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## **Associations of Vigorous-intensity Physical Activity with Biomarkers in Youth**

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The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and the results of the present study do not constitute endorsement by ACSM.

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## ABSTRACT

**Introduction:** Physical activity (PA) conveys known cardiometabolic benefits to youth, but the contribution of vigorous-intensity PA (VPA) to these benefits is unknown. Therefore, we sought to determine, a) the associations between VPA and cardiometabolic biomarkers independent of moderate-intensity PA (MPA) and time sedentary, and b) the accelerometer cutpoint that best represents the threshold for health-promoting VPA in youth. **Methods:** Data from the International Children's Accelerometry Database (ICAD) were analyzed in 2015. The relationship between cardiometabolic biomarkers and 4 categories of VPA estimated via 3 sets of cutpoints were examined using isotemporal substitution quantile regression modeling at the 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, and 90<sup>th</sup> percentile of the distribution of each biomarker, separately. Age, sex, accelerometer wear time, sedentary time, and MPA were controlled for while allowing substitution for light-intensity PA. Data from 11,588 youth (4-18yrs) from 11 ICAD studies (collected 1998-2009) were analyzed. **Results:** Only 32 of 360 significant associations were observed. Significant, negative relationships were observed for VPA with waist circumference and insulin. Replacing light intensity PA with VPA (corresponding to at the 25<sup>th</sup> to 90<sup>th</sup> percentiles of VPA) was associated with a .67 (-1.33, -0.01; P = .048) to 7.30cm (-11.01, -3.58; P < .001) lower waist circumference using Evenson and ICAD cutpoints (i.e., higher CPM). VPA levels were associated with 12.60 (-21.28, -3.92; P = .004) to 27.03 pmol/l (-45.03, -9.03; P = .003) lower insulin levels at the 75<sup>th</sup> to 90<sup>th</sup> percentiles using Evenson and ICAD cutpoints when substituted for light PA. **Conclusions:** Substituting light PA with VPA was inversely associated with waist circumference and insulin. However, VPA was inconsistently related to the remaining biomarkers after controlling for time sedentary and MPA.

**Keywords:** Movement; cardiometabolic; adiposity; insulin.

## INTRODUCTION

Emerging research utilizing international samples (7, 17) has indicated that many children globally are spending an insufficient amount of time engaging in physical activity (PA) and an excessive amount of time engaging in sedentary behaviors. Engaging in international guideline recommendations (38) of 60 minutes per day (min/day) of moderate-to-vigorous physical activity (MVPA) is inversely associated with biomarkers of cardiometabolic health (13, 25) including lower rates of obesity (17) independent of time spent sedentary. While the benefits of MVPA are well established cross-sectionally (7) and longitudinally (6), few studies of PA in youth have examined the contribution of specific intensities to the association, despite a growing body of literature that suggests that vigorous-intensity physical activity (VPA) may be more important for the prevention and amelioration of cardiometabolic risk factors (13, 39). A small number of studies have employed an objective measure of PA to examine associations with cardiometabolic biomarkers. These studies suggest that VPA is independently associated with cardiorespiratory fitness (positive) (23), BMI (negative) (17), adiposity (negative) (32), HDL cholesterol (positive) (22), fasting glucose (negative) (31), and fasting insulin (negative) (1). However, an extensive examination of the literature suggests that the relationship between VPA and cardiometabolic biomarkers is inconsistent, potentially due to small samples, definition of VPA, and other methodological limitations (11).

Complicating examinations of the relations between VPA and cardiometabolic biomarkers is an issue of measurement of VPA, or more specifically, the threshold for which VPA occurs. While imperfect, accelerometers are still considered one of the best objective measures available for epidemiological studies of PA (5, 28), but the processing of data generated by accelerometers

(e.g., “counts”) lacks uniformity or consistency across studies (18), which can lead to misclassification of exercise intensity (12) and/or lack of comparability across studies (3, 4). Since the choice of cutpoint is a de facto selection of an intensity threshold with all other sources of variability held constant (e.g., monitor brand, epoch), and no standard exists for the VPA cutpoint, it is imperative to consider a range of accelerometer cutpoints for VPA if the relationship between VPA and cardiometabolic biomarkers is to be studied.

The benefits of MVPA in youth are well established, but little research has been conducted to examine the contribution of PA intensity in cardiometabolic health in youth. Therefore, the objective of the present investigation was to determine, a) the associations between VPA and cardiometabolic biomarkers independent of moderate physical activity (MPA) and sedentary time, and b) the accelerometer cutpoint that best represents the threshold for health-promoting VPA in a diverse sample of youth.

## **MATERIALS/SUBJECTS AND METHODS**

### **Study Design**

Data were utilized from the International Children’s Accelerometry Database (ICAD, <http://www.mrc-epid.cam.ac.uk/Research/Studies/>), which was established to pool data on PA from studies in youth worldwide. A comprehensive description of the ICAD can be found elsewhere (34). Briefly, in 2008 19 studies were identified from a PubMed search that used an Actigraph (Actigraph, LLC, Pensacola, FL, USA) accelerometer and included a minimum of 400 participants aged 3 to 18 years. Six additional studies were identified through professional colleagues, with 21 studies ultimately contributing data to the final database (7, 34). For the

current study, 11 studies were included (7, 34), which are presented in brief with the variables each contributed in Table 1 [details of the Avon Longitudinal Study of Parents and Children (ALSPAC) are available at [www.bris.ac.uk/alspac](http://www.bris.ac.uk/alspac) and including the data that are available via a fully searchable data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary>)]. Ethical approval for the present study was attained from participating institutions, and data-sharing agreements were established prior to contribution of data.

## **Participants**

Data from 11,588 youth (4-18yrs), representing 11 studies from Brazil, Europe, and the United States from the ICAD were analyzed. Data from studies conducted between 1998 and 2009 were included in the present analyses if the dataset contained PA, age, sex, and at least one biomarker of a cardiometabolic risk [defined as “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (2)].

## **Measurements**

*Physical activity.* A comprehensive description of the measurement of PA has been published previously (34). ICAD data were reanalyzed to allow for comparability across studies by aggregating data to a 60-second epoch. The criterion of 60 minutes of consecutive zeros was utilized to designate non-wear time, with a tolerance for 2 minutes of nonzero epochs (35). Participants with three or more days with 600 minutes of valid wear time were included in analyses. VPA was defined by cutpoints from Pate (26), Evenson (8), and the ICAD workgroup (7, 34). These cutpoints were selected because they represent the most generous, lowest

threshold defining VPA [Pate  $\geq$  3,365 counts/min (CPM)], a medium threshold (Evenson  $\geq$  4,012 CPM), to the most stringent, highest threshold for VPA (ICAD  $\geq$  6,000 CPM).

*Cardiometabolic biomarkers.* Eight cardiometabolic biomarkers reflecting a diverse array of health indices were collected, including; waist circumference [as a proxy for adiposity (30)]; systolic and diastolic blood pressure (hemodynamics); high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting triglycerides (lipid metabolism); fasting glucose and fasting insulin (glucose metabolism). Details of data collection procedures can be found elsewhere (7, 34). Waist circumference (WC) was assessed midway between the lower rib margin and the iliac crest using a metal tape (10), except in the NHANES (National Health and Nutrition Examination Survey) where WC was measured just above the iliac crest at the mid-axillary line using similar equipment (36). Resting blood pressure was measured using standard procedures, reported previously (7). Markers of lipid and glucose metabolism were assessed using standard clinical procedures described in detail elsewhere (36).

### **Statistical Analysis**

Descriptive analyses of accelerometer-derived estimates of  $\text{min}\cdot\text{day}^{-1}$  spent in sedentary, MPA, and VPA were computed across all studies using three sets of cutpoints to define PA intensities. To evaluate the cross-sectional association of cardiometabolic biomarkers and time spent in VPA, a series of isotemporal substitution quantile regression models were estimated for each set of cutpoints separately (20, 21, 40). Quantile regression models were employed since biomarkers are often non-normal in their distribution, and quantile regression models are not influenced by normality and are free from distributional assumptions (19). Individual models for each



biomarker as the dependent variable were estimated. Time spent in VPA, defined by one of the 3 sets of cutpoints, separately, served as the primary independent variable. Because of its non-normal distribution,  $\text{min}\cdot\text{day}^{-1}$  spent in VPA was placed into 4 categories – none (0mins/d – reference category), low (lower 33%), middle (middle 33%), and high (upper 33%) – based on the distribution of VPA for each of the 3 sets of cutpoints. The relationship between cardio-metabolic biomarkers and 4 categories of VPA min/d [none (0 min/d – reference category), low ( $7.2_{\text{Pate}}, 4.0_{\text{Evenson}}, 1.5_{\text{ICAD}}$  min/d), medium ( $18.6_{\text{Pate}}, 11.0_{\text{Evenson}}, 3.5_{\text{ICAD}}$  min/d), and high ( $42.7_{\text{Pate}}, 28.9_{\text{Evenson}}, 11.9_{\text{ICAD}}$  min/d)] estimated via 3 sets of cutpoints [Pate: sedentary = 0 - 152 counts/min (CPM), MPA = 1677 – 3364, VPA =  $\geq 3,365$  CPM; Evenson: sedentary = 0 - 100 CPM, MPA = 2296 – 4011, VPA =  $\geq 4,012$  CPM; and ICAD: sedentary = 0 - 100 CPM, MPA = 3000 – 6000, VPA =  $\geq 6,001$  CPM] —were examined using isotemporal substitution quantile regression modeled at the 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, and 90<sup>th</sup> percentiles of the distribution of each biomarker. Included in each model were age (years), sex, average total daily wear time, and  $\text{min}\cdot\text{day}^{-1}$  in sedentary and MPA distilled using the corresponding cutpoint for VPA. Since light PA (LPA) was the only intensity excluded from the models, all estimates are interpreted as substituting “x” amount of LPA with VPA. Separate models were estimated for each study and for each set of cutpoints used to define VPA within each study. An example of the modeling approach is: insulin serving as the dependent variable, with 3 separate models using VPA levels (i.e., low, middle and high, with no VPA as the referent group) reduced with each of the sets of cutpoints for each study, run separately. Statistical significance was set at  $P = .05$ .

