYHS), Denmark); Dr P Hallal, Postgraduate Program in Epidemiology, Federal University of Pelotas, Brazil (1993 Pelotas Birth Cohort); Prof KF Janz, Department of Health and Human Physiology, Department of Epidemiology, University of Iowa, Iowa City, US (Iowa Bone Development Study); Dr K Kordas, School of Social and Community Medicine, University of Bristol, UK (Avon Longitudinal Study of Parents and Children (ALSPAC)); Dr S Kriemler, Institute of Social and Preventive Medicine, University of Zürich, Switzerland (Kinder-Sportstudie (KISS)); Dr A Page, Centre for Exercise, Nutrition and Health Sciences, University of Bristol, UK; 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 Neigbourhoods (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, University of Cambridge, UK (Sport, Physical activity and Eating behaviour: Environmental Determinants in Young people (SPEEDY)).

Keywords: ICAD (International Children's Accelerometry Database), accelerometer, metabolically healthy obesity.

Running Title: Metabolic health across weight statuses

Contact Information:
Prof Ulf Ekelund,
Department of Sports Medicine, Norwegian School of Sports Sciences,
Ullevål Stadion, 0806, Oslo, Norway
ulf.ekelund@nih.no

Word Count: 3498/3500

Funding: The Faculty of Physical Education and Recreation at the University of Alberta and the Norwegian School of Sport Sciences provided funding for NK to travel to the Norwegian School of Sport Sciences to collaborate on this manuscript. VC is supported by a Canadian Institutes of Health Research (CIHR) New Investigator Salary Award. 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 Research Council of Norway (249932/F20), the Medical Research Council [MC_UU_12015/3; MC_UU_12015/7], Bristol University, Loughborough University and Norwegian School of Sport Sciences.

Conflict of Interests: All authors declare that they have no conflict of interests.

What is already known about this subject?

•Weight status does not always predict metabolic health

•Heterogeneity exists for childhood metabolic health definitions

•Inconsistent relationships exist for physical activity and sedentary behaviour within and across metabolic health-weight status groups

What does this study add?

•Objectively measured physical activity and sedentary behaviour relate differently to metabolic health and weight status

•Relatively high prevalence of metabolically unhealthy classification existed for all weight statuses

•Using multiple definitions of metabolic health does not fully address the heterogeneity of definitions

Objectives: To examine the prevalence of metabolic health across weight statuses, and associations with physical activity and sedentary time.

Methods: Six studies (n=4581) from the International Children's Accelerometry Database (ICAD) were used. Sedentary time, light physical activity, and moderate to vigorous physical activity (MVPA) were accelerometer-derived. Individuals were classified with normal weight (NW), overweight, and obesity. Strict and lenient composite definitions of metabolic health were created. Binomial and multinomial logistic regressions controlling for age, sex, study, and accelerometer wear time were conducted.

Results: Metabolically unhealthy (MU) prevalence was 26.4% and 45.6% based on two definitions. Across definitions, higher sedentary time was associated with higher odds of MU classification compared to metabolically healthy (MH) for the NW group. Higher MVPA was associated with lower odds of MU classification compared to MH, for NW and overweight groups. For multinomial logistic regressions, higher MVPA was associated with lower odds of MH-obese, and MU-NW, -overweight, and -obese classifications, compared to MH-NW group. Furthermore, higher sedentary time was associated with higher odds of MU-NW classification, compared to MH-normal weight group.

Conclusions: Higher MVPA was beneficial for metabolic health and weight status, whereas lower sedentary time was beneficial for metabolic health alone—though associations were weak.

Introduction

The relationship between overweight and obesity with poor metabolic health is well documented in children and adolescents (1). For example, associations have been found between an overweight and obese weight status with lower high density lipoprotein-cholesterol (HDL) as well as elevated measures of fasting glucose, triglycerides, and blood pressure (2, 3). However, recent research adds to the debate of whether obesity is invariably associated with poor metabolic health (4, 5). The subset of individuals with obesity and good metabolic health are categorized with metabolically healthy obesity. This classification could help prioritize and tailor treatment options for paediatric obesity practitioners (6). Conversely, though normal weight status is predominantly associated with better metabolic health compared to overweight and obesity, a normal weight status does not guarantee optimal metabolic health (4). Thus, individuals can be categorized as metabolically unhealthy normal weight. Since this group of children receives less attention (4), the detection of metabolic abnormalities may go unnoticed until the early onset of chronic diseases (e.g., hypertension). Research differentiating metabolic health between weight status groups could guide future clinical interventions aimed at improving the metabolic health and weight status of children and adolescents.

Within the current literature on metabolic health across weight statuses, the definition of metabolic health is debated. Some strict definitions of metabolic health prohibit moderately elevated ("at-risk") metabolic health risk factors (5, 7), whereas lenient definitions allow one "high" risk factor in isolation (8). Some researchers question the appropriateness of this allowance (9) suggesting a metabolically healthy individual could have one isolated at-risk value but no high risk values (9). Based on the heterogeneity of metabolic health definitions in children and adolescents, multiple definitions will help to broaden comparability between studies.

