Objectively Measured Time Spent Sedentary Is Associated With Insulin Resistance Independent of Overall and Central Body Fat in 9- to 10-Year-Old Portuguese Children

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OBJECTIVE — We examined the independent relationships between objectively measured physical activity and insulin resistance in Portuguese children.

RESEARCH DESIGN AND METHODS — This is a school-based, cross-sectional study in 147 randomly selected girls (aged 9.8 ± 0.3 years; 27.8 ± 9.3% body fat) and 161 boys (aged 9.8 ± 0.3 years; 22.0 ± 9.2% body fat). Physical activity was assessed by the Actigraph accelerometer for 4 days and summarized as time spent sedentary (accelerometer counts <500/min), in light-intensity (accelerometer counts 500–2,000/min), and in moderate- and vigorous-intensity activity (accelerometer counts >2,001/min). We measured total and central fat mass by dual-energy X-ray absorptiometry. Insulin resistance was expressed as the homeostasis model assessment score.

RESULTS — Time (min/day) spent sedentary was significantly and positively associated with insulin resistance (β-coefficient = 0.001 [95% CI 0.0002–0.002]; $P = 0.013$). Time spent in moderate- and vigorous-intensity physical activity (−0.002 [−0.003 to −0.001]; $P = 0.0009$) and overall physical activity (−0.001 [−0.008 to 0.003]; $P < 0.0001$) were significantly and inversely associated with insulin resistance. All associations remained statistically significant, although they were attenuated after further adjustments for sex, birth weight, sexual maturity, and total or central fat mass ($P < 0.03$).

CONCLUSIONS — Physical activity is associated with insulin resistance independent of total and central fat mass in children. Our results emphasize the importance of decreasing sedentary behavior and increasing time spent in moderate- and vigorous-intensity activity in children, which may have beneficial effects on metabolic risk factors regardless of the degree of adiposity.

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Abbreviations: DEXA, dual-energy X-ray absorptiometry; HOMA-IR, homeostasis model assessment of insulin resistance; MVPA, moderate- and vigorous-intensity physical activity.

The prevalence of childhood overweight and obesity is increasing at an alarming rate worldwide (1–4). Excessive body fat is associated with numerous adverse health consequences, including impaired glucose tolerance, hyperinsulimenia, and type 2 diabetes. Central obesity and especially visceral fat are recognized to predispose children and adolescents to the development of insulin resistance and type 2 diabetes (5,6).

Physical activity may counteract the adverse effect of obesity on insulin resistance in children. Previous studies examining the associations between physical activity and insulin resistance have been conducted in overweight children (7) or in children predisposed to type 2 diabetes due to a family history of the disease (8). Furthermore, most previous observational studies (9–12) have used relatively imprecise self-report methods to assess physical activity, which preclude the ability to quantify dose-response associations and determine the influence of different subcomponents (time spent sedentary and at light-, moderate-, and vigorous-intensity activity) of physical activity on insulin resistance. It is also unclear whether physical activity is associated with insulin resistance independent of overall and central adiposity (8,10–12), and some (9) have suggested a sex difference for the association between activity with insulin resistance.

We have previously shown that objectively measured overall physical activity is associated with insulin sensitivity in Danish 9- to 10-year-old children (13). However, that study did not assess which of the subcomponents of physical activity were related to insulin sensitivity, with skinfold measurements used as an indicator of overall adiposity. Dual-energy X-ray absorptiometry (DEXA) can be used to quantify both overall and central fat mass (14–16), which makes this method preferable to skinfold measurements. Therefore, the aim of the present study

was to examine the independent relationships between objectively measured physical activity and insulin resistance in Portuguese children.

RESEARCH DESIGN AND METHODS

— This is a cross-sectional, population-based study in 9- to 10-year-old Portuguese children who were part of the European Youth Heart Study; selection criteria has been reported elsewhere (17). A total of 530 healthy children from the county of Madeira, Portugal, were sampled and invited to participate in the study, along with their parents. Of these, 72 children refused to wear the activity monitor, 96 children were excluded due to not meeting the inclusion criteria (see below), and 37 children were excluded due to faulty activity monitors. Complete anthropometric, body composition, and clinical and physical activity measurements were available in 308 (147 girls and 161 boys) children. There were no significant differences ($P > 0.05$) in body weight, height, BMI, sum of skinfolds, waist circumference, fasting triglycerides, insulin, glucose, HDL cholesterol, and cardio-respiratory fitness between those with complete data compared with the rest of children. After written informed consent was obtained from a parent or guardian, and all data were collected at the University of Madeira.

