BRIEF REPORT

Physical Activity Attenuates the Effect of Low Birth Weight on Insulin Resistance in Adolescents

Findings From Two Observational Studies

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OBJECTIVE—To examine whether physical activity influences the association between birth weight and insulin resistance in adolescents.

RESEARCH DESIGN AND METHODS—The study comprised adolescents who participated in two cross-sectional studies: the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study (n = 520, mean age = 14.6 years) and the Swedish part of the European Youth Heart Study (EYHS) (n = 269, mean age = 15.6 years). Participants had valid data on birth weight (parental recall), BMI, sexual maturation, maternal education, breastfeeding, physical activity (accelerometry, counts/minute), fasting glucose, and insulin. Insulin resistance was assessed by homeostasis model assessment–insulin resistance (HOMA-IR). Maternal education level and breastfeeding duration were reported by the mothers.

RESULTS—There was a significant interaction of physical activity in the association between birth weight and HOMA-IR (logarithmically transformed) in both the HELENA study and the EYHS (P = 0.05 and P = 0.03, respectively), after adjusting for sex, age, sexual maturation, BMI, maternal education level, and breastfeeding duration. Stratified analyses by physical activity levels (below/above median) showed a borderline inverse association between birth weight and HOMA-IR in the low-active group (standardized β = −0.094, P = 0.09, and standardized β = −0.156, P = 0.06, for HELENA and EYHS, respectively), whereas no evidence of association was found in the high-active group (standardized β = −0.031, P = 0.62, and standardized β = 0.053, P = 0.55, for HELENA and EYHS, respectively).

CONCLUSIONS—Higher levels of physical activity may attenuate the adverse effects of low birth weight on insulin sensitivity in adolescents. More observational data, from larger and more powerful studies, are required to test these findings. ***Diabetes* 60:2295–2299, 2011**

A low birth weight is associated with lower insulin sensitivity in youth (1,2) and with an increased risk of type 2 diabetes later in life (3). Insulin resistance is the major metabolic disorder in the early stages of type 2 diabetes development (4). Identification of lifestyle factors able to reduce insulin resistance and the risk of type 2 diabetes associated with a low birth weight at early stages of life is important from a clinical point of view.

It is known that physical activity is associated with a better metabolic profile and insulin sensitivity in children and adolescents (5,6). We hypothesized that higher levels of physical activity may attenuate the adverse effect of low birth weight on insulin sensitivity. We tested this hypothesis in two cross-sectional studies conducted on adolescents: the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study and the Swedish part of the European Youth Heart Study (EYHS).

RESEARCH DESIGN AND METHODS

The HELENA study aimed to obtain standardized, reliable, and comparable data from a sample of European adolescents on a broad battery of nutrition and health-related parameters. Data collection took place during 2006 and 2007 in 10 European cities from nine countries. A detailed description of the HELENA sampling and recruitment methodology, harmonization processes, data collection, analysis strategies, and quality control activities has been published elsewhere (7). In the HELENA study, one-third of the classes were randomly selected for blood collection (8). Sampling was balanced by center, age, and sex (7). After receiving complete information about the aims and methods of the study, all the parents/guardians signed a consent, and adolescents gave assent to participate in the study. The protocol was approved by the Human Research Review Committees of the centers involved.

The EYHS was designed to examine the interactions between personal, environmental, and lifestyle influences on the risk factors for future cardiovascular diseases. Data collection took place from 1998 to 1999 in seven municipalities in the Stockholm area and one in Örebro, Sweden. Study design, selection criteria, and sample calculations were reported elsewhere (9). One parent or legal guardian and all adolescents provided written informed consent. The study was approved by local ethical committees.