Beyond the aforementioned metabolic health definition debate, inconsistent evidence exists for the associations of physical activity and sedentary behaviour within and across metabolic health-weight status groups. For physical activity, inverse (10) and null (8, 9) associations have been observed between questionnaire based moderate to vigorous physical activity (MVPA) estimates and metabolically healthy obesity, and null associations have been observed for pedometer based measurements (5, 10). For sedentary behaviour, questionnaire based estimates of screen time have shown no association (8, 10). Inconsistent findings in previous research may be the due to the information bias associated with the measures of MVPA and sedentary behaviour (11), and lacking intensity estimates in the pedometer measures (5, 10). Objective measures (e.g., accelerometry) could address this limitation with more valid and reliable measures of physical activity and sedentary time while also capturing different intensities of movement (e.g., light physical activity (LPA) and MVPA) (12). Findings from this research could guide clinical recommendations by determining which specific lifestyle changes (e.g., MVPA, LPA, or sedentary behaviour) provide the most benefit for different metabolic health-weight status groups.

The objectives of this study were to examine: the prevalence of metabolically healthy versus metabolically unhealthy classifications (using a strict and lenient definition) across weight status in a large sample of children and adolescents; and associations of physical activity and sedentary time within and across metabolic health-weight status groups.

Methods

Study design

The International Children's Accelerometry Database (ICAD) (http://www.mrc-epid.cam.ac.uk/research/studies/icad) has pooled objectively measured Actigraph accelerometer data (ActiGraph

LLC, Pensacola, Florida) from children and adolescents (13). This dataset used standardized data reduction techniques on 46,131 raw Actigraph data files (13). Additionally, when available, accompanying anthropometric, demographic (e.g., age, sex), and cardiometabolic health measures were pooled. Participant ages ranged from 3-18 years, and represented 20 studies worldwide.

Participants

For the present analyses, studies were included if measurements were available for: height and weight; diastolic and systolic blood pressure; and fasting blood glucose, insulin, triglycerides, and high density lipoprotein cholesterol (HDL-C). A total of six studies from Denmark, Estonia, Portugal, and the United States (2 samples) with children and adolescents aged 5-18 years (n=10,040) collected between 1996-2008 were available (14, 15, 16, 17).

Measurements

Physical Activity and Sedentary Time

A full description of the assessment of physical activity and sedentary time has previously been reported (13). Raw accelerometer data provided to the ICAD from the various studies was processed using specifically developed and commercially available software (KineSoft, version 3.3.20, Saskatchewan, Canada; http://kinesoft.org). Files were reintegrated to 60-second epochs, and non-wear time was defined as zero counts for 60 minutes while allowing 2 minutes of nonzero interruptions (18). Valid wear-time was defined as having accelerometer data for ≥1 day with ≥ 600 minutes, and all accelerometer files not meeting this definition were removed. Using ≥1 day of wear time is in line with previous ICAD analyses (19, 20, 21), and details regarding the appropriateness of this threshold can be found elsewhere (22). Accelerometer cut-points used in the current study were developed by Trost et al. (23). Sedentary time was defined as <100

counts/minute, while LPA and MVPA were differentiated by age-specific accelerometer cut-points previously validated to correspond with four metabolic equivalents (23).

Weight Status

Across studies, height and weight were measured using standardized procedures, with limited between-study variation. Body mass index (BMI) was calculated by dividing weight (kilograms) by height (metres) squared. Individuals were then categorized with normal weight, overweight, and obesity based on age- and sex-specific cut-offs (24). Due to limited numbers, underweight individuals (z-score $\leq$ -1.0) were classified as normal weight.

Metabolic Health Risk Factors

All systolic and diastolic blood pressure measurements were performed in a rested condition. Measurements were derived from manual and automatic methods. Manual mercury sphygmomanometer readings were used in two of the studies, and recorded as the average of two or three readings (15, 16). The other four studies used a Dinamap XL vital signs monitor, which measured blood pressure every second minute during a 10-minute period and used the average of the final three readings (14, 17). Additionally, blood glucose, insulin, triglycerides, and HDL-C were measured in the fasted state using standard clinical procedures previously described, with limited between-study variation (14, 15, 16, 17).

In order to create metabolic health composite definitions, each metabolic health risk factor was categorized as ‘normal’, ‘at risk’, and ‘high risk’ based on the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (2), with the exception of homeostatic model of assessment for insulin resistance. Since no recommendations for HOMA-IR existed in the aforementioned guidelines, cut-offs were adapted from a study with a similar age range to the current study (25). A full list of each metabolic health risk cut-off can be found in Table 1. To broaden the comparability and interpretation of findings, a strict and lenient

definition of metabolic health were adopted similar to Heinzle et al. (9). Within the lenient definition individuals were defined as metabolically unhealthy if they had more than one metabolic risk factor classified as 'at risk', or if any metabolic risk factor was classified as 'high risk'. Within the strict definition, individuals were defined as metabolically unhealthy if they had any metabolic risk factor classified as 'at risk' or 'high risk'.

Statistical Analysis

Statistical analyses were performed using SPSS version 23. To address objective one, descriptive statistics were calculated and expressed as means (standard deviations) for continuous variables, and frequencies (percentage) for categorical variables. To address objective two, separate logistic regressions were run in each weight status category (i.e., normal weight, overweight, and obese) with each accelerometer variable individually ran as the independent variable (i.e., sedentary time, LPA, and MVPA) and metabolic health as the dependent variable. All regression models categorized the odds of being in the metabolically unhealthy group compared to the metabolically healthy reference group. Next, multinomial logistic regressions were calculated with each accelerometer variable of interest individually ran as the independent variable, and metabolic health-weight status groups (e.g., metabolically healthy-obese, metabolically unhealthy-normal weight) as the dependent variables. All regression models estimated the odds of being in each metabolic health-weight status group compared to the normal weight-metabolically healthy referent group. Regression models were run for both definitions of metabolic health. Due to the different proportions of time each accelerometer variable would contribute to the total day, MVPA was expressed in units of 10 minutes/day and LPA and sedentary time were expressed in units of 60 minutes/day within regression analyses. All

regression analyses controlled for age, sex, study, and accelerometer wear time. Statistical significance was set at $P<0.05$ for all analyses.