Meta-analytical techniques were used to combine the quantile regression model coefficients and standard errors for each biomarker across the 11 studies for each of the 3 sets of cutpoints,

separately. Random effects inverse variance weighting was used to pool effects across studies and within study for each set of cutpoints. The study served as the unit of analysis for each quantile and category of VPA. For instance, the VPA estimates representing the lowest 33<sup>rd</sup> of the distribution of VPA regressed on the 10<sup>th</sup> quantile of insulin were combined across all studies for a given biomarker. All quantile regression analyses were conducted in 2015 using Stata (v.13.0, College Station, TX) and all meta-analytic analyses were conducted using Comprehensive Meta-Analysis (v2.2, Englewood, NJ).

## **RESULTS**

Descriptive information for each study is presented in Table 2. The average amount of VPA  $\text{min}\cdot\text{day}^{-1}$  for each set of cutpoints (highest to lowest) by tertile ranged from 1.5 to 7.2  $\text{min}/\text{day}$  for the lowest tertile, the medium tertile 3.5 to 18.6  $\text{min}/\text{day}$ , and the highest tertile 11.9 to 42.7  $\text{min}/\text{day}$ . The results of the pooled meta-analytic effects for each quantile and level of VPA across each cardiometabolic biomarker are presented in the supplemental table (see Table, Supplemental Digital Content 1, Results of meta-analytical combination of quantile regression model coefficients and standard errors for each risk factor across the 11 studies for each of the three sets of accelerometer cutpoints)

### **Relationship of volume of VPA with cardiometabolic biomarkers**

Substituting LPA with VPA was inconsistently related to systolic/diastolic blood pressure, fasting triglycerides, HDL, or LDL after controlling for time sedentary and MPA at all tertiles of VPA volume, with only 32 of a possible 360 associations statistically significant ( $P < .05$ ). Independent of  $\text{min}\cdot\text{day}^{-1}$  spent sedentary and in MPA, substituting LPA with VPA was

associated with a .67 to 7.30 cm smaller waist circumference at the 50<sup>th</sup> to 90<sup>th</sup> percentiles. Relationships were observed for all three tertiles of VPA, but relationships at the lowest tertile of VPA volume were significant at only the highest cutpoint value (i.e., ICAD). Substituting LPA with VPA was associated with 12.6 to 27.0 pmol/l lower insulin values at the 75<sup>th</sup> to 90<sup>th</sup> percentiles. Relationships were observed for all three tertiles of VPA, but relationships at the lowest tertile of VPA were significant at only the highest tertiles of VPA volume for the highest cutpoint value (i.e., ICAD).

### **Influence of cutpoint**

Independent of min·day<sup>-1</sup> spent sedentary and in MPA, substituting LPA with the high volume of VPA defined via Pate cutpoints was associated with a smaller waist circumference only at the 90<sup>th</sup> percentile. For VPA determined via Evenson cutpoints, substituting LPA for medium and high VPA levels were associated with a smaller waist circumference at the 25<sup>th</sup> to 90<sup>th</sup> centiles. Substituting LPA with the lowest, medium, and highest volumes of VPA reduced via ICAD cutpoints was associated with a smaller waist circumference at the 50<sup>th</sup> to 90<sup>th</sup>, the 75<sup>th</sup> and 90<sup>th</sup>, and the 25<sup>th</sup> to 90<sup>th</sup>, respectively. Across all other biomarkers (i.e., SBP, DBP, HDL, LDL, glucose, and triglycerides), no consistent associations or patterns were observed, with only 9 significant associations observed from a possible 270 tested (<5%; see Figure).

### **DISCUSSION**

The present study is the first of this scope (e.g., sample size, diversity of national origin) to examine the relationship between VPA and cardiometabolic biomarkers in youth. The results are consistent with previous studies using more homogeneous samples, such as Carson et al. (6)

where no association was found between diastolic blood pressure and VPA, but a significant negative association was reported between waist circumference and VPA in children of the 2<sup>nd</sup> and 3<sup>rd</sup> quartiles (relative to the 1<sup>st</sup>). The more nuanced analyses presented here, taken with those of Carson et al. (6), provide additional insight into the complex relationship between VPA and cardiometabolic biomarkers (11, 25). The results suggest that substituting modest amounts of LPA for VPA may have cardiometabolic benefits above and beyond those conveyed by MPA and avoidance of sedentary behavior (24). Of potentially greater importance, the current results suggest that these health supportive associations are most pronounced in those who have undesirable levels of these biomarkers, specifically those with relatively large waist circumference or fasting insulin levels. If these relationships are found to be robust in longitudinal and experimental studies, then a specific frequency and duration of VPA could be incorporated as a distinct component of a PA “prescription” for youth (24). However, it must be noted that VPA was independently associated with only two of the markers examined. Therefore, while VPA may relay meaningful health benefits, the number of markers exhibiting those benefits may be few relative to less intense movement.

These results, taken with a growing body of literature demonstrating the independent health benefits of VPA for youth (6, 11, 14, 16, 17, 23, 24, 37), support the assertion that this intensity should be considered when setting policy recommendations for PA of youth. For example, it has been shown previously that as little as 9 (15) to 14 minutes (17) of VPA per day is associated with less adiposity in Canadian (15) and multinational samples of youth (17). These previous findings, derived from independent samples, are consistent with the present findings showing an association of substituting 11.9 to 42.7 min/day of LPA for VPA. While this is a considerable

range, with the top end (42.7 min/day) potentially impractical, consistent benefits were seen for VPA defined by the ICAD cutpoints, which even in the high volume category represented 11.9 min/day of VPA, is potentially achievable for most youth (39). Therefore, the present findings suggest a modest duration (e.g., approximately 10 min) of high intensity PA may be related to health benefits in youth who exhibit undesirable levels of insulin or waist circumference.

While the present study has a number of strengths, including an objective measure of PA, a large sample size, a diverse and international sample, and an advanced analytical approach, the present results should be considered in light of a number of limitations. First, all data were cross-sectional in nature, therefore causality cannot be assumed. For example, it is possible that children with smaller waist circumference are more vigorously active because it is less cumbersome for them to do so. However, the nature of our analyses, which examined the relationship of VPA and waist circumference at different quantiles of waist circumference, is less supportive of this possibility. Second, while these cross-sectional results are supportive of VPA specific PA recommendations for youth, it is unknown if changes in youth VPA levels will result in meaningful changes in diastolic blood pressure, HDL, cholesterol, insulin or adiposity. While a recent study is supportive of the latter three (29), the literature is mixed on the relationship between increased VPA and blood pressure (9, 11, 27, 33), and very few studies have examined the responsiveness of insulin or other markers of glucose metabolism (11, 13). Third, the database we utilized lacks standardized dietary data or genetic data that might confound the observed relationships. For example, children with higher levels of VPA may consume fewer calories, or possess a genetic make-up supportive of a positive biomarker profile. This possibility cannot be ruled out using the currently available data. Despite these limitations, this study

represents one of the largest to date that examined VPA in relation to cardiometabolic biomarkers in youth.

In summary, the present results suggest few significant or clinically meaningful associations between VPA and most cardiometabolic biomarkers studied in youth, but health promoting associations were observed between VPA and select cardiometabolic biomarkers (i.e., insulin, waist circumference), with the associations observed at higher levels of the biomarkers and higher volumes of VPA. As such, VPA may have unique metabolic health benefits beyond those conveyed by MPA or minimizing time spent sedentary. The present results also suggest that higher VPA cutpoints represent an intensity that is associated with healthier insulin levels and waist circumference. Future longitudinal and intervention studies are needed to determine the temporal relationship between these variables, the modifiability of VPA, and the effect of increased VPA on biomarkers in youth. If these results are indeed robust, then a less time consuming, more intense dose of PA may be a viable option for youth seeking to achieve or maintain cardiovascular health.

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## **ICAD COLLABORATORS**

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## REFERENCES

1. Alhassan S, Robinson TN. Objectively measured physical activity and cardiovascular disease risk factors in African American girls. *Ethn Dis*. 2008;18(4):421-6.
2. Biomarkers Definitions Working G. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89-95.
3. Bornstein DB, Beets MW, Byun W, Welk G, Bottai M, Dowda M, et al. Equating accelerometer estimates of moderate-to-vigorous physical activity: In search of the Rosetta Stone. *J Sci Med Sport*. 2011;14(5):404-10.
4. Brazendale K, Beets MW, Bornstein DB, Moore JB, Pate RR, Weaver RG, et al. Equating accelerometer estimates among youth: The Rosetta Stone 2. *J Sci Med Sport*. 2016;19(3):242-9.
5. Butte NF, Ekelund U, Westerterp KR. Assessing Physical Activity Using Wearable Monitors: Measures of Physical Activity. *Med Sci Sports Exerc*. 2012;44(1S):S5-S12.
6. Carson V, Rinaldi RL, Torrance B, Maximova K, Ball GD, Majumdar SR, et al. Vigorous physical activity and longitudinal associations with cardiometabolic risk factors in youth. *Int J Obes (Lond)*. 2014;38(1):16-21.
7. Ekelund U, Luan Ja, 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(7):704-12.
8. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. *J Sports Sci*. 2008;26(14):1557-65.