Anthropometric and body composition measurements

Height was measured, without shoes, to the nearest 0.5 cm using a portable Harpenden stadiometer. Weight was measured to the nearest 0.1 kg with a calibrated-beam balance scale while the children were wearing light clothing. BMI was calculated as a weight in kilograms divided by the square of height in meters. Overweight and obesity was defined according to age-specific cut points (18). Waist circumference was measured twice with a metal anthropometric tape midway between the lower rib margin and the iliac crest at the end of a gentle expiration, and the average of the two measures was used for analysis. DEXA was used to assess total and regional body composition (QDR-1500; Hologic, Waltman, MA) (pencil-beam mode, software version 5.67 enhanced whole-body analysis). Following the protocol for DEXA described by the manufacturer, a step phantom with six fields of acrylic and aluminum of varying thickness and known absorptive properties was scanned alongside each subject to serve as an external standard for the analysis of different tissue composition. Fat-free mass was defined as the sum of the fat-free soft tissue and total-body mineral content from the whole-body scans. The same technician positioned the children, performed the scans, and completed the scan analysis according to the operator's manual using the standard analysis protocol.

Sexual maturation was assessed by the investigators, using Tanner's five-stage scale for breast development in girls and pubic hair in boys (19). Children were stratified as prepubertal (Tanner stage 1) or having started puberty (Tanner stages 2 and 3). Data on birth weight, parental socioeconomic status, body weight, and height were collected by self-report.

Blood samples

After a 12-h overnight fast, venous blood samples were taken from the antecubital vein and collected into EDTA vacutainer tubes. Samples were aliquoted and separated within 30 min and stored at −80°C until transport to World Health Organization–certified laboratories for analyses (Cambridge, U.K.). Samples were analyzed for serum glucose and insulin. Glucose was analyzed using the hexokinase method, measured on an Olympus AU600 autoanalyser for all samples (Olympus Diagnostica, Hamburg, Germany). Plasma-specific insulin was determined by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels. Cross-reactivity was <0.2% with intact proinsulin at 400 pmol/l and <1% with 32–33 split proinsulin at 400 pmol/l. Interassay coefficients of variation were 6.6% at 28.6 pmol/l ($n = 99$), 4.8% at 153.1 pmol/l ($n = 102$), and 6.0% at 436.7 pmol/l ($n = 99$), respectively.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by dividing the product of fasting glucose (mmol/l) and fasting insulin (μU/ml) by 22.5 (20). This method serves as a valuable surrogate for the assessment of insulin resistance in nondiabetic children (21). We defined insulin resistance as HOMA-IR >3.16 (22).

Assessment of physical activity

Physical activity was assessed using the computer science and applications accelerometer, also known as the MTI Actigraph (Manufacturing Technology, Fort Walton Beach, FL), over 2 weekdays and 2 weekend days, as previously described (23). Briefly, the children wore the accelerometer attached to an elastic waistband on the right hip; volunteers were instructed to wear the monitors during the daytime, except while sleeping, bathing, and during aquatic activities. Activity data were stored on a minute-by-minute basis and were downloaded to a computer before analysis. Physical activity components, including wearing time, were derived as previously described (24), using a special written software (MAHUffe [available at www.mrc-epid.cam.ac.uk]). We first deleted missing data defined as sequences of ≥10 consecutive 0s. We thereafter excluded from analysis all children who did not manage to record ≥600 min/day of activity for ≥3 days. The following variables were derived from the software: total volume of physical activity (counts/min/day) and time (min/day) spent in sedentary activities (<500 counts/min) and at light-intesity (500–1,999 counts/min), moderate-intensity (≥2,000 counts/min), and vigorous-intensity (≥3,000 counts/min) physical activity. Children spent <3% of the daytime at a vigorous-intensity level. Therefore, time spent in moderate- and vigorous-intensity activities were combined into one single variable (moderate- and vigorous-intensity physical activity [MVPA]). Our threshold for MVPA (>2,000 counts/min) corresponds to a walking speed of ~3–4 km/h (21).