Results

After excluding participants with unusable accelerometer data (n=529) and missing metabolic risk and weight status variables (n=4930), a final sample of 4581 was included in the analyses. Participant characteristics for the final sample are presented in Table 2. Excluded participants did not differ based on age and sex compared to included participants. However, excluded participants did differ based on which individual study they were pooled from, with the NHANES and CoSCIS studies having the most missing data. This is intuitive since NHANES data included accelerometer data from ages 6-18 and metabolic data from 12-18 (thus excluding all children under 12 years), and only the baseline data from the CoSCIS study was used (thus excluding two other time points from this study). Children wore accelerometers for an average of 13.6 hours per day, of which 48.0% was spent in sedentary time, 44.0% in LPA, and 8.0% in MVPA.

The proportion of participants in the 'normal', 'at risk', and 'high risk' groups for individual metabolic risk factors is presented in Table 3. For individual metabolic risk factors, triglyceride values had the most 'at risk' (N=741), while HOMA-IR values had the most 'high risk' (N=400) classifications. A total of 1172 (25.6%) children and adolescents were classified as metabolically unhealthy with the lenient definition (up to one 'at risk' value), and 2065 (45.1%) with the strict definition (no 'at-risk' value allowance). Therefore, 893 (43.2%) individuals within the strict definition were unhealthy based on only one 'at-risk' score.

Results of the separate logistic regressions categorizing metabolically unhealthy groups according to time spent sedentary, in LPA and MVPA (mins/day) within each weight status

group are presented in Table 4. Each additional 60 minutes/day of sedentary time was associated with 8-11% higher odds of metabolically unhealthy classification for the normal weight group, compared to the metabolically healthy group. As well, each additional 10 minutes/day of MVPA was associated with lower odds of metabolically unhealthy classification in normal weight and overweight groups, compared to the metabolically healthy group.

Results of the multinomial logistic regression categorizing metabolic health-weight status groups according to time spent sedentary and in LPA and MVPA are presented in Table 5. Within both definitions, each additional 60 minutes of sedentary time was associated with higher odds of metabolically unhealthy-normal weight classification compared to the metabolically healthy-normal weight group. As well, each additional 10 minutes of MVPA was associated with lower odds of metabolically healthy- obese as well as metabolically unhealthy-normal weight , -overweight, and -obese classification, compared to the metabolically healthy-normal weight group.

Discussion

The results of this study suggest that higher time spent in MVPA was consistently associated with lower odds of metabolically unhealthy classification in the groups with normal weight and overweight. No associations were observed in the group with obesity. Further, higher time spent sedentary was consistently associated with higher odds of metabolically unhealthy classification for the group with normal weight. Higher time spent in MVPA was generally associated with lower odds of being in all other metabolic health-weight status groups, compared to the metabolically healthy-normal weight group. However, for sedentary time and LPA, significant odds were only observed for metabolically unhealthy group classifications, when compared to the metabolically healthy-normal weight group. This may suggest that increasing MVPA

influences weight status and metabolic health, whereas decreasing sedentary time and increasing LPA mainly influences metabolic health. However, magnitude of associations were small.

According to the two definitions, 64.0% and 77.5% of children and adolescents with obesity in this sample were metabolically unhealthy. In a national sample from the United States, Heinzle et al. (9) found prevalences of 43.7% and 92.4% in children and adolescents with obesity using two similar definitions. Variation in prevalences could be explained by differences in age between the studies and the current study did not include measures of C-reactive protein. Additionally, Heinzle et al. (9) used a representative sample from the United States, whereas the current study represents an international sample that is not representative of all included countries. However, the current study included the same representative sample (i.e., NHANES) as Heinzle et al. (9). Nevertheless, using two definitions in this sample 26.4% and 45.6% of children and adolescents of all weight statuses were classified as metabolically unhealthy. Additionally, 39.9% of individuals with a normal weight status were classified as metabolically unhealthy based at least one 'at-risk' metabolic measurement, which is also in line with previous research (4). Given the potential long-term health implications, these trends could be considered alarming. For example, in children, elevated blood lipids and glucose and blood pressure is associated with adult atheroschlerosis progression (26, 27, 28), and hypertension risk (29), respectively. However, future longitudinal research is needed to determine the true risk of the current 'at-risk' cut-offs in this age group.