For the current study, we selected adolescents from the HELENA study and the Swedish part of the EYHS with valid data on sex, age, birth weight, BMI, sexual maturation, maternal education, breastfeeding, objectively measured physical activity, and fasting glucose and insulin concentrations. A total of 520 adolescents from the HELENA study (12.5–17.5 years old) and 269 adolescents from the EYHS (14.5–16.5 years old) met all these criteria and were therefore included in the analyses. The adolescents from the HELENA study included in

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the analyses did not differ from those not included in terms of birth weight, physical activity, and homeostasis model assessment–insulin resistance (HOMA-IR) (all $P > 0.6$). In the EYHS, the adolescents included did not differ from those not included regarding birth weight and physical activity (both $P > 0.7$), but they differed in HOMA-IR levels (2.0 ± 0.9 vs. 2.3 ± 1.3 for included vs. not included individuals, respectively; $P < 0.01$).

Physical examination. Body weight and height were measured using standardized procedures, as previously described (10,11), and BMI was calculated as body weight (kg) divided by height (m) squared. Sexual maturation status was assessed during a medical examination by a trained medical staff (Tanner stages ranging from 1 to 5) according to Tanner and Whitehouse (12).

Newborn birth weight. Birth weight data were recalled by the parents. To note, in the EYHS, the validity of parents-reported birth weight data was previously verified in a randomly selected sample by comparing the reported data with measured birth weights from parent-held baby books directly obtained from hospital records (13).

Physical activity. Detailed descriptions of the assessment of physical activity in the HELENA study (14,15) and the EYHS (11) have been published elsewhere. Briefly, adolescents were asked to wear an accelerometer (Actigraph) for 7 or 4 consecutive days (HELENA and EYHS, respectively) during all waking hours, except for water-based activities. The time sampling interval (epoch) was set at 15 or 60 s, for the HELENA and EYHS, respectively.

Accelerometer data from all participants in both studies were analyzed centrally by the same research group (Karolinska Institute). At least 3 days of recording with a minimum of 8 or 10 h of registration per day, for the HELENA study and EYHS, respectively, were necessary to be included in the study. Bouts of ≥20 min of consecutive zero counts were deleted from the data and thus not analyzed (HELENA and EYHS). Average physical activity was computed as the total number of counts divided by total wearing period in minutes and expressed as counts per minute.

Insulin resistance. We used HOMA-IR as a marker of insulin resistance, calculated as fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5. Serum concentrations of glucose and insulin were measured after an overnight fast. In the HELENA study, glucose was measured on the Dimension R×L clinical chemistry system (Dade Behring, Schwalbach, Germany), and insulin was measured by a solid-phase two-site chemiluminescent immunometric assay with an Immulite 2000 analyzer (DPC Biermann, Bad Nauheim, Germany) (8). In the EYHS, glucose was measured on an Olympus AU600 autoanalyzer (Olympus Diagnostica, Hamburg, Germany), and insulin was analyzed using an immunometric method on a Modular Analytics Modul E (Elecsys, Roche Diagnostics, Mannheim, Germany) (16).

Confounders. In addition to the confounders described above (sex, age, sexual maturation, and BMI), maternal education level and duration of breastfeeding were reported by the mothers and considered in the analyses.

Statistical analysis. All statistical analyses were performed using PASW (Predictive Analytics SoftWare, formerly SPSS, version 18.0). The level of significance was set at ≤0.05. HOMA-IR was logarithmically transformed (Ln) and entered in linear regression models as a dependent variable. Main exposures were physical activity, birth weight, and the interaction term physical activity × birth weight. Birth weight was normally distributed, and physical activity was squared root transformed to achieve a more symmetrical distribution. Sex, age, sexual maturation, BMI, maternal education, and breastfeeding were also entered into the models as covariates. Interactions with sex were examined; since no significant interaction was found in either the HELENA study ($P = 0.99$) or the EYHS ($P = 0.63$), the analyses were performed for boys and girls together. The association between birth weight and HOMA-IR was further examined, stratifying by high/low (above/below sex-, age-, and study-specific median) levels of physical activity. All the analyses were performed separately for the HELENA study and the EYHS.