9. Farpour-Lambert NJ, Aggoun Y, Marchand LM, Martin XE, Herrmann FR, Beghetti M. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. *J Am Coll Cardiol.* 2009;54(25):2396-406.
10. Golding J, Pembrey M, Jones R, Team AS. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatr Perinat Epidemiol.* 2001;15(1):74-87.
11. Gralla MH, McDonald SM, Breneman C, Beets MW, Moore JB. Associations of Objectively Measured Vigorous Physical Activity With Body Composition, Cardiorespiratory Fitness, and Cardiometabolic Health in Youth: A Review. *Am J Lifestyle Med.* 2016.
12. Guinhouya CB, Lemdani M, Vilhelm C, Durocher A, Hubert H. Actigraph-defined moderate-to-vigorous physical activity cut-off points among children: statistical and biobehavioural relevance. *Acta Paediatrica.* 2009;98(4):708-14.
13. Gutin B, Owens S. The influence of physical activity on cardiometabolic biomarkers in youths: a review. *Pediatr Exerc Sci.* 2011;23(2):169-85.
14. Gutin B, Yin Z, Humphries MC, Barbeau P. Relations of moderate and vigorous physical activity to fitness and fatness in adolescents. *Am J Clin Nutr.* 2005;81(4):746-50.
15. Hay J, Maximova K, Durksen A, Carson V, Rinaldi RL, Torrance B, et al. Physical activity intensity and cardiometabolic risk in youth. *Arch Pediatr Adolesc Med.* 2012;166(11):1022-9.
16. Irving HM, Adlaf EM, Allison KR, Paglia A, Dwyer JJM, Goodman J. Trends in vigorous physical activity participation among Ontario adolescents, 1997-2001. *Can J Public Health.* 2003;94(4):272-4.

17. Katzmarzyk PT, Barreira TV, Broyles ST, Champagne CM, Chaput JP, Fogelholm M, et al. Physical Activity, Sedentary Time, and Obesity in an International Sample of Children. *Med Sci Sports Exerc.* 2015;47(10):2062-9.
18. Kim Y, Beets MW, Welk GJ. Everything you wanted to know about selecting the "right" Actigraph accelerometer cut-points for youth, but...: a systematic review. *J Sci Med Sport.* 2012;15(4):311-21.
19. Koenker R, Bassett G. Regression Quantiles. *Econometrica.* 1978;46(1):33-50.
20. Koenker R, Hallock KF. Quantile Regression. *J Econ Perspect.* 2001;15(4):143-56.
21. Koenker R, Xiao ZJ. Inference on the quantile regression process. *Econometrica.* 2002;70(4):1583-612.
22. Martinez-Gomez D, Eisenmann JC, Moya JM, Gomez-Martinez S, Marcos A, Veiga OL. The role of physical activity and fitness on the metabolic syndrome in adolescents: effect of different scores. The AFINOS Study. *J Physiol Biochem.* 2009;65(3):277-89.
23. Moore JB, Beets MW, Barr-Anderson DJ, Evenson KR. Sedentary time and vigorous physical activity are independently associated with cardiorespiratory fitness in middle school youth. *J Sports Sci.* 2013;31(14):1520-5.
24. Owens S, Galloway R, Gutin B. The Case for Vigorous Physical Activity in Youth. *Am J Lifestyle Med.* 2015.
25. Owens S, Gutin B. Physical Activity and Cardiometabolic Biomarkers in Youths: A 2013 Update. *Curr Cardiovasc Risk Rep.* 2014;8(2):1-8.
26. Pate RR, Almeida MJ, McIver KL, Pfeiffer KA, Dowda M. Validation and calibration of an accelerometer in preschool children. *Obesity (Silver Spring).* 2006;14(11):2000-6.

27. Platat C, Wagner A, Klumpp T, Schweitzer B, Simon C. Relationships of physical activity with metabolic syndrome features and low-grade inflammation in adolescents. *Diabetologia*. 2006;49(9):2078-85.
28. Rachele JN, McPhail SM, Washington TL, Cuddihy TF. Practical physical activity measurement in youth: a review of contemporary approaches. *World J Pediatr*. 2012;8(3):207-16.
29. Racil G, Ben Ounis O, Hammouda O, Kallel A, Zouhal H, Chamari K, et al. Effects of high vs. moderate exercise intensity during interval training on lipids and adiponectin levels in obese young females. *Eur J Appl Physiol*. 2013;113(10):2531-40.
30. Reilly JJ, Kelly J, Wilson DC. Accuracy of simple clinical and epidemiological definitions of childhood obesity: systematic review and evidence appraisal. *Obes Rev*. 2010;11(9):645-55.
31. Rizzo NS, Ruiz JR, Oja L, Veidebaum T, Sjostrom M. Associations between physical activity, body fat, and insulin resistance (homeostasis model assessment) in adolescents: the European Youth Heart Study. *Am J Clin Nutr*. 2008;87(3):586-92.
32. Ruiz JR, Rizzo NS, Hurtig-Wennlof A, Ortega FB, Warnberg J, Sjostrom M. Relations of total physical activity and intensity to fitness and fatness in children: the European Youth Heart Study. *Am J Clin Nutr*. 2006;84(2):299-303.
33. Schmitz KH, Jacobs DR, Jr., Hong CP, Steinberger J, Moran A, Sinaiko AR. Association of physical activity with insulin sensitivity in children. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*. 2002;26(10):1310-6.

34. 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.
35. 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(1):181-8.
36. US Department of Health and Human Services. Anthropometry and physical activity monitor procedures manual. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2005. p. 132.
37. Vankim NA, Nelson TF. Vigorous physical activity, mental health, perceived stress, and socializing among college students. *Am J Health Promot*. 2013;28(1):7-15.
38. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva, Switzerland: WHO Press, 2010.
39. Yin Z, Moore JB, Johnson MH, Vernon MM, Gutin B. The impact of a 3-year after-school obesity prevention program in elementary school children. *Childhood Obesity*. 2012;8(1):60-70.
40. Yu KM, Lu ZD, Stander J. Quantile regression: applications and current research areas. *J Roy Stat Soc D-Stat*. 2003;52:331-50.

**Figure:** Combination of quantile regression model coefficients and standard errors for each risk factor across the 11 studies for each of the three sets of accelerometer cutpoints.

### **Supplemental Digital Content**

Supplemental table.doc—Results of meta-analytical combination of quantile regression model coefficients and standard errors for each risk factor across the 11 studies for each of the three sets of accelerometer cutpoints.

Figure 1a

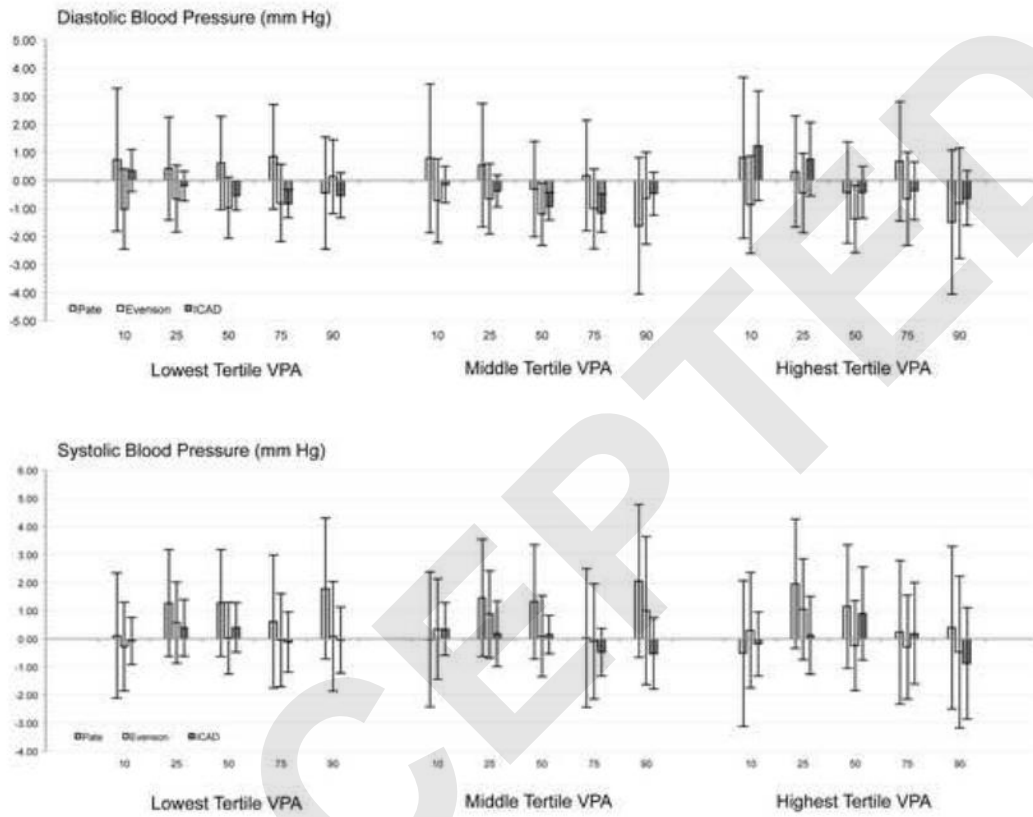




Figure 1b.