Of the children classifed as metabolically unhealthy, the most frequent 'high risk' metabolic markers were HOMA-IR (8.7%), followed by blood lipids (i.e., triglycerides and HDL-C). The current thresholds for metabolic health were chosen based on the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and

Adolescents (2), except for HOMA-IR, since no thresholds were provided within the guidelines. Searching the literature for HOMA-IR cut-offs yielded many definitions (30) but ultimately a decision was made based on the similarities in age between Kurtoğlu et al. (25) and the current sample. Therefore, this definition of insulin resistance may be limited due to a lack of expert concensus. However, relying on expert concensus from the Integrated Guidelines may also have limitations in the distinction of metabolic health. For instance, for HDL-C classifications 9.0% individuals were classified as 'at-risk' (1.13-1.04 mmol/L), while 7.5% individuals were classified as 'high-risk' (≤1.03 mmol/L). Considering the similar frequencies classified as 'at-risk' and 'high-risk' these thresholds may be limited. Based on a lack of concensus for a HOMA-IR and potential limitations of the other thresholds, efforts are needed to advance the current recommended cut-points. Most importantly, a need exists to determine the level of exposure of metabolic markers which put children and adolescents 'at-risk' for future chronic disease. Additionally, the current cut-off values for the majority of metabolic markers were not fully age- and sex-adjusted. Based on the variability of metabolic markers as a function of age and sex, recent research has proposed various methods to create age- and sex-adjusted metabolic thresholds categorizing children with metabolic risk (31, 32, 33). Thus, future cut-off recommendations could also consider age- and sex-adjusted metabolic thresholds associated with elevated risk.

Higher MVPA was associated with lower odds of being metabolically unhealthy in normal weight and overweight individuals, whereas higher sedentary time was associated with higher odds of being metabolically unhealthy in normal weight individuals. The lack of associations for MVPA and sedentary time with metabolic health in obese participants may be explained by low variability in both MVPA and sedentary time in this group combined with a

fairly low prevalence of obesity (7.3%) in our sample.While previous studies have examined associations of physical activity and sedentary time with individual and clustered metabolic risk markers (21, 34, 35), few have categorized children and adolescents as metabolically healthy/unhealthy across weight status categories (4). However, in agreement with previous research (8), we found null associations for sedentary time with metabolic health in obese individuals.Comparisons across the literature are also difficult since previous studies, to our knowledge, have not used objective accelerometer measurements (4). Consequently, these studies have not included a measure of LPA, so LPA-specific comparisons are not possible. Future work should build on this study by also measuring physical activity objectively, to better understand the associations of LPA with metabolic health-weight status groupings.

While research examining objectively measured physical activity and sedentary behaviour across and within metabolic health-weight status groups was not found, similar research has compared objectively measured MVPA and sedentary behaviour in separate models, while adjusting for adiposity indicators in children and adolescents. For instance, a cross-sectional study of European children and adolescents (n=1708) concluded that both MVPA and sedentary time were separately associated with clustered metabolic risk when controlling for waist circumference (35). Therefore, the current study reinforces the implication that both MVPA and sedentary time are important for the metabolic health of children and adolescents. However, the current study indicates that MVPA is additionally beneficial for weight status, regardless of metabolic health. Further research is needed to determine why MVPA and sedentary time have different effects on metabolic health and weight status.

It is important to note that the statistically significant findings observed between sedentary time, MVPA, and weight status and metabolic health were small and therefore the clinical significance is debatable. This is in line with the one previous significant finding between questionnaire derived MVPA and metabolically health obesity classification (10). According to one criteria, all significant findings in the current study have weak strength of associations (36). However, studies pooled in this analysis were cross-sectional and observational, so the magnitude of effects could be impacted by measurement error and residual confounding. Future work using stronger study designs could determine the clinical significance of increasing MVPA and decreasing sedentary time to improve weight status and metabolic health. Additionally, thresholds defining metabolic health in children and adolescents should be strengthened with longitudinal studies, and as previously mentioned potentially converted to age- and sex-appropriate values.

When determining the effect of sedentary time, LPA, and MVPA on weight status and metabolic health, it could be argued that these behaviours should be mutually-adjusted for one another to determine independent effects, especially since some of the behaviours are not strongly correlated (e.g., sedentary time and MVPA). Previous studies on sedentary time, MVPA, and health in children and adolescents that mutually adjusted for the other behaviours found MVPA was strongly associated with metabolic outcomes independent of sedentary time, whereas sedentary time was unrelated to metabolic health outcomes (21, 34). However, some have suggested these behaviours are co-dependent and should not be mututally adjusted (37, 38). For instance, during waking hours, if a child or adolescent reduced sedentary time, it would have to be replaced with LPA or MVPA. Recent advances in statistical analyses to handle co-dependent

data, such as compositional analyses (38) and iso-temporal substitution models (39) should be explored in future research as alternative methods for understanding these relationships.

A major strength of this study was objective accelerometer and metabolic risk factor measurements. Another major strength was the large database from several developed, Western countries, which greatly enhances the generalizability of the findings to similar countries. However, further research is needed to determine the relevance of these findings in different cultural contexts. Additionally, the use of a minimum of 1 day of accelerometer wear-time may not represent true habitual activity patterns. Furthermore, many participants were excluded for invalid accelerometer data (5.3%) and missing metabolic risk factor and weight status variables (49.1%), though these participants did not differ with included participants on age and sex. Further, the large database limited the amount of covariates available for analysis. Therefore, unmeasured covariates (e.g., diet, sleep, socioeconomic status, ethnicity) could have introduced residual confounding. This study was also limited by the heterogeneity of definitions within the metabolic health literature. In an attempt to address this heterogeneity, two definitions of metabolic health were used. Some researchers have opted out of categorical metabolic cut-points to address this heterogeneity, and instead create sample specific z-scores for metabolic markers (40), which have also been age- and sex-adjusted (32, 33). Additional caution should be used when interpreting the prevalences of metabolic health, considering the heterogeneity of studies (e.g., sample sizes, and age ranges) within this dataset. Finally, the study was cross-sectional so causality cannot be assumed, and even the potential for reverse-causality cannot be ruled out.

