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Does physical activity and aerobic fitness moderate the association between birth weight and metabolic risk in youth? The European Youth Heart Study

Running Head: Birth weight, activity and metabolic risk

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Abstract

Objective: Lower birth weight has been associated with greater risk of metabolic diseases. This study aimed to examine whether physical activity and aerobic fitness may modify associations between birth weight and metabolic risk.

Research Design and Methods: The European Youth Heart Study is a population based study of 9 and 15 year olds (n=1,254). Birth weight was maternally reported. Skin fold measures were used to calculate body fat and Fat Mass Index (FMI=fat mass(kg)/height²). Insulin was measured using fasting blood samples. Physical activity was measured using a hip worn accelerometer (MTI Actigraph) for >600 minutes/day for ≥ 3 days, and expressed as 'average activity' (counts per minute) and time spent in above moderate intensity activity (MVPA, >2000 cpm). Aerobic fitness was assessed using a maximal cycle ergometry test (watts/kg FFM).

Results: Higher birth weight was associated with higher FMI ($\beta=0.49$, 95%CI: 0.21, 0.80, $p=0.001$) and greater waist circumference ($\beta=0.90$, 95%CI: 0.32, 1.47, $p<0.001$), adjusted for sex, age group, sexual maturity, height and SES. Lower birth weight was associated with higher fasting insulin only after further adjustment for adolescent waist circumference and height ($\beta=-0.059$, 95%CI: -0.107, -0.011 $p=0.016$). There was no evidence for any modification of the associations following adjustment for physical activity or aerobic fitness.

Conclusions: The present study did not find any evidence that physical activity or aerobic fitness can moderate the associations between higher birth weight and increased fat mass and greater waist circumference, or between lower birth weight and insulin resistance, in healthy children and adolescents.