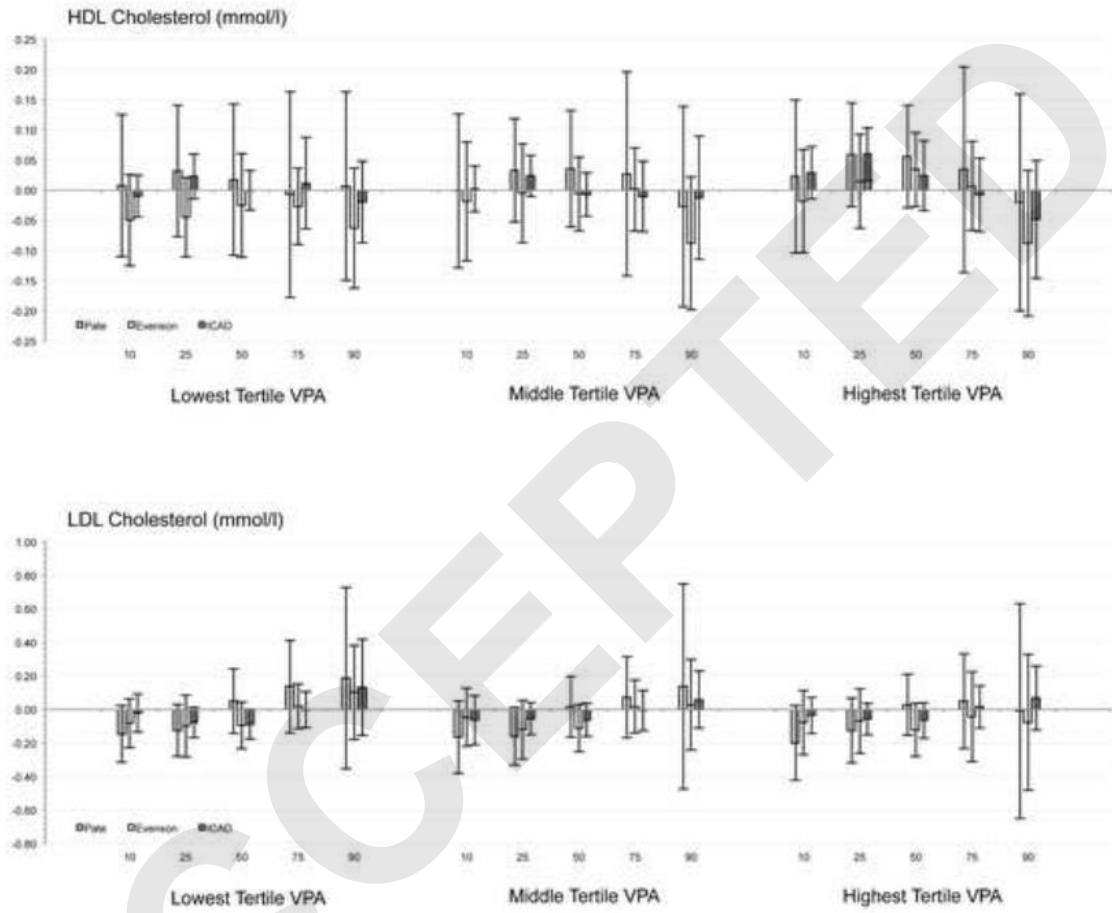


Figure 1c.

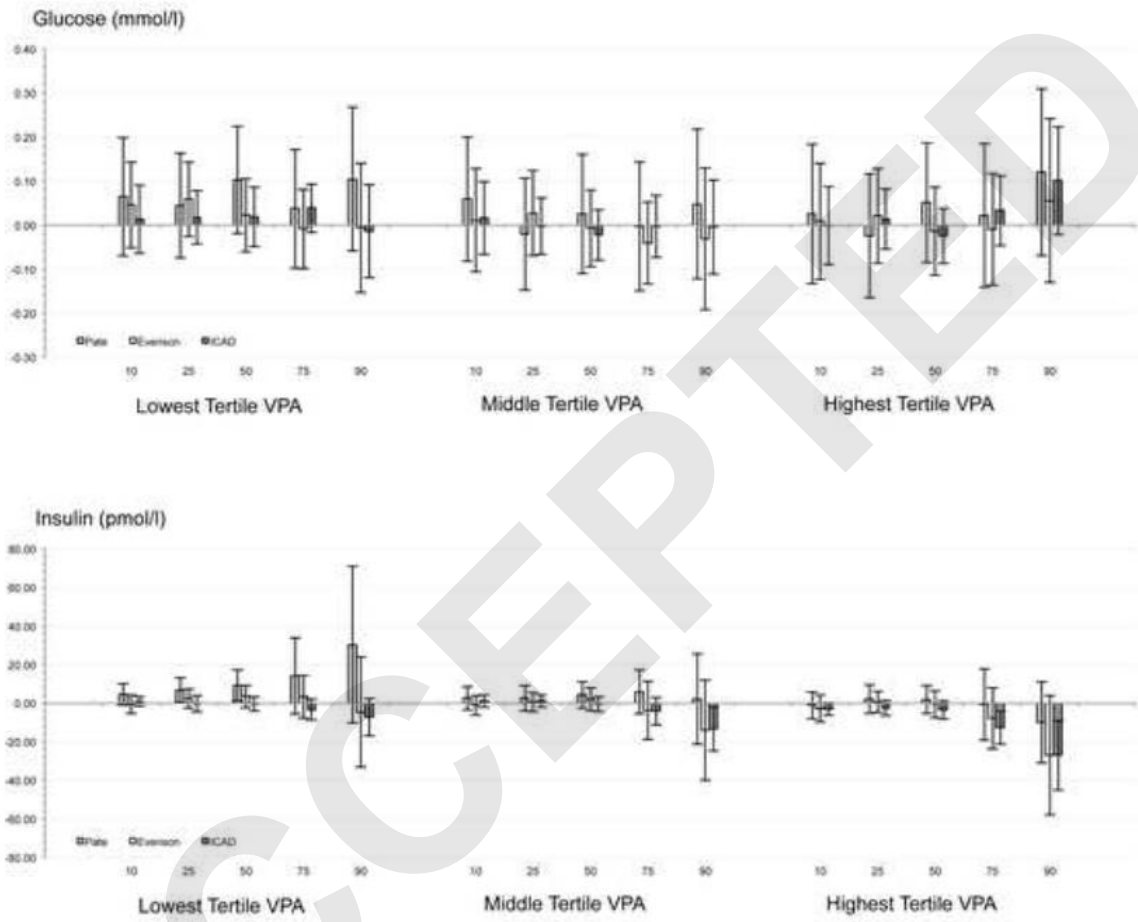
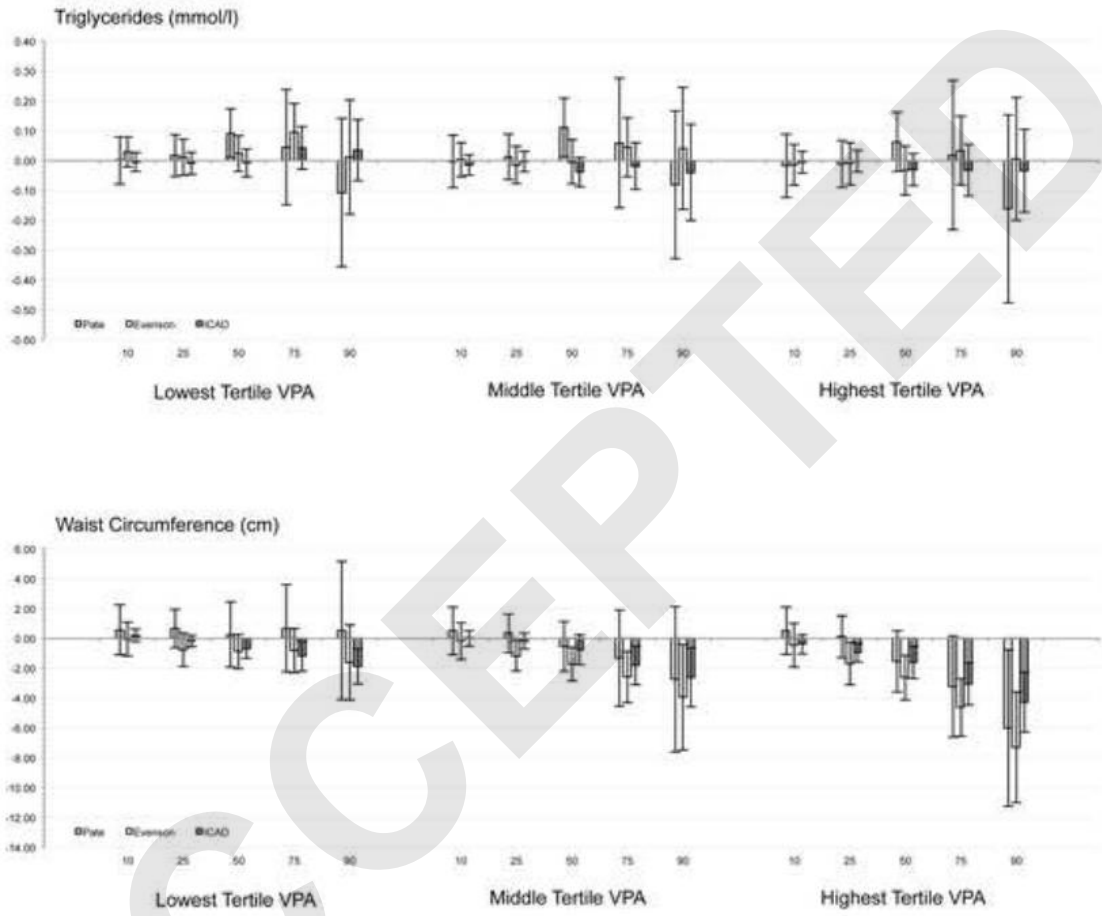


Figure 1d.