Conclusion

A high prevelance of at least one ‘at-risk’ metabolic risk factor was found in all weight status groups. Furthermore, higher MVPA appeared to be beneficial for weight status and metabolic

health, whereas lower sedentary time and more LPA appear to be beneficial for metabolic health alone. However, overall the effect sizes were small. To better assess the clinical significance of the findings in this study, future research should build on these findings with stronger study designs and exploration of different metabolic health thresholds.

Acknowledgements

The authors thank all participants and funders of the original studies that contributed data to ICAD, all ICAD collaborators, Professor Chris Riddoch, Professor Ken Judge and Dr Pippa Griew.

References

1. Must A, Strauss RS. Risks and consequences of childhood and adolescent obesity. *Int J Obes Relat Metab Disord* 1999;**23 Suppl 2:** S2-11.

2. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;**128 Suppl 5:** S213-256.

3. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and Determinants of Insulin Resistance Among U.S. Adolescents. *A population-based study* 2006;**29:** 2427-2432.

4. Ding WQ, Yan YK, Zhang MX, Cheng H, Zhao XY, Hou DQ*, et al.* Hypertension outcomes in metabolically unhealthy normal-weight and metabolically healthy obese children and adolescents. *Journal of Human Hypertension* 2015;**29:** 548-554.

5. Senechal M, Wicklow B, Wittmeier K, Hay J, MacIntosh AC, Eskicioglu P*, et al.* Cardiorespiratory Fitness and Adiposity in Metabolically Healthy Overweight and Obese Youth. *Pediatrics* 2013;**132:** E85-E92.

6. Hadjiyannakis S, Buchholz A, Chanoine JP, Jetha MM, Gaboury L, Hamilton J*, et al.* The Edmonton Obesity Staging System for Pediatrics: A proposed clinical staging system for paediatric obesity. *Paediatr Child Health* 2016;**21:** 21-26.

7. Li S, Chen W, Srinivasan SR, Xu J, Berenson GS. Relation of childhood obesity/cardiometabolic phenotypes to adult cardiometabolic profile: the Bogalusa Heart Study. *Am J Epidemiol* 2012;**176 Suppl 7:** S142-149.

8. Camhi SM, Waring ME, Sisson SB, Hayman LL, Must A. Physical activity and screen time in metabolically healthy obese phenotypes in adolescents and adults. *Journal of obesity* 2013;**2013:** 984613-984613.

9. Heinzle S, Ball GDC, Kuk JL. Variations in the prevalence and predictors of prevalent metabolically healthy obesity in adolescents. *Pediatric Obesity* 2015.

10. Prince RL, Kuk JL, Ambler KA, Dhaliwal J, Ball GDC. Predictors of Metabolically Healthy Obesity in Children. *Diabetes Care* 2014;**37:** 1462-1468.

11. Helmerhorst HJF, Brage S, Warren J, Besson H, Ekelund U. A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *The International Journal of Behavioral Nutrition and Physical Activity* 2012;**9:** 103-103.

12. Trost SG. State of the art reviews: measurement of physical activity in children and adolescents. *American Journal of Lifestyle Medicine* 2007;**1:** 299-314.

13. Sherar LB, Griew P, Esliger DW, Cooper AR, Ekelund U, Judge K*, et al.* International children's accelerometry database (ICAD): design and methods. *BMC Public Health* 2011;**11:** 485.

14. Eiberg S, Hasselstrom H, Gronfeldt V, Froberg K, Svensson J, Andersen LB. Maximum oxygen uptake and objectively measured physical activity in Danish children 6-7 years of age: the Copenhagen school child intervention study. *Br J Sports Med* 2005;**39:** 725-730.

15. Prevention CfDCa. National Health and Nutrition Examination Survey. Laboratory Procedures Manual. 2004.

16. Prevention CfDCa. National Health and Nutrition Examination Survey. Laboratory Procedures Manual. 2005.

17. Riddoch C, Edwards D, Page A, Froberg K, Anderssen SA, Wedderkopp N*, et al.* The European Youth Heart Study—cardiovascular disease risk factors in children: rationale, aims, study design, and validation of methods. *J Phys Act Health* 2005;**2:** 115-129.

18. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc* 2008;**40:** 181-188.

19. Sherar LB, Griffin TP, Ekelund U, Cooper AR, Esliger DW, van Sluijs EMF*, et al.* Association between maternal education and objectively measured physical activity and sedentary time in adolescents. *Journal of Epidemiology and Community Health* 2016;**70:** 541-548.

20. Corder K, Sharp SJ, Atkin AJ, Andersen LB, Cardon G, Page A*, et al.* Age-related patterns of vigorous-intensity physical activity in youth: The International Children's Accelerometry Database. *Preventive medicine reports* 2016;**4:** 17-22.

21. Ekelund U, Luan J, Sherar LB, Esliger DW, Griew P, Cooper A. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *Jama* 2012;**307:** 704-712.

22. Toftager M, Kristensen PL, Oliver M, Duncan S, Christiansen LB, Boyle E*, et al.* Accelerometer data reduction in adolescents: effects on sample retention and bias. *International Journal of Behavioral Nutrition and Physical Activity* 2013;**10:** 140.

23. Trost SG, Pate RR, Sallis JF, Freedson PS, Taylor WC, Dowda M*, et al.* Age and gender differences in objectively measured physical activity in youth. *Med Sci Sports Exerc* 2002;**34:** 350-355.

24. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes* 2012;**7:** 284-294.

25. Kurtoğlu S, Hatipoğlu N, Mazıcıoğlu M, Kendirici M, Keskin M, Kondolot M. Insulin Resistance in Obese Children and Adolescents: HOMA−IR Cut−Off Levels in the Prepubertal and Pubertal Periods. *Journal of Clinical Research in Pediatric Endocrinology* 2010;**2:** 100-106.

26. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between Multiple Cardiovascular Risk Factors and Atherosclerosis in Children and Young Adults. *New England Journal of Medicine* 1998;**338:** 1650-1656.

27. Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: The cardiovascular risk in young finns study. *Jama* 2003;**290:** 2277-2283.

28. McGill HC, McMahan CA, Malcom GT, Oalmann MC, Strong JP, Group atPDoAiYR. Relation of Glycohemoglobin and Adiposity to Atherosclerosis in Youth. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1995;**15:** 431-440.

29. Bao W, Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa Heart Study. *Am J Hypertens* 1995;**8:** 657-665.

30. de Andrade MIS, Oliveira JS, Leal VS, da Lima NMS, Costa EC, de Aquino NB*, et al.* Identification of cutoff points for Homeostatic Model Assessment for Insulin Resistance index in adolescents: systematic review. *Revista Paulista de Pediatria* 2016;**34:** 234-242.

31. Cureau FV, Ekelund U, Bloch KV, Schaan BD. Does body mass index modify the association between physical activity and screen time with cardio-metabolic risk factors in adolescents[quest] Findings from a countrywide survey. *Int J Obes* 2016.

32. Peplies J, Jimenez-Pavon D, Savva SC, Buck C, Gunther K, Fraterman A*, et al.* Percentiles of fasting serum insulin, glucose, HbA1c and HOMA-IR in pre-pubertal normal weight European children from the IDEFICS cohort. *Int J Obes* 2014;**38:** S39-S47.

33. Andersen LB, Lauersen JB, Br, #xf8, nd JC, Anderssen SA*, et al.* A New Approach to Define and Diagnose Cardiometabolic Disorder in Children. *Journal of Diabetes Research* 2015;**2015:** 10.

34. Stamatakis E, Coombs N, Tiling K, Mattocks C, Cooper A, Hardy LL*, et al.* Sedentary Time in Late Childhood and Cardiometabolic Risk in Adolescence. *Pediatrics* 2015;**135:** e1432-e1441.

35. Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European youth heart study. *Diabetologia* 2007;**50:** 1832-1840.

36. Oleckno WA. Essential epidemiology : principles and applications. Waveland: Long Grove, Ill. :, 2002.

37. Pedisic Z. Measurement Issues and Poor Adjustments for Physical Activity and Sleep Undermine Sedentary Behaviour Research - the Focus Should Shift to the Balance between Sleep, Sedentary Behaviour, Standing and Activity. *Kinesiology* 2014;**46:** 135-146.

38. Chastin SF, Palarea-Albaladejo J, Dontje ML, Skelton DA. Combined effects of time spent in physical activity, sedentary behaviors and sleep on obesity and cardio-metabolic health markers: A novel compositional data analysis approach. *PloS one* 2015;**10:** e0139984.

39. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal Substitution Paradigm for Physical Activity Epidemiology and Weight Change. *Am J Epidemiol* 2009;**170:** 519-527.

40. Machado-Rodrigues AM, Leite N, Coelho-e-Silva MJ, Martins RA, Valente-dos-Santos J, Mascarenhas LP*, et al.* Independent association of clustered metabolic risk factors with cardiorespiratory fitness in youth aged 11-17 years. *Ann Hum Biol* 2014;**41:** 271-276.

Table 1: Categorization of Metabolic Health Risk Factors

	Normal	At risk	High risk
Triglycerides (mmol/L)	≤ 0.84[1] ≤ 1.01[2]	0.85-1.13[1] 1.02 -1.47[2]	≥ 1.14[1] ≥ 1.48[2]
HDL-C (mmol/L)	≥ 1.18	1.17-1.04	≤ 1.03
Systolic blood pressure (mmHg)	≤ 89th percentile[3]	90th-94th percentile[3]	≥ 95th percentile[3]
Diastolic blood pressure (mmHg)	≤ 89th percentile[3]	90th-94th percentile[3]	≥ 95th percentile[3]
Glucose (mmol/L)	≤ 5.55	5.56-6.99	≥ 7.00
HOMA-IR	<2.22[4] <2.67[5] <3.82[6] <5.22[7]		≥2.22[4] ≥2.67[5] ≥3.82[6] ≥5.22[7]

HDL-C = High density lipoprotein-cholesterol.
1 Age ≤ 9
2 Age > 9
3 Age, sex, and height specific percentiles.
4 Age ≤ 10, and sex = female
5 Age ≤ 11, and sex = male
6 Age > 10, and sex = female
7 Age > 11, and sex = male