RESULTS

The characteristics of adolescents from the HELENA study and the EYHS included in this study are shown in Table 1. Figure 1 graphically shows the interaction (standardized β regression slopes) between birth weight and HOMA-IR according to physical activity levels in the HELENA study and EYHS, i.e., the negative regression slope was flattened in the more active group (above the median of physical activity) compared with the less active one in both studies. The interaction was significant in both the HELENA study and the EYHS ($P = 0.05$ and $P = 0.03$, respectively), after adjusting for sex, age, sexual maturation, BMI, maternal education level, and breastfeeding duration. Stratified analyses by physical activity levels (below/above median) showed a borderline inverse association between birth weight and HOMA-IR in the low-active group (standardized β = −0.094, $P = 0.09$, and standardized β = −0.156,

TABLE 1
Characteristics of the samples from the HELENA study and the EYHS

	HELENA (n = 572)		EYHS (n = 274)	
	Boys (n = 247)	Girls (n = 325)	Boys (n = 127)	Girls (n = 147)
Age (years)	14.6 (1.2)	14.6 (1.1)	15.7 (0.4)	15.6 (0.4)
Sexual maturation [n (%)]				
Tanner stage I	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tanner stage II	24 (9.7)	18 (5.5)	2 (1.6)	0 (0.0)
Tanner stage III	49 (19.8)	68 (20.9)	4 (3.1)	7 (4.8)
Tanner stage IV	86 (34.8)	146 (44.9)	20 (15.7)	72 (49.0)
Tanner stage V	83 (33.6)	93 (28.6)	101 (79.5)	68 (46.3)
Weight (kg)	59.7 (13.1)	55.5 (10.3)	63.7 (10.9)	57.8 (9.2)
Height (cm)	169.6 (10.1)	162.0 (7.2)	175.5 (7.6)	165.7 (6.1)
BMI (kg/m^2)	20.6 (3.3)	21.1 (3.4)	20.6 (2.7)	21.0 (2.8)
Average PA (counts/minute)	494 (151)	387 (125)	560 (207)	487 (150)
Birth weight (kg)	3.5 (0.6)	3.3 (0.5)	3.6 (0.6)	3.4 (0.7)
Exclusive breastfeeding [n (%)]				
Never	57 (24.6)	67 (21.8)	16 (12.7)	13 (9.0)
1–5 months	145 (62.8)	197 (64.2)	85 (67.5)	110 (75.8)
≥6 months	29 (12.6)	43 (14.0)	25 (19.8)	22 (15.2)
Maternal education [n (%)]				
Lower than university	139 (58.9)	216 (68.6)	82 (65.6)	87 (59.2)
University	97 (41.1)	99 (31.4)	43 (34.4)	60 (40.8)
Glucose (mmol/L)	5.2 (0.4)	5.0 (0.4)	5.1 (0.4)	4.9 (0.4)
Insulin (mUI/L)	9.4 (5.8)	10.3 (5.6)	8.3 (3.5)	9.6 (3.9)
HOMA-IR	2.2 (1.3)	2.3 (1.3)	1.9 (0.9)	2.1 (1.0)

Data are means (SD), unless otherwise indicated. There were 34 and 3 missing values for breastfeeding in the HELENA study and the EYHS, respectively. There were 21 and 2 missing data for maternal education in the HELENA study and the EYHS, respectively. PA, physical activity.