Statistical methods

Data are presented as means ± SD. All variables were checked for normality. Fasting insulin and HOMA-IR were logarithmically transformed to normalize their distribution. Differences in body composition variables, physical activity patterns, and biochemical variables between sexes were determined by ANOVA. Pearson's correlation coefficients were used to examine the bivariate associations between insulin resistance (HOMA-IR) and each of the physical activity components. Multiple linear regression analysis was used to test the independent associations between physical activity variables and insulin resistance. Model building was performed by first assessing the associations between sex, sexual maturity, and birth weight with insulin resistance, thereafter introducing the subcomponents of physical activity in separate models, as some of these variables were highly correlated with each other ($r > 0.70$). All physical activity subcomponents were adjusted for the amount of time the monitor was worn. Finally, we adjusted our mod-

Table 1—*Physical characteristics of the children*

	All	Boys	Girls
n	308	161	147
Age (years)	9.81 ± 0.3	9.81 ± 0.3	9.82 ± 0.3
Weight (kg)	34.1 ± 7.8	34.3 ± 7.7	33.9 ± 7.8
Height (m)	1.37 ± 0.1	1.37 ± 0.1	1.37 ± 0.1
BMI (kg/m²)	18.0 ± 3.1	18.1 ± 3.2	17.9 ± 3.0
Waist circumference (cm)	61.5 ± 7.3	63.4 ± 7.3	59.4 ± 6.6*
Birth weight (kg)	3.40 ± 0.52	3.46 ± 0.55	3.32 ± 0.48†
Total physical activity (counts/min)	654 ± 240	724 ± 268	577 ± 178*
Sedentary activity (min/day)	315 ± 90	307 ± 95	323 ± 84
Light activity (min/day)	287 ± 49	278 ± 47	296 ± 49*
Moderate and vigorous activity (min/day)	177 ± 64	195 ± 67	157 ± 54†
Fat mass (kg)	9.10 ± 5.6	8.19 ± 5.6	10.1 ± 5.4†
Fat mass (%)	24.8 ± 9.4	21.9 ± 9.0	28.0 ± 8.8*
Trunk fat mass (kg)	2.82 ± 2.5	2.39 ± 2.5	3.29 ± 2.5†
Central fat mass (kg)	0.67 ± 0.6	0.59 ± 0.5	0.77 ± 0.5†
Glucose (mmol/l)	5.2 ± 0.3	5.2 ± 0.3	5.2 ± 0.4
Insulin (μU/ml)	6.1 ± 3.5	5.3 ± 2.8	7.0 ± 3.9*
HOMA-IR	1.21 (1.10–1.32)	1.09 (0.99–1.19)	1.38 (1.26–1.50)*

Data are means ± SD or geometric means (95% CI). *$P < 0.001$ and †$P < 0.05$ for sex differences.

els for total fat mass or central fat mass assessed by DEXA. We included the interaction term sex by physical activity separately for each physical activity component model in order to explore whether sex or sexual maturity modified any of the associations between physical activity and insulin resistance. Similarly, a three-way interaction term (sex times sexual maturation times physical activity) was also introduced into the respective models. Finally, we introduced socioeconomic status and parental BMI and substituted fat mass by waist circumference as potential confounding variables, but adjustment for these variables did not change the magnitude or direction of associations and were therefore excluded from our final models. All data were analyzed in their continuous form but were stratified into quartiles of time spent sedentary and at MVPA for illustrative purposes. Data were analyzed using the Statistical Package for Social Sciences (SPSS version 13.0 for Windows; SPSS, Chicago, IL), and the level of significance was set at $P < 0.05$.