Table 2: Participant characteristics

		All	*CoSCIS*	*Denmark EYHS*	*Estonia EYHS*	*NHANES 2005-6*	*NHANES 2003-4*	*Portugal EYHS*
Country		Various	Denmark	Denmark	Estonia	Unites States	Unites States	Portugal
Number of Participants		4581 (100%)	418 (9.1%)	1166 (25.5%)	648 (14.1%)	555 (12.1%)	621 (13.6%)	1173 (25.6%)
Age (years)		11.8 (3.3)	6.7 (0.4)	11.3 (2.6)	12.5 (3.0)	14.9 (1.8)	14.9 (1.8)	10.6 (2.6)
Sex	*Male*	2265 (49.4%)	229 (54.8%)	532 (45.6%)	288 (44.4%)	277 (49.9%)	350 (56.4%)	589 (50.2%)
	Female	2316 (50.6%)	189 (45.2%)	634 (54.4%)	360 (55.6%)	278 (50.1%)	271 (43.6%)	584 (49.8%)
Accelerometer Variables	*Valid days (days)*	3.9 (1.5)	2.5 (0.7)	4.0 (1.2)	3.7 (0.6)	4.6 (1.9)	4.7 (1.9)	3.7 (1.2)
	Total Wear time (hr/day)	13.6 (1.6)	12.9 (1.5)	13.5 (1.2)	13.7 (1.0)	14.0 (1.9)	14.3 (2.4)	13.5 (1.2)
	Sedentary Time (hr/day)	6.5 (2.1)	4.7 (1.5)	6.3 (2.0)	5.9 (1.9)	7.9 (2.0)	8.0 (2.2)	6.4 (1.7)
	LPA (hr/day)	6.0 (1.3)	6.0 (0.9)	6.1 (1.4)	6.6 (1.2)	5.6 (1.3)	5.8 (1.3)	5.9 (1.2)
	MVPA (hr/day)	1.1 (0.8)	2.2 (0.9)	1.1 (0.8)	1.2 (0.8)	0.5 (0.4)	0.6 (0.5)	1.2 (0.7)
BMI Categories	*Normal Weight*	3542 (77.3%)	372 (89.0%)	993 (85.2%)	582 (89.8%)	358 (64.5%)	380 (61.2%)	856 (73.0%)
	Overweight	706 (15.4%)	39 (9.3%)	148 (12.7%)	60 (9.3%)	102 (18.4%)	134 (21.6%)	223 (19.0%)
	Obese	333 (7.3%)	7 (1.7%)	24 (2.1%)	6 (0.9%)	95 (17.1%)	107 (17.2%)	94 (8.0%)

Abbreviations: CoSCIS, Copenhagen School Child Intervention Study; EYHS, European Youth Heart Study; NHANES, National Health And Nutrition Examination Survey; LPA, light-intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity; BMI, body mass index.
Values represent mean (standard deviation) for continuous, and frequency (percent) for categorical variables.

Table 3: Metabolic Health Risk Factors in Isolation

		All	*CoSCIS*	*Denmark EYHS*	*Estonia EYHS*	*NHANES 2005-6*	*NHANES 2003-4*	*Portugal EYHS*
HOMA-IR	*No risk*	4181 (91.3%)	408 (97.6%)	1032 (88.5%)	607 (93.7%)	474 (85.4%)	545 (87.8%)	1117 (95.2%)
	High Risk	400 (8.7%)	10 (2.4%)	134 (11.5%)	41 (6.3%)	81 (14.6%)	76 (12.2%)	56 (4.8%)
Systolic Blood Pressure	*No Risk*	4359 (95.2%)	402 (96.2%)	1091 (93.6%)	602 (92.9%)	524 (94.4%)	593 (95.5%)	1147 (97.8%)
	At Risk	100 (2.2%)	9 (2.2%)	28 (2.4%)	16 (2.5%)	20 (3.6%)	13 (2.1%)	14 (1.2%)
	High Risk	122 (2.7%)	7 (1.7%)	47 (4.0%)	30 (4.6%)	11 (2.0%)	15 (2.4%)	12 (1.0%)
Diastolic Blood Pressure	*No Risk*	4517 (98.6%)	413 (98.8%)	1149 (98.5%)	640 (98.8%)	542 (97.7%)	604 (97.3%)	1169 (99.7%)
	At Risk	48 (1.0%)	3 (0.7%)	12 (1.0%)	8 (1.2%)	9 (1.6%)	13 (2.1%)	3 (0.3%)
	High Risk	16 (0.3%)	2 (0.5%)	5 (0.4%)	0 (0.0%)	4 (0.7%)	4 (0.6%)	1 (0.1%)
Glucose	*No Risk*	4060 (88.6%)	416 (99.5%)	1017 (87.2%)	588 (90.7%)	473 (85.2%)	564 (90.8%)	1002 (85.4%)
	At Risk	510 (11.1%)	2 (0.5%)	147 (12.6%)	60 (9.3%)	77 (13.9%)	53 (8.5%)	171 (14.6%)
	High Risk	11 (0.2%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	5 (0.9%)	4 (0.6%)	0 (0.0%)
TG	*No Risk*	3460 (75.5%)	365 (87.3%)	823 (70.6%)	508 (78.4%)	395 (71.2%)	434 (69.9%)	935 (79.7%)
	At Risk	741 (16.2%)	30 (7.2%)	233 (20.0%)	101 (15.6%)	101 (18.2%)	117 (18.8%)	159 (13.6%)
	High Risk	380 (8.3%)	23 (5.5%)	110 (9.4%)	39 (6.0%)	59 (10.6%)	70 (11.3%)	79 (6.7%)
HDL-C	*No Risk*	3824 (83.5%)	377 (90.2%)	1006 (86.3%)	530 (81.8%)	418 (75.3%)	464 (74.7%)	1029 (87.7%)
	At Risk	412 (9.0%)	31 (7.4%)	91 (7.8%)	57 (8.8%)	63 (11.4%)	77 (12.4%)	93 (7.9%)
	High Risk	345 (7.5%)	10 (2.4%)	69 (5.9%)	61 (9.4%)	74 (13.3%)	80 (12.9%)	51 (4.3%)

Abbreviations: CoSCIS, Copenhagen School Child Intervention Study; EYHS, European Youth Heart Study; NHANES, National Health And Nutrition Examination Survey; HDL-C, high density lipoprotein-cholesterol; TG, Triglycerides.
Values represent mean (standard deviation) for continuous, and frequency (percent) for categorical variables.