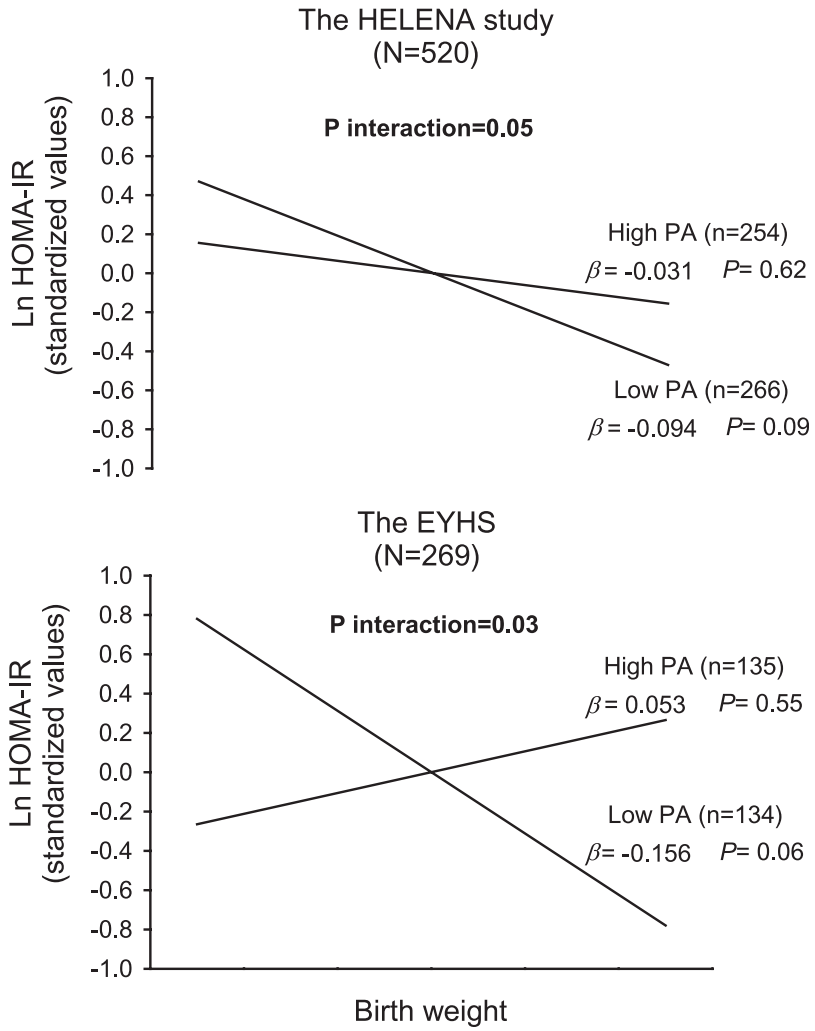

FIG. 1. Graphical representation of the standardized regression slopes (birth weight – Ln HOMA-IR) by levels of physical activity in adolescents from the HELENA study and the EYHS. High/low physical activity was defined as being above/below the age-, sex-, and study-specific median values for average physical activity (counts/minute). The regression models were adjusted for sex, age, sexual maturation, BMI, maternal education, and breastfeeding. The standardized coefficients are interpreted as the number of SDs that the outcome changes as a result of 1-SD change in the predictor. PA, physical activity.

$P = 0.06$, for the HELENA study and EYHS, respectively), whereas no evidence of association was found in the high-active group (standardized $\beta = -0.031$, $P = 0.62$, and standardized $\beta = 0.053$, $P = 0.55$, for the HELENA study and EYHS, respectively). When ANCOVA (adjusted by the same set of confounders) was conducted using birth weight groups (tertiles), the associations between birth weight and HOMA-IR (Fig. 2) were consistent with those observed in the regression analyses (Fig. 1).

For exploratory purposes, we examined in the HELENA study whether the results were affected after the exclusion of participants with <35 weeks of gestation (i.e., preterm babies, $n = 28$, 5.1% of the study sample) and additional adjustment for gestational age. We observed that the associations between birth weight and HOMA-IR remained different by levels of physical activity, i.e., standardized $\beta = -0.131$ and $P = 0.03$ in low-active participants, whereas $\beta = -0.046$ and $P = 0.50$ in high-active participants. Likewise, further adjustment for study center in the HELENA study did not alter the results. The P value for interaction was 0.048, and the association between birth weight and HOMA-IR was borderline significant in the low–physically active group ($\beta = -0.089$, $P = 0.07$), whereas no evidence of association was observed in the high–physically active group ($\beta = -0.018$, $P = 0.74$).