RESULTS — Descriptive characteristics are presented in Table 1. Age, weight, height, and BMI did not differ significantly between boys and girls. Total and regional body fat, percentage fat mass, fasting insulin, and HOMA-IR were significantly higher in girls than in boys. Significant sex differences were also observed for physical activity components. Boys spent significantly less time at light-intensity activity and more time at MVPA than girls. Time spent sedentary did not differ significantly between boys and girls. A total of 18.5% of children (20.4% girls and 16.8% boys) were classified as overweight, and an additional 8.8% children (8.2% girls and 9.3% boys) were obese. Fifteen children (three normal weight, three overweight, and nine obese) were insulin resistant.

Time spent sedentary was significantly correlated with time spent at light-intensity activity ($r = -0.15$, $P = 0.008$) and with time spent at MVPA ($r = -0.70$, $P < 0.0001$). Time spent at light-intensity activity was not correlated with time spent at moderate- and vigorous-intensity activity ($r = 0.05$, $P = 0.50$). Time spent sedentary was significantly and positively associated with fasting insulin ($r = 0.21$, $P < 0.0001$) and HOMA-IR ($r = 0.21$, $P < 0.0001$). Time spent at moderate- and vigorous-intensity physical activity was significantly and inversely correlated with fasting insulin and HOMA-IR ($r = -0.23$ and -0.24, respectively; $P < 0.0001$). Similarly, total physical activity (counts/min) was also significantly and inversely associated with fasting insulin and HOMA-IR ($r = -0.27$ and -0.28, respectively; $P < 0.0001$). All associations were attenuated but were still statistically significant after further adjustment for sex and monitored time (partial $r = <0.05$). Time spent at light intensity was not associated with fasting insulin ($r = 0.10$, $P = 0.08$) or HOMA-IR ($r = 0.10$, $P = 0.08$), and these nonsignificant associations remained after further adjustment for sex and monitored time.

Table 2 displays the regression coefficients (95% CI) for the association between subcomponents of physical activity and insulin resistance. Time spent sedentary was significantly and positively associated with HOMA-IR ($P = 0.013$) after adjustment for sex, sexual maturity, and birth weight. Total physical activity ($P < 0.0001$) and time spent at moderate-intensity activity ($P = 0.0009$) were also significantly but inversely associated with HOMA-IR after adjustment for the same confounders as above. No association was observed between time spent at light-intensity activity and insulin resistance and no significant two- or three-way interactions were observed for any of our models.

We thereafter adjusted our models for total fat mass or central fat mass (Table 2). These adjustments attenuated the associations between physical activity variables and insulin resistance. However, time spent sedentary was positively associated with HOMA-IR after further adjustments for total or central fat mass ($P = 0.027$), and time spent in MVPA ($P = 0.011$) and overall physical activity ($P = 0.007$) were significantly and inversely associated with HOMA-IR after adjustment for total or central fat mass. Physical activity variables explained 8–9% of the variance in HOMA-IR with a full model including

Table 2—*Multiple linear regression coefficients (95% CI) for the association between objectively measured components of physical activity with insulin resistance (HOMA-IR) in Portuguese children* (n = 308)

	Model 1		Model 2		Model 3	
Outcome (HOMA-IR)	β-Coefficient (95% CI)	*P* value	β-Coefficient (95% CI)	*P* value	β-Coefficient (95% CI)	*P* value
Sex (girls)	0.370 (0.22–0.52)	<0.0001	0.18 (0.04–0.31)	0.01	0.20 (0.07–0.33)	0.001
Sexual maturity (Tanner 1)	−0.410 (−0.59 to −0.23)	<0.0001	−0.17 (−0.33 to −0.004)	0.045	−0.19 (−0.35 to −0.02)	0.025
Birth weight (kg)	−0.060 (−0.18–0.06)	0.33	−0.14 (−0.24 to −0.03)	0.013	−0.10 (−0.21 to 0.006)	0.065
Fat mass (kg)	—	—	0.05 (0.04–0.06)	<0.0001	—	—
Central fat mass (kg)	—	—	—	—	0.48 (0.38–0.59)	<0.0001
Total physical activity (cpm)	−0.001 (−0.008 to −0.003)	<0.0001	−0.0003 (−0.0006 to −0.00001)	0.007	−0.0003 (−0.0006 to −0.0009)	0.007
Sedentary (min/day)	0.001 (0.0002–0.002)	0.003	0.001 (0.000001–0.002)	0.012	0.0008 (0.00009–0.002)	0.009
Light (min/day)	0.0003 (−0.001 to 0.002)	0.75	−0.0002 (0.002 to 0.001)	0.81	−0.0002 (−0.002 to 0.001)	0.76
MVPA (min/day)	−0.002 (−0.003 to −0.001)	0.002	−0.001 (−0.002 to −0.0003)	0.017	−0.001 (−0.003 to −0.001)	0.022