Table 4. Logistic regression categorizing metabolically unhealthy according to min/day of sedentary time, LPA, MVPA within each weight status group

	Odds Ratio (95% Confidence Intervals)[a]					
	Normal Weight (n=3542)		**Overweight (n=706)**		**Obese (n=333)**	
	MH	*MU*	*MH*	*MU*	*MH*	*MU*
			Lenient Definition			
Sedentary time (min/day)	1.00 (ref.)	1.08 (1.02, 1.14)†	1.00 (ref.)	1.11 (1.00, 1.24)	1.00 (ref.)	1.03 (0.87, 1.21)
LPA (min/day)	1.00 (ref.)	0.95 (0.89, 1.02)	1.00 (ref.)	0.93 (0.82, 1.05)	1.00 (ref.)	1.01 (0.83, 1.22)
MVPA (min/day)	1.00 (ref.)	0.95 (0.93, 0.98)†	1.00 (ref.)	0.94 (0.89, 0.99)†	1.00 (ref.)	0.95 (0.86, 1.03)
			Strict definition			
Sedentary time (min/day)	1.00 (ref.)	1.11 (1.05, 1.16)†	1.00 (ref.)	1.05 (0.95, 1.16)	1.00 (ref.)	1.02 (0.84, 1.24)
LPA (min/day)	1.00 (ref.)	0.93 (0.88, 0.98)†	1.00 (ref.)	1.01 (0.90, 1.15)	1.00 (ref.)	1.00 (0.80, 1.24)
MVPA (min/day)	1.00 (ref.)	0.95 (0.94, 0.97)†	1.00 (ref.)	0.94 (0.90, 0.98)†	1.00 (ref.)	0.97 (0.88, 1.07)

Abbreviations: MH, metabolically healthy; MU metabolically unhealthy; LPA, light-intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity.

[a]Odds ratio represent the odds of being classified in each metabolic health-weight status group (metabolically healthy=referent group) with each additional 10 minutes of MVPA, as well as each additional 60 minutes of LPA and sedentary time. Analyses controlled for age, sex, study, and accelerometer wear time.

†Significant at $P<0.05$

Table 5. Multinomial logistic regression categorizing metabolic-weight status group membership according to min/day of sedentary time, LPA, and MVPA

	Odds Ratio (95% Confidence Intervals)[a]					
	Lenient Definition					
	Metabolically Healthy (n=3410)			**Metabolically Unhealthy (n=1171)**		
	Normal Weight (n=2840)	**Overweight (n=449)**	**Obese (n=120)**	**Normal Weight (n=702)**	**Overweight (n=257)**	**Obese (n=213)**
Sedentary time (min/day)	1.00 (ref.)	1.00 (0.93, 1.07)	1.10 (0.96, 1.25)	1.09 (1.03, 1.15)†	1.09 (1.00, 1.19)	1.09 (0.98, 1.20)
LPA (min/day)	1.00 (ref.)	1.05 (0.96, 1.14)	1.01 (0.86, 1.18)	0.95 (0.89, 1.02)	0.98 (0.88, 1.09)	1.04 (0.93, 1.18)
MVPA (min/day)	1.00 (ref.)	0.97 (0.95, 1.00)†	0.90 (0.85, 0.96)†	0.95 (0.93, 0.97)†	0.92 (0.88, 0.96)†	0.85 (0.80, 0.90)†
	Strict definition					
	Metabolically Healthy (n=2516)			**Metabolically Unhealthy (n=2065)**		
	Normal Weight (n=2129)	**Overweight (n=312)**	**Obese (n=75)**	**Normal Weight (n=1413)**	**Overweight (n=394)**	**Obese (n=258)**
Sedentary time (min/day)	1.00 (ref.)	1.04 (0.96, 1.13)	1.11 (0.94, 1.31)	1.11 (1.06, 1.16)†	1.08 (1.00, 1.16)†	1.12 (1.02, 1.23)†
LPA (min/day)	1.00 (ref.)	0.99 (0.89, 1.09)	1.00 (0.82, 1.23)	0.93 (0.88, 0.98)†	1.01 (0.92, 1.10)	1.01 (0.91, 1.13)
MVPA (min/day)	1.00 (ref.)	0.98 (0.95, 1.01)	0.90 (0.83, 0.97)†	0.95 (0.94, 0.97)†	0.92 (0.89, 0.95)†	0.85 (0.81, 0.89)†

Abbreviations: LPA, light-intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity.

[a]Odds ratio represent the odds of being classified corresponding metabolic health-weight status groups compared to the metabolically healthy-normal weight group (metabolically healthy-normal weight = referent) with each additional 10 minutes of MVPA, as well as each additional 60 minutes of LPA and sedentary time. Analyses controlled for age, sex, study, and accelerometer wear time.

†Significant at $P \leq 0.05$