**Table 1.** List of studies contributing data with cardiometabolic biomarkers present in analytical dataset.

Study ID in the ICAD database	1	4	5	6	9	10	11	12	14	15	20	
Study	ALSPAC	CoSCIS	DEYHS	EEYHS	MAGIC	NHANES (2005-6)	NEYHS	NHANES (2003-4)	Pelotas	PEYHS	KISS	Total # of studies contributing biomarker
<b>Biomarker</b>												
Diastolic Blood Pressure (mm Hg)	•	•	•	•	•	•	•	•	•	•		10
Systolic Blood Pressure (mm Hg)	•	•	•	•	•	•	•	•	•	•		10
HDL Cholesterol (mmol/l)		•	•	•		•	•	•		•	•	8
LDL Cholesterol (mmol/l)		•	•	•		•	•	•		•	•	8
Glucose (mmol/l)		•	•	•		•		•		•	•	7
Insulin (pmol/l)		•	•	•		•		•		•	•	7
Triglycerides (mmol/l)		•	•	•		•	•	•		•	•	8
Waist Circumference (cm)	•	•	•	•	•	•	•	•	•	•	•	11
Number of Biomarkers Measured	3	8	8	8	3	8	6	8	3	8	6	

**Abbreviations:** ALSPAC, Avon Longitudinal Study of Parents and Children; CoSCIS, Copenhagen School Child Intervention Study; DEYHS: Denmark European Youth Heart Study; EEYHS: Estonia European Youth Heart Study; ICAD: International Children’s Accelerometry Database; KISS, Kinder Sportstudie; MAGIC, Movement and Activity Glasgow Intervention in Children; NHANES, National Health and Nutrition Examination Survey; NEYHS: Norway European Youth Heart Study; Pelotas: Pelotas 1993 Birth Cohort; PEYHS: Portugal European Youth Heart Study; SPEEDY, Sport, Physical Activity and Eating Behavior: Environmental Determinants in Young People.

**Table 2.** Descriptive statistics for demographic, physical activity, and cardiometabolic biomarkers variables by study.

Study	ALSPAC			CoSCIS			DEYHS			EEYHS			MAGIC			NHANES (2005-6)		
	Numb	M	(SD)	Numb	M	(SD)	Numb	M	(SD)	Numb	M	(SD)	Numb	M	(SD)	Numb	M	(SD)
Sex (% male)	5340	52.8		263	46.4		1143	55.6		436	57.8		195	52.3		1619	49.8	
Age (years)	5340	11.74	(0.23)	263	9.54	(0.38)	1143	12.22	(2.95)	436	12.42	(3.00)	195	4.17	(0.31)	1619	12.54	(3.34)
Height (cm)	5312	150.6	(7.23)	262	139.7	(5.94)	1143	152.3	(16.5)	436	152.8	(17.4)	195	102.8	(4.26)	1618	152.0	(17.4)
Weight (kg)	5317	43.40	(9.84)	262	33.25	(5.59)	1143	45.30	(15.6)	436	44.56	(15.7)	195	17.26	(2.58)	1619	51.01	(20.7)
Physical Activity (min/day)																		
ICAD cutpoints																		
Sedentary time	5340	370.8	(71.3)	263	352.9	(74.6)	1143	412.0	(121.)	436	373.5	(106.)	195	226.4	(65.5)	1619	443.7	(127.)
Moderate PA	5340	31.8	(17.9)	263	30.2	(14.6)	1143	25.1	(18.0)	436	33.4	(23.0)	195	23.1	(13.2)	1619	21.4	(16.0)
Vigorous PA	5340	4.0	(5.3)	263	4.7	(4.6)	1143	4.6	(6.3)	436	3.7	(5.9)	195	3.1	(3.3)	1619	4.1	(6.5)
Evenson cutpoints																		
Sedentary time	5340	370.8	(71.3)	263	352.9	(74.6)	1143	412.0	(121.)	436	373.5	(106.)	195	226.4	(65.5)	1619	443.7	(127.)
Moderate PA	5340	40.5	(17.1)	263	42.3	(16.1)	1143	33.4	(19.9)	436	41.1	(24.5)	195	37.8	(16.7)	1619	30.1	(17.5)
Vigorous PA	5340	16.9	(13.1)	263	16.5	(10.9)	1143	14.8	(13.7)	436	17.9	(16.3)	195	11.3	(8.6)	1619	12.7	(12.8)
Pate cutpoints																		
Sedentary time	5340	412.3	(71.0)	263	390.0	(75.8)	1143	450.8	(120.)	436	414.6	(108.)	195	259.3	(69.5)	1619	483.0	(127.)
Moderate PA	5340	58.4	(20.3)	263	66.5	(21.7)	1143	52.2	(27.9)	436	60.5	(33.0)	195	67.9	(24.2)	1619	49.7	(24.7)
Vigorous PA	5340	27.5	(17.5)	263	26.5	(14.7)	1143	22.9	(18.1)	436	28.3	(20.7)	195	19.2	(12.6)	1619	19.6	(16.7)
Diastolic Blood Pressure	5250	58.69	(6.55)	262	61.36	(5.45)	1143	60.79	(6.19)	436	61.50	(7.27)	195	60.69	(6.53)	1402	57.75	(10.6)
Systolic Blood Pressure (mm)	5250	105.4	(9.71)	262	103.6	(8.19)	1143	104.8	(9.99)	436	106.1	(10.8)	195	97.04	(7.63)	1411	107.0	(10.2)
HDL Cholesterol (mmol/l)	–	–	–	211	1.61	(0.35)	1088	1.51	(0.35)	430	1.43	(0.29)	–	–	–	1482	1.42	(0.34)
LDL Cholesterol (mmol/l)	–	–	–	211	2.33	(0.57)	1088	2.39	(0.64)	430	2.94	(0.70)	–	–	–	404	2.30	(0.67)

Triglycerides (mmol/l)	-	-	-	211	0.53	(0.23)	1088	0.82	(0.41)	430	0.78	(0.34)	-	-	-	404	0.90	(0.48)
Glucose (mmol/l)	-	-	-	214	4.82	(0.46)	1088	5.08	(0.39)	430	5.07	(0.38)	-	-	-	411	5.18	(0.46)
Waist Circumference (cm)	5314	67.96	(9.19)	262	61.89	(6.39)	1141	65.37	(9.16)	436	62.29	(7.94)	195	51.09	(4.07)	1602	73.35	(14.7)
Insulin (pmol/l)	-	-	-	206	5.74	(3.01)	1086	57.17	(36.7)	426	54.42	(31.8)	-	-	-	404	78.17	(56.5)

Study	NEYHS			NHANES (2005-06)			Pelotas			PEYHS			KISS		
	Numbe	M	(SD)	Numbe	M	(SD)	Numbe	M	(SD)	Numbe	M	(SD)	Numbe	M	(SD)
Sex (percent male)	274	51.1		1507	48.8		360	46.4		807	51.2		567	52.7	
Age (years)	274	9.69	(0.32)	1507	12.71	(3.28)	360	13.32	(0.31)	807	11.28	(3.13)	567	9.94	(2.08)
Height (cm)	273	139.3	(6.39)	1496	153.5	(17.40)	360	158.1	(8.25)	806	144.2	(14.91)	564	139.8	(13.37)
Weight (kg)	273	33.20	(5.68)	1497	52.51	(20.68)	359	51.18	(12.11)	807	41.36	(14.43)	564	34.86	(10.38)
Physical Activity (min/day)															
ICAD cutpoints															
Sedentary time	274	346.5	(108.4)	1507	449.7	(134.5)	360	777.9	(107.5)	807	418.6	(105.6)	567	631.8	(181.6)
Moderate PA	274	36.2	(21.2)	1507	23.7	(17.4)	360	21.9	(16.1)	807	25.8	(19.2)	567	37.8	(18.9)
Vigorous PA	274	7.6	(10.4)	1507	4.4	(6.2)	360	0.6	(1.5)	807	2.2	(3.5)	567	5.5	(6.1)
Evenson cutpoints															
Sedentary time	274	346.5	(108.4)	1507	449.7	(134.5)	360	777.9	(107.5)	807	418.6	(105.6)	567	631.8	(181.6)
Moderate PA	274	45.6	(22.5)	1507	32.3	(17.8)	360	33.2	(20.7)	807	37.2	(21.9)	567	51.8	(18.7)
Vigorous PA	274	22.5	(17.5)	1507	14.0	(13.6)	360	7.7	(7.9)	807	11.8	(11.5)	567	20.3	(14.4)
Pate cutpoints															
Sedentary time	274	385.7	(109.0)	1507	488.5	(135.6)	360	818.0	(108.8)	807	454.9	(104.5)	567	672.8	(184.6)
Moderate PA	274	66.5	(29.5)	1507	51.6	(23.9)	360	49.5	(27.5)	807	57.8	(28.3)	567	78.9	(23.7)
Vigorous PA	274	34.0	(22.3)	1507	21.6	(18.1)	360	15.7	(12.9)	807	20.7	(17.2)	567	32.8	(18.9)