Model 1 adjusted for sex, sexual maturity, and birth weight. Model 2 additionally adjusted for overall fat mass. Model 3 additionally adjusted for central fat mass. Time variables are additionally adjusted for measurement time.

sex, sexual maturity, birth weight, and total fat mass, explaining between 32 and 34% of the variance in HOMA-IR (data not shown). We thereafter substituted waist circumference for central fat mass and reanalysed our models, but this did not materially change the results.

Figure 1 shows the adjusted geometric means of HOMA-IR stratified by quartiles of time spent sedentary (Fig. 1*A*) (P for trend = 0.043) and time spent at MVPA (Fig. 1*B*) (P for trend = 0.11). Post hoc analyses revealed significant differences ($P < 0.05$) between the first and fourth quartile for time spent sedentary and at moderate and vigorous intensity.

CONCLUSIONS — This is the first study suggesting that objectively measured time spent sedentary is associated with insulin resistance in 9- to 10-year-old healthy, prepubertal children, independent of sex, birth weight, sexual maturity, and total or central fat mass. Further, these associations were consistent for both continuous and categorical analyses and suggest that reducing sedentary behavior and increasing the amount of time spent at MVPA may have beneficial effects on insulin resistance in healthy children.

When interpreting the results from this study, the following limitations need consideration. First, our study was cross-sectional, thus limiting inferences of causality and its direction. Second, although we controlled for the confounding effect of sex, sexual maturity, birth weight, and total or central fat mass, it is possible that other unmeasured confounders such as genetic variation and dietary factors could explain our findings. Third, our results may only be generalizable to Portuguese 9- to 10-year-old children. However, given the increasing evidence of an independent association between objectively measured physical activity and metabolic risk factors in children and adolescents (13,25,26), it is likely that our results are generalizable to a large proportion of healthy children living in affluent societies. Even though we assessed physical activity using an objective and valid method (27), some limitations remain. The monitor must be removed during bathing and other water activities, and it does not accurately pick up upper-body movement and other activities that involve minimal vertical acceleration of the body, such as cycling. Furthermore, limitations are inherent in all intensity thresholds used to summarize accelerometry data (28); how-