DISCUSSION

The results suggest that higher levels of physical activity may attenuate the adverse effects of a low birth weight on insulin sensitivity in adolescents. The interaction effect observed was marginally significant; however, the fact that this finding was observed in two different epidemiological studies conducted on adolescents strengthens the conclusions.

Our findings contrast with those of Ridgway et al. (17), who did not observe an interaction in the association between birth weight and insulin/HOMA-IR by level of objectively measured physical activity in children and adolescents from Denmark, Portugal, Estonia, and Norway ($n = 1{,}254$). However, our results are in agreement with those from two studies assessing physical activity (using questionnaires) in middle-aged men (18) and older adults (19). Laaksonen et al. (18) observed that a low size at birth, as assessed by ponderal index (birth length [m]/birth weight $[kg]^3$), was associated with hyperinsulinemia only in less active men ($n = 267$). Likewise, Eriksson et al. (19)

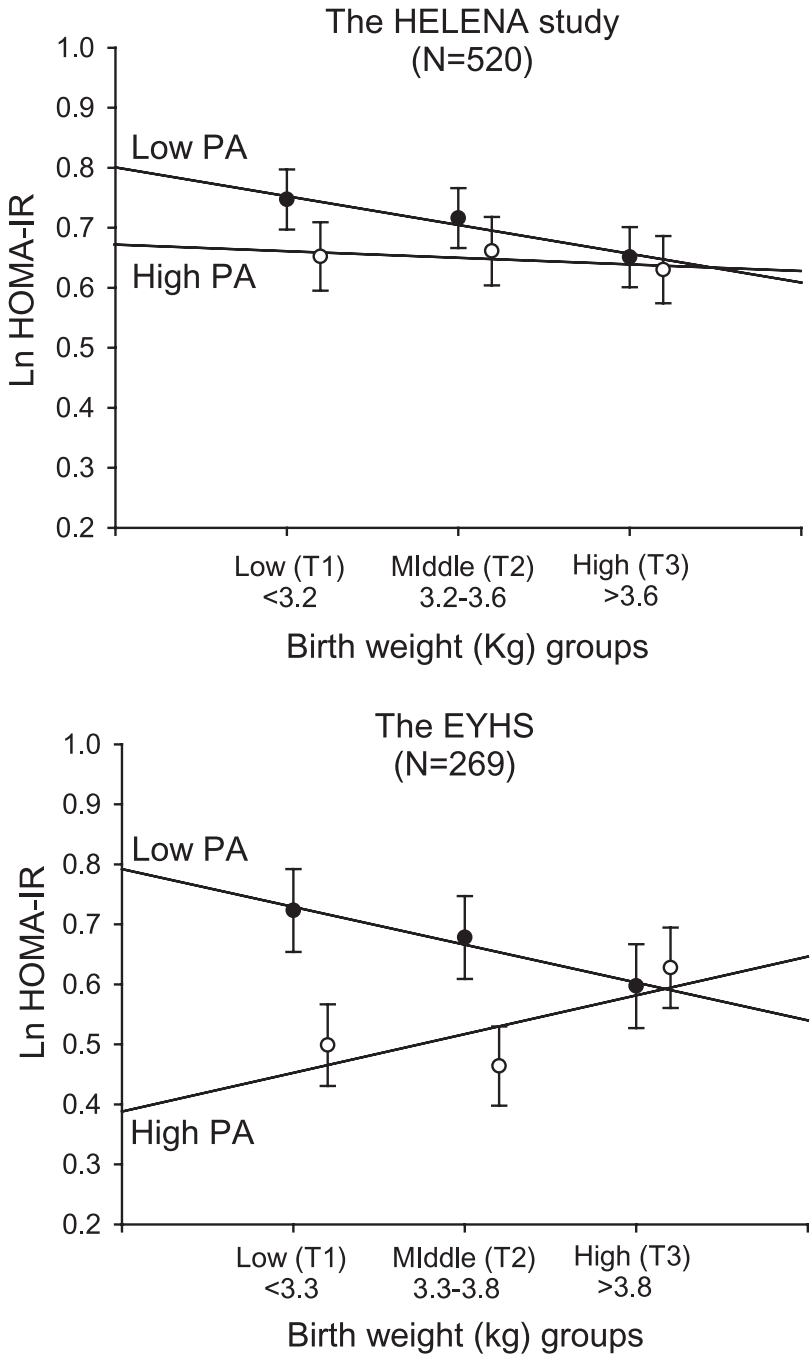

FIG. 2. Adjusted means (and SEs) for Ln HOMA-IR according to birth weight groups and levels of physical activity in adolescents from the HELENA study and the EYHS. High/low physical activity was defined as being above/below the age-, sex-, and study-specific median values for average physical activity (counts/minute). The ANCOVA models were adjusted for sex, age, sexual maturation, BMI, maternal education, and breastfeeding. Fitted lines for the means given are also represented. PA, physical activity; T, tertile.

concluded that subjects predisposed to type 2 diabetes because of a small birth weight were strongly protected from glucose intolerance by regular exercise (n = 500).

Insulin acts upon a variety of tissues within the body; however, those of particular interest for regulating glucose homeostasis are the skeletal muscle, liver, and adipose tissue. Several studies have shown that subjects born with a low birth weight had alterations in the expression or function in the insulin-signaling components in both adipose tissue and skeletal muscle (i.e., GLUT4, PKC, p85, p110β, or insulin receptor substate-1) (20,21). Our data suggest that higher levels of physical activity might attenuate the effect of low birth weight on insulin resistance in adolescence. Physical activity–induced physiological adaptations, such as increases in levels of GLUT4 and glycogen synthase activity (22) or changes in the expression and/or activity of proteins involved in insulin signal transduction in skeletal muscle (23), might underlie an increased insulin sensitivity. Detailed information on molecular and metabolic mechanisms of insulin resistance, with reference to physical activity, has been discussed elsewhere (24).