Diastolic Blood Pressure (mm	273	62.52	(5.96)	1299	57.87	(11.51)	360	68.40	(11.03)	807	55.74	(6.46)	–	–	–
Systolic Blood Pressure (mm	274	102.9	(7.76)	1315	106.2	(10.18)	360	110.7	(13.98)	807	98.23	(9.85)	–	–	–
HDL Cholesterol (mmol/l)	65	1.55	(0.32)	1420	1.42	(0.33)	–	–	–	788	1.57	(0.33)	566	1.63	(0.36)
LDL Cholesterol (mmol/l)	58	2.88	(0.96)	686	2.31	(0.69)	–	–	–	788	2.19	(0.60)	567	2.11	(0.61)
Triglycerides (mmol/l)	48	0.92	(0.33)	687	0.95	(0.54)	–	–	–	788	0.71	(0.33)	521	0.62	(0.27)
Glucose (mmol/l)	–	–	–	457	4.98	(0.48)	–	–	–	788	5.19	(0.44)	499	4.59	(0.39)
Waist Circumference (cm)	273	60.23	(5.42)	1485	74.18	(14.81)	359	68.71	(8.53)	806	64.28	(8.41)	559	59.57	(6.95)
Insulin (pmol/l)	–	–	–	448	70.75	(59.96)	–	–	–	787	36.24	(23.17)	500	7.39	(4.28)

**Abbreviations:** ALSPAC, Avon Longitudinal Study of Parents and Children; CSCIS, Copenhagen School Child Intervention Study; DEYHS: Denmark European Youth Heart Study; EYHS: Estonia European Youth Heart Study; ICAD: International Children’s Accelerometry Database; KISS, Kinder Sportstudie; MAGIC, Movement and Activity Glasgow Intervention in Children; NA, not available; NHANES, National Health and Nutrition Examination Survey; NEYHS: Norway European Youth Heart Study; PEACH, Personal and Environmental Associations with Children’s Health; Pelotas: Pelotas 1993 Birth Cohort; PEYHS: Portugal European Youth Heart Study; SPEEDY, Sport, Physical Activity and Eating Behavior: Environmental Determinants in Young People.

**Supplemental Table.** Results of meta-analytical combination of quantile regression model coefficients and standard errors for each risk factor across the 11 studies for each of the three sets of accelerometer cutpoints.

Cardiometabolic Biomarker	VPA Tertile	Quantile of Risk Factor	Pate 3,365 counts/min					Evenson 4,012 counts/min					ICAD 6,000 counts/min				
			M	SE	(95CI)	p	M	SE	(95CI)	p	M	SE	(95CI)	p			
Diastolic Blood Pressure (mm Hg)	1	10	0.74	±1.30	(-1.81, 3.28)	0.571	-1.02	±0.73	(-2.45, 0.41)	0.164	0.36	±0.38	(-0.40, 1.11)	0.354			
		25	0.43	±0.94	(-1.41, 2.26)	0.650	-0.65	±0.61	(-1.84, 0.54)	0.286	-0.20	±0.27	(-0.73, 0.34)	0.470			
		50	0.62	±0.85	(-1.05, 2.29)	0.467	-0.97	±0.56	(-2.06, 0.12)	0.081	<b>-0.55</b>	<b>±0.26</b>	<b>(-1.06, -0.03)</b>	<b>0.039</b>			
		75	0.84	±0.95	(-1.02, 2.71)	0.377	-0.80	±0.71	(-2.19, 0.58)	0.256	-0.83	±0.26	(-1.33, -0.33)	0.001			
		90	-0.45	±1.02	(-2.45, 1.55)	0.657	0.13	±0.67	(-1.19, 1.45)	0.847	-0.54	±0.41	(-1.34, 0.26)	0.189			
	2	10	0.79	±1.36	(-1.86, 3.45)	0.559	-0.72	±0.76	(-2.21, 0.78)	0.347	-0.15	±0.33	(-0.80, 0.50)	0.657			
		25	0.54	±1.12	(-1.66, 2.74)	0.631	-0.65	±0.64	(-1.91, 0.60)	0.308	-0.38	±0.29	(-0.95, 0.20)	0.200			
		50	-0.31	±0.87	(-2.01, 1.39)	0.722	<b>-1.20</b>	<b>±0.57</b>	<b>(-2.32, -0.09)</b>	<b>0.034</b>	<b>-0.92</b>	<b>±0.25</b>	<b>(-1.41, -0.43)</b>	<b>&lt;0.001</b>			
		75	0.17	±1.01	(-1.80, 2.14)	0.866	-1.01	±0.73	(-2.44, 0.42)	0.165	<b>-1.16</b>	<b>±0.35</b>	<b>(-1.84, -0.47)</b>	<b>&lt;0.001</b>			
		90	-1.62	±1.24	(-4.05, 0.81)	0.192	-0.63	±0.84	(-2.27, 1.01)	0.451	-0.47	±0.39	(-1.24, 0.29)	0.228			
	3	10	0.81	±1.46	(-2.06, 3.68)	0.582	-0.87	±0.89	(-2.60, 0.87)	0.327	1.23	±1.00	(-0.72, 3.19)	0.216			
		25	0.31	±1.01	(-1.67, 2.29)	0.758	-0.45	±0.72	(-1.87, 0.97)	0.536	0.76	±0.67	(-0.55, 2.07)	0.257			
		50	-0.43	±0.92	(-2.24, 1.37)	0.638	<b>-1.37</b>	<b>±0.61</b>	<b>(-2.57, -0.17)</b>	<b>0.025</b>	-0.43	±0.48	(-1.36, 0.51)	0.371			
		75	0.68	±1.08	(-1.44, 2.80)	0.531	-0.66	±0.85	(-2.33, 1.00)	0.436	-0.37	±0.53	(-1.40, 0.66)	0.481			
		90	-1.48	±1.31	(-4.06, 1.09)	0.258	-0.81	±1.00	(-2.78, 1.15)	0.419	-0.63	±0.50	(-1.61, 0.35)	0.208			
Systolic Blood Pressure (mm Hg)	1	10	0.11	±1.14	(-2.12, 2.35)	0.920	-0.28	±0.80	(-1.85, 1.30)	0.731	-0.07	±0.43	(-0.91, 0.77)	0.876			
		25	1.27	±0.97	(-0.63, 3.18)	0.189	0.58	±0.74	(-0.87, 2.02)	0.433	0.39	±0.51	(-0.61, 1.40)	0.444			
		50	1.28	±0.98	(-0.63, 3.19)	0.190	0.03	±0.65	(-1.25, 1.31)	0.965	0.40	±0.45	(-0.48, 1.28)	0.369			
		75	0.62	±1.21	(-1.75, 2.98)	0.609	-0.05	±0.85	(-1.71, 1.62)	0.956	-0.12	±0.55	(-1.18, 0.95)	0.833			
		90	1.80	±1.28	(-0.71, 4.31)	0.161	0.08	±0.99	(-1.86, 2.03)	0.932	-0.04	±0.60	(-1.21, 1.12)	0.940			
	2	10	-0.01	±1.23	(-2.43, 2.40)	0.991	0.35	±0.91	(-1.44, 2.13)	0.703	0.35	±0.48	(-0.58, 1.28)	0.463			
		25	1.46	±1.06	(-0.63, 3.54)	0.171	0.88	±0.79	(-0.68, 2.44)	0.269	0.18	±0.60	(-0.98, 1.35)	0.757			
		50	1.32	±1.04	(-0.72, 3.35)	0.204	0.10	±0.74	(-1.34, 1.54)	0.892	0.15	±0.35	(-0.53, 0.84)	0.658			
		75	0.03	±1.26	(-2.44, 2.51)	0.980	-0.08	±1.05	(-2.14, 1.97)	0.936	-0.47	±0.44	(-1.33, 0.39)	0.282			
		90	2.06	±1.39	(-0.66, 4.78)	0.138	1.01	±1.35	(-1.64, 3.65)	0.456	-0.52	±0.64	(-1.78, 0.74)	0.420			
	3	10	-0.52	±1.33	(-3.12, 2.09)	0.697	0.31	±1.05	(-1.75, 2.38)	0.767	-0.18	±0.58	(-1.32, 0.96)	0.752			