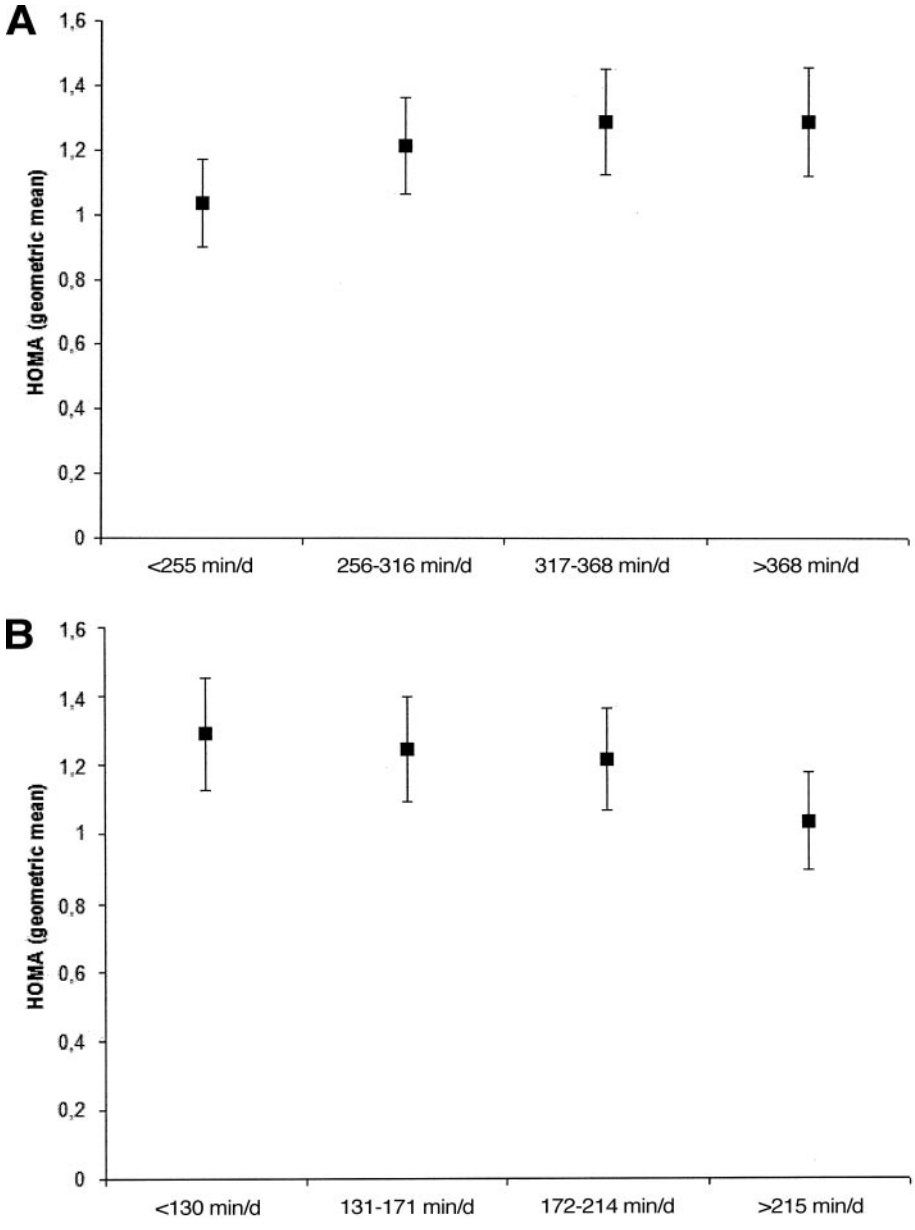

Figure 1—*Adjusted geometric means of HOMA-IR stratified by quartiles of time spent sedentary* (A) (P *for trend = 0.043) and time spent at MVPA* (B) (P *for trend = 0.11) in 9- to 10-year-old Portuguese children* (n = *308). Post hoc analyses revealed significant differences* (P < *0.05) between the first and fourth quartile for time spent sedentary and at moderate and vigorous intensity. Data are adjusted for sex, sexual maturity, birth weight, and fat mass.*

ever, our threshold for moderate- and vigorous-intensity activity is consistent with our previous studies (23,26). The threshold used for time spent sedentary is a compromise between the lowest (<100 cpm) (29) and highest (<1,100 cpm) (30) published sedentary cut points. However, reanalysing our data using the lower cut point (<100 cpm) did not change any of our results. We used a 1-min epoch when assessing physical activity by accelerometry, this may be a potential limitation as this epoch length may underestimate the amount of time spent in vigorous-intensity activity in children (31). However, it is highly unlikely that this would change the direction of the observed associations, but it may attenuate them. Regardless, the use of an objective method for assessing physical activity and its subcomponents in this study must be considered as a major strength. Other strengths include our precise measure of total and central fat mass by DEXA and the collection of fasting blood samples in a randomly selected population of young children. Our results also highlight the limitations of using BMI as a measure of body composition when comparing differences between sexes. Indeed, fat mass and percentage body fat measured by DEXA were significantly higher in girls than in boys, whereas there was no difference in BMI. Furthermore, we did not observe any difference in height between sexes, which may have contributed to the nonsignificant difference in BMI.

Nine children (five girls and four boys) did not accumulate ≥60 min of moderate-intensity physical activity according to current recommendations of health-enhancing physical activity in youth (32,33). However, we have recently suggested that physical activity levels may need to be higher than the current guidelines of 1 h of moderate-intensity physical activity per day (26). Our study was not powered to examine nonlinearity; thus, studies that seek to determine whether there is a threshold for the association between physical activity and insulin resistance in children are required. Regardless, these results support our previous findings (13), underscoring the importance of reducing sedentary time in relation to insulin resistance in children.