Some limitations need to be considered. The study samples are relatively small. On the other hand, the accuracy of the objective methodology used for physical activity and the

inclusion of two different studies in a single report must be acknowledged. As in previous studies (17,18), information on gestational age was lacking in the EYHS and should be considered as a limitation. Exploratory analyses in the HELENA study participants were in agreement with other studies (25,26); the inclusion of gestational age in the analyses did not modify the association of small birth weight with insulin resistance or glucose tolerance.

Because some methodological differences between the HELENA study and EYHS existed (e.g., method to assess glucose and insulin, and accelerometry criteria), data from both studies were analyzed separately instead of pooling them together. The fact that the results from both studies concurred suggests that the study conclusion is confirmed regardless of differences in methodology, data collection year, age range (12.5–17.5 years in the HELENA study and 14.5–16.5 years in the EYHS), and geographical origin of the adolescent sample.

In conclusion, the present results suggest that being more active might attenuate the adverse effects of low birth weight on insulin resistance in adolescents. This finding has important social and clinical implications and supports that promotion of physical activity is beneficial also in young people at higher risk because of their low birth weight. More observational data from larger and more powerful studies are required to test these findings.

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F.B.O. did the statistical analysis. A.H.-W. acquired data. M.G.-G., L.A.M., D.M., A.K., F.G., K.W., and M.S. were mainly responsible for the concept and design of the study and acquired data. All authors had full access to all data in the study and take responsibility for the integrity of data and the accuracy of data analysis. All authors were involved in the analysis and interpretation of data, drafting the manuscript, and critical revision of the manuscript for important intellectual content.

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