		25	1.97	±1.17	(-0.33, 4.27)	0.094	1.05	±0.92	(-0.75, 2.85)	0.252	0.13	±0.71	(-1.26, 1.53)	0.851
		50	1.15	±1.12	(-1.05, 3.35)	0.306	-0.24	±0.82	(-1.84, 1.37)	0.773	0.90	±0.85	(-0.76, 2.56)	0.286
		75	0.24	±1.31	(-2.33, 2.80)	0.857	-0.29	±0.94	(-2.15, 1.56)	0.756	0.19	±0.92	(-1.61, 1.99)	0.833
		90	0.41	±1.48	(-2.49, 3.30)	0.784	-0.47	±1.38	(-3.18, 2.24)	0.734	-0.88	±1.01	(-2.86, 1.11)	0.386
HDL Cholesterol (mmol/l)	1	10	0.01	±0.06	(-0.11, 0.13)	0.899	-0.05	±0.04	(-0.13, 0.03)	0.200	-0.01	±0.02	(-0.04, 0.03)	0.587
		25	0.03	±0.06	(-0.08, 0.14)	0.563	-0.04	±0.03	(-0.11, 0.02)	0.188	0.02	±0.02	(-0.01, 0.06)	0.227
		50	0.02	±0.06	(-0.11, 0.14)	0.786	-0.03	±0.04	(-0.11, 0.06)	0.563	0.00	±0.02	(-0.03, 0.03)	0.987
		75	-0.01	±0.09	(-0.18, 0.16)	0.934	-0.03	±0.03	(-0.09, 0.04)	0.407	0.01	±0.04	(-0.06, 0.09)	0.758
		90	0.01	±0.08	(-0.15, 0.16)	0.932	-0.06	±0.05	(-0.16, 0.04)	0.213	-0.02	±0.03	(-0.09, 0.05)	0.569
	2	10	0.00	±0.07	(-0.13, 0.13)	0.987	-0.02	±0.05	(-0.12, 0.08)	0.712	0.00	±0.02	(-0.04, 0.04)	0.904
		25	0.03	±0.04	(-0.05, 0.12)	0.451	-0.01	±0.04	(-0.09, 0.08)	0.901	0.02	±0.02	(-0.01, 0.06)	0.171
		50	0.04	±0.05	(-0.06, 0.13)	0.469	-0.01	±0.03	(-0.07, 0.06)	0.847	-0.01	±0.02	(-0.04, 0.03)	0.688
		75	0.03	±0.09	(-0.14, 0.20)	0.755	0.00	±0.04	(-0.07, 0.07)	0.968	-0.01	±0.03	(-0.07, 0.05)	0.722
		90	-0.03	±0.08	(-0.19, 0.14)	0.750	-0.09	±0.06	(-0.20, 0.02)	0.117	-0.01	±0.05	(-0.11, 0.09)	0.811
	3	10	0.02	±0.06	(-0.10, 0.15)	0.725	-0.02	±0.04	(-0.10, 0.07)	0.681	0.03	±0.02	(-0.01, 0.07)	0.189
		25	0.06	±0.04	(-0.03, 0.14)	0.182	0.01	±0.04	(-0.06, 0.09)	0.709	<b>0.06</b>	<b>±0.02</b>	<b>(0.02, 0.10)</b>	<b>0.008</b>
		50	0.06	±0.04	(-0.03, 0.14)	0.198	0.03	±0.03	(-0.03, 0.10)	0.273	0.02	±0.03	(-0.03, 0.08)	0.416
		75	0.03	±0.09	(-0.14, 0.21)	0.694	0.01	±0.04	(-0.07, 0.08)	0.849	-0.01	±0.03	(-0.07, 0.05)	0.795
		90	-0.02	±0.09	(-0.20, 0.16)	0.822	-0.09	±0.06	(-0.21, 0.03)	0.155	-0.05	±0.05	(-0.15, 0.05)	0.334
LDL Cholesterol (mmol/l)	1	10	-0.15	±0.09	(-0.31, 0.02)	0.090	-0.08	±0.07	(-0.23, 0.06)	0.270	-0.02	±0.06	(-0.14, 0.09)	0.725
		25	-0.12	±0.08	(-0.28, 0.03)	0.112	-0.10	±0.09	(-0.28, 0.09)	0.295	-0.08	±0.05	(-0.17, 0.01)	0.096
		50	0.05	±0.10	(-0.15, 0.24)	0.619	-0.09	±0.07	(-0.23, 0.04)	0.182	-0.09	±0.05	(-0.17, 0.00)	0.055
		75	0.14	±0.14	(-0.14, 0.41)	0.334	0.02	±0.07	(-0.11, 0.15)	0.787	0.00	±0.05	(-0.11, 0.11)	0.978
		90	0.19	±0.28	(-0.35, 0.73)	0.497	0.10	±0.14	(-0.18, 0.38)	0.478	0.13	±0.15	(-0.15, 0.42)	0.368
	2	10	-0.17	±0.11	(-0.38, 0.05)	0.132	-0.05	±0.09	(-0.22, 0.13)	0.606	-0.06	±0.07	(-0.21, 0.08)	0.402
		25	-0.16	±0.09	(-0.33, 0.01)	0.067	-0.12	±0.09	(-0.30, 0.05)	0.178	-0.06	±0.05	(-0.15, 0.04)	0.259
		50	0.02	±0.09	(-0.16, 0.20)	0.859	-0.11	±0.07	(-0.25, 0.03)	0.127	-0.06	±0.05	(-0.16, 0.04)	0.214
		75	0.07	±0.12	(-0.17, 0.32)	0.555	0.02	±0.08	(-0.14, 0.18)	0.833	-0.01	±0.06	(-0.13, 0.11)	0.918
		90	0.14	±0.31	(-0.47, 0.75)	0.659	0.03	±0.14	(-0.24, 0.30)	0.837	0.06	±0.09	(-0.11, 0.23)	0.499
	3	10	-0.20	±0.11	(-0.42, 0.02)	0.082	-0.08	±0.10	(-0.27, 0.11)	0.420	-0.04	±0.06	(-0.14, 0.07)	0.514
		25	-0.13	±0.10	(-0.32, 0.07)	0.204	-0.07	±0.10	(-0.26, 0.13)	0.492	-0.06	±0.05	(-0.15, 0.04)	0.244
		50	0.03	±0.09	(-0.15, 0.21)	0.761	-0.12	±0.08	(-0.28, 0.04)	0.132	-0.06	±0.05	(-0.17, 0.04)	0.232
		75	0.05	±0.14	(-0.23, 0.33)	0.729	-0.04	±0.14	(-0.31, 0.23)	0.757	0.02	±0.06	(-0.11, 0.14)	0.815
		90	-0.01	±0.33	(-0.65, 0.63)	0.979	-0.08	±0.21	(-0.48, 0.33)	0.713	0.07	±0.10	(-0.12, 0.26)	0.487

Glucose (mmol/l)	1	10	0.06	±0.07	(-0.07, 0.20)	0.346	0.05	±0.05	(-0.05, 0.14)	0.355	0.01	±0.04	(-0.06, 0.09)	0.734
		25	0.04	±0.06	(-0.07, 0.16)	0.461	0.06	±0.04	(-0.03, 0.14)	0.175	0.02	±0.03	(-0.04, 0.08)	0.562
		50	0.10	±0.06	(-0.02, 0.22)	0.101	0.02	±0.04	(-0.06, 0.11)	0.593	0.02	±0.03	(-0.05, 0.09)	0.585
		75	0.04	±0.07	(-0.10, 0.17)	0.589	-0.01	±0.05	(-0.10, 0.08)	0.845	0.04	±0.03	(-0.02, 0.09)	0.168
		90	0.10	±0.08	(-0.06, 0.27)	0.210	-0.01	±0.08	(-0.15, 0.14)	0.934	-0.01	±0.05	(-0.12, 0.09)	0.802
	2	10	0.06	±0.07	(-0.08, 0.20)	0.413	0.01	±0.06	(-0.11, 0.13)	0.852	0.02	±0.04	(-0.07, 0.10)	0.706
		25	-0.02	±0.07	(-0.15, 0.11)	0.757	0.03	±0.05	(-0.07, 0.12)	0.577	0.00	±0.03	(-0.07, 0.06)	0.943
		50	0.03	±0.07	(-0.11, 0.16)	0.711	-0.01	±0.04	(-0.09, 0.08)	0.871	-0.02	±0.03	(-0.08, 0.04)	0.453
		75	0.00	±0.07	(-0.15, 0.14)	0.966	-0.04	±0.05	(-0.13, 0.05)	0.398	0.00	±0.04	(-0.07, 0.07)	0.941
		90	0.05	±0.09	(-0.12, 0.22)	0.581	-0.03	±0.08	(-0.19, 0.13)	0.707	0.00	±0.05	(-0.11, 0.10)	0.932
	3	10	0.03	±0.08	(-0.13, 0.18)	0.751	0.01	±0.07	(-0.12, 0.14)	0.896	0.00	±0.05	(-0.09, 0.09)	0.986
		25	-0.02	±0.07	(-0.16, 0.12)	0.735	0.02	±0.05	(-0.09, 0.13)	0.701	0.01	±0.03	(-0.05, 0.08)	0.697
		50	0.05	±0.07	(-0.08, 0.19)	0.462	-0.01	±0.05	(-0.11, 0.09)	0.782	-0.02	±0.03	(-0.09, 0.04)	0.445
		75	0.02	±0.08	(-0.14, 0.19)	0.791	-0.01	±0.06	(-0.14, 0.12)	0.887	0.03	±0.04	(-0.05, 0.11)	0.413
		90	0.12	±0.10	(-0.07, 0.31)	0.213	0.06	±0.10	(-0.13, 0.24)	0.557	0.10	±0.06	(-0.02, 0.22)	0.107
Insulin (pmol/l)	1	10	4.56	±2.82	(-0.96, 10.08)	0.106	-0.57	±2.43	(-5.34, 4.20)	0.815	0.94	±1.26	(-1.52, 3.40)	0.453
		25	<b>6.88</b>	<b>±3.19</b>	<b>(0.63, 13.13)</b>	<b>0.031</b>	2.39	±2.49	(-2.50, 7.27)	0.338	-0.18	±2.13	(-4.36, 4.00)	0.932
		50	<b>9.17</b>	<b>±4.14</b>	<b>(1.06, 17.28)</b>	<b>0.027</b>	3.54	±2.93	(-2.21, 9.28)	0.228	-0.33	±1.87	(-4.00, 3.34)	0.860
		75	14.32	±10.1 <sub>1</sub>	(-5.49, 34.13)	0.157	3.41	±5.67	(-7.70, 14.52)	0.548	-3.38	±2.76	(-8.79, 2.02)	0.220
		90	30.37	±20.7 <sub>3</sub>	(-10.27, 71.01)	0.143	-4.51	±14.6 <sub>5</sub>	(-33.22, 24.20)	0.758	-7.23	±4.94	(-16.91, 2.45)	0.143
	2	10	2.63	±3.13	(-3.50, 8.76)	0.401	-1.03	±2.63	(-6.19, 4.13)	0.696	1.10	±1.60	(-2.03, 4.23)	0.492
		25	2.64	±3.37	(-3.96, 9.25)	0.433	0.56	±2.47	(-4.29, 5.40)	0.822	1.11	±1.62	(-2.06, 4.28)	0.492
		50	4.25	±3.44	(-2.49, 10.99)	0.217	2.11	±3.08	(-3.93, 8.14)	0.494	-0.40	±1.99	(-4.30, 3.51)	0.842
		75	5.89	±5.78	(-5.44, 17.22)	0.308	-3.63	±7.72	(-18.76, 11.50)	0.638	-4.12	±3.65	(-11.28, 3.04)	0.259
		90	2.22	±11.9 <sub>8</sub>	(-21.25, 25.70)	0.853	-13.89	±13.2 <sub>8</sub>	(-39.93, 12.14)	0.296	-13.27	±5.83	(-24.68, -1.85)	<b>0.023</b>
	3	10	-1.07	±3.59	(-8.11, 5.96)	0.765	-2.74	±3.56	(-9.72, 4.24)	0.442	-2.96	±1.63	(-6.15, 0.22)	0.068
		25	2.10	±3.76	(-5.28, 9.47)	0.577	0.71	±2.77	(-4.72, 6.14)	0.798	-2.40	±2.05	(-6.42, 1.62)	0.241
		50	1.90	±3.74	(-5.43, 9.24)	0.611	-0.44	±3.60	(-7.49, 6.61)	0.903	-3.44	±2.45	(-8.24, 1.37)	0.161
		75	-0.67	±9.42	(-19.13, 17.78)	0.943	-7.88	±8.07	(-23.69, 7.93)	0.329	-12.60	±4.43	(-21.28, -3.92)	<b>0.004</b>