Evidence from exercise-training studies in obese children suggests that moderate-and vigorous-intensity exercise is associated with a favorable metabolic profile (7). Some (9–13), but not all (8), previous observational studies have reported an independent association between physical activity and insulin sensitivity in children. For example, subjectively measured physical activity was significantly associated with fasting insulin and insulin sensitivity independent of age, sex, race, maturation, BMI, percent body fat, waist circumference, and lipid levels in 10- to 16-year-old children (10). Further, Ku et al. (34) observed an association between insulin sensitivity and vigorous-intensity but not with moderate-intensity physical activity, independent of body fat and fat distribution. However, these studies assessed physical activity by self-report, which may limit the ability to accurately examine the influence of different subdimensions of physical activity, as these are likely to be reported with different degrees of error. Furthermore, the validity of self-reported physical activity in children is usually considered to be poor (35).

Previous studies from the European Youth Heart Study have examined the association between objectively measured physical activity and metabolic risk fac-

tors in children (13,25,26). In these studies, an inverse association was observed between the total volume of physical activity and metabolic risk factors, independent of skinfold-assessed body fat. The results from the present study are novel, extending our previous observations. First, we examined the association between subcomponents of physical activity and insulin resistance, with the results suggesting that time spent sedentary and at moderate- and vigorous-intensity activity are associated with insulin resistance in a dose-response manner. Second, our results suggest that these associations are independent of precisely measured total or central fat mass and other confounding factors including birth weight.

Identifying the detailed associations between subcomponents of physical activity, insulin resistance, and other metabolic disease risk factors is important to inform primary prevention and future interventions aimed at increasing physical activity in children. Our observations are the first suggesting that objectively measured time spent sedentary is associated with insulin resistance in children and corroborate previous observations in overweight adults with a family history of type 2 diabetes (36). Similarly, Healy et al. (37) also suggested that objectively measured time spent sedentary was positively associated with glucose intolerance in adult Australian healthy men and women using the same assessment method. Taken together, reducing time devoted to sedentary behaviors and simultaneously increasing the amount of time spent at moderate- and vigorous-intensity activity is likely to have significant metabolic health benefits not only in adults but also in healthy prepubertal children, regardless of their levels of adiposity. Interestingly, our results suggest that sedentary time should be replaced with moderate- and vigorous-intensity physical activity but not with light-intensity activity, as light-intensity activity does not seem to confer any benefit in relation to insulin resistance. This may at least partly be explained by the large amount of time devoted to moderate- and vigorous-intensity activity in these children combined with a strong inverse correlation between moderate- and vigorous-intensity activity and time spent sedentary. From a public health perspective, this may mean that promoting activities such as active play, active commuting by walking or bicycling, sports, and other outdoor leisure activities usually performed at a moderate intensity should be prioritized. This is in agreement with current recommendations for physical activity in children (32,33).

In conclusion, time spent sedentary and at MVPA is associated with insulin resistance independent of total or central fat mass in healthy Portuguese children. Reducing sedentary behavior and increasing the totality of activity may have beneficial effects on metabolic risk factors, even in prepubertal children. The development and implementation of multidimensional strategies focused on reducing sedentary behaviors and increasing overall involvement in different types of moderate-intensity activity are critically important in the primary prevention of metabolic disorders at young age.

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L.B.S. and U.E. drafted the manuscript and did the data analysis. L.B.S., S.A.A., C.J.R., L.B.A., U.E., and K.F. contributed to the concept and design of the European Youth Heart Study (EYHS). U.E., C.J.R., and L.B.A. are members of the physical activity group within the EYHS. L.B.S., S.A.A., and K.F. obtained funding for the EYHS. U.E., R.O. and A.L.Q. were responsible for cleaning and analyzing physical activity data. R.O. and A.L.Q. collected all data, organized the data, and analyzed the dual-energy X-ray absorptiometry data. All authors contributed to the interpretation and discussion of the results and approved the final manuscript.

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