		90	-9.98	±10.6 <sub>9</sub>	(-30.93, 10.98)	0.351	-26.89	±15.8 <sub>3</sub>	(-57.91, 4.14)	0.089	-27.03	±9.18	(-45.03, -9.03)	0.003
Triglycerides (mmol/l)	1	10	0.00	±0.04	(-0.08, 0.08)	0.990	0.03	±0.03	(-0.02, 0.08)	0.255	0.00	±0.02	(-0.04, 0.03)	0.781
		25	0.02	±0.04	(-0.05, 0.09)	0.630	0.01	±0.03	(-0.05, 0.07)	0.722	-0.01	±0.02	(-0.05, 0.03)	0.593
		50	<b>0.09</b>	<b>±0.04</b>	<b>(0.01, 0.17)</b>	<b>0.029</b>	0.02	±0.03	(-0.04, 0.08)	0.446	-0.01	±0.02	(-0.05, 0.04)	0.750
		75	0.04	±0.10	(-0.15, 0.24)	0.655	<b>0.10</b>	<b>±0.05</b>	<b>(0.00, 0.19)</b>	<b>0.050</b>	0.04	±0.04	(-0.03, 0.11)	0.245
		90	-0.11	±0.13	(-0.36, 0.14)	0.398	0.01	±0.10	(-0.18, 0.20)	0.905	0.04	±0.05	(-0.07, 0.14)	0.492
	2	10	0.00	±0.05	(-0.09, 0.09)	0.954	0.00	±0.03	(-0.05, 0.06)	0.906	-0.01	±0.02	(-0.05, 0.02)	0.411
		25	0.01	±0.04	(-0.06, 0.09)	0.743	-0.01	±0.03	(-0.08, 0.05)	0.647	0.00	±0.02	(-0.04, 0.03)	0.884
		50	<b>0.11</b>	<b>±0.05</b>	<b>(0.01, 0.21)</b>	<b>0.027</b>	0.00	±0.04	(-0.08, 0.07)	0.903	-0.04	±0.02	(-0.09, 0.01)	0.115
		75	0.06	±0.11	(-0.16, 0.28)	0.595	0.05	±0.05	(-0.05, 0.14)	0.371	-0.02	±0.04	(-0.10, 0.06)	0.645
		90	-0.08	±0.13	(-0.33, 0.17)	0.525	0.04	±0.10	(-0.16, 0.25)	0.693	-0.04	±0.08	(-0.20, 0.12)	0.630
	3	10	-0.02	±0.05	(-0.12, 0.09)	0.745	-0.01	±0.03	(-0.08, 0.05)	0.691	0.00	±0.02	(-0.04, 0.03)	0.792
		25	-0.01	±0.04	(-0.09, 0.07)	0.788	-0.01	±0.04	(-0.08, 0.06)	0.783	0.00	±0.02	(-0.04, 0.04)	0.950
		50	0.06	±0.05	(-0.04, 0.16)	0.216	-0.03	±0.04	(-0.11, 0.05)	0.424	-0.03	±0.03	(-0.08, 0.02)	0.277
		75	0.02	±0.13	(-0.23, 0.27)	0.885	0.03	±0.06	(-0.08, 0.15)	0.564	-0.03	±0.04	(-0.12, 0.06)	0.477
		90	-0.16	±0.16	(-0.48, 0.15)	0.315	0.01	±0.10	(-0.20, 0.21)	0.959	-0.03	±0.07	(-0.17, 0.10)	0.626
Waist Circumference (cm)	1	10	0.58	±0.85	(-1.09, 2.24)	0.497	-0.04	±0.58	(-1.18, 1.09)	0.939	0.21	±0.21	(-0.20, 0.62)	0.323
		25	0.67	±0.66	(-0.63, 1.96)	0.314	-0.75	±0.57	(-1.88, 0.38)	0.193	-0.18	±0.19	(-0.55, 0.20)	0.357
		50	0.26	±1.11	(-1.93, 2.44)	0.818	-0.87	±0.60	(-2.05, 0.31)	0.147	<b>-0.67</b>	<b>±0.34</b>	<b>(-1.33, -0.01)</b>	<b>0.048</b>
		75	0.69	±1.49	(-2.23, 3.61)	0.642	-0.81	±0.76	(-2.31, 0.68)	0.285	<b>-1.19</b>	<b>±0.51</b>	<b>(-2.19, -0.19)</b>	<b>0.020</b>
		90	0.53	±2.36	(-4.10, 5.17)	0.822	-1.62	±1.29	(-4.14, 0.90)	0.209	<b>-1.86</b>	<b>±0.61</b>	<b>(-3.05, -0.67)</b>	<b>0.002</b>
	2	10	0.50	±0.81	(-1.09, 2.10)	0.537	-0.18	±0.63	(-1.40, 1.05)	0.779	0.01	±0.27	(-0.52, 0.53)	0.978
		25	0.35	±0.66	(-0.95, 1.66)	0.595	<b>-1.17</b>	<b>±0.52</b>	<b>(-2.18, -0.15)</b>	<b>0.024</b>	-0.16	±0.28	(-0.71, 0.38)	0.554
		50	-0.54	±0.85	(-2.21, 1.13)	0.525	<b>-1.73</b>	<b>±0.57</b>	<b>(-2.86, -0.61)</b>	<b>0.003</b>	-0.76	±0.52	(-1.77, 0.26)	0.143
		75	-1.32	±1.65	(-4.55, 1.92)	0.425	<b>-2.58</b>	<b>±0.88</b>	<b>(-4.30, -0.86)</b>	<b>0.003</b>	<b>-1.80</b>	<b>±0.66</b>	<b>(-3.10, -0.51)</b>	<b>0.006</b>
		90	-2.73	±2.48	(-7.60, 2.14)	0.272	<b>-3.94</b>	<b>±1.80</b>	<b>(-7.47, -0.41)</b>	<b>0.029</b>	<b>-2.62</b>	<b>±1.00</b>	<b>(-4.58, -0.66)</b>	<b>0.009</b>
	3	10	0.53	±0.81	(-1.06, 2.11)	0.514	-0.45	±0.75	(-1.91, 1.01)	0.543	-0.38	±0.33	(-1.03, 0.26)	0.247
		25	0.12	±0.72	(-1.28, 1.53)	0.864	<b>-1.68</b>	<b>±0.73</b>	<b>(-3.10, -0.26)</b>	<b>0.020</b>	<b>-0.94</b>	<b>±0.32</b>	<b>(-1.56, -0.31)</b>	<b>0.003</b>
		50	-1.53	±1.05	(-3.59, 0.52)	0.144	<b>-2.63</b>	<b>±0.76</b>	<b>(-4.12, -1.14)</b>	<b>&lt;0.001</b>	<b>-1.61</b>	<b>±0.56</b>	<b>(-2.70, -0.51)</b>	<b>0.004</b>
		75	-3.23	±1.73	(-6.62, 0.16)	0.062	<b>-4.62</b>	<b>±0.99</b>	<b>(-6.56, -2.68)</b>	<b>&lt;0.001</b>	<b>-3.05</b>	<b>±0.72</b>	<b>(-4.45, -1.65)</b>	<b>&lt;0.001</b>
		90	<b>-6.00</b>	<b>±2.68</b>	<b>(-11.25, -0.74)</b>	<b>0.025</b>	<b>-7.30</b>	<b>±1.89</b>	<b>(-11.01, -3.58)</b>	<b>&lt;0.001</b>	<b>-4.28</b>	<b>±1.02</b>	<b>(-6.29, -2.27)</b>	<b>&lt;0.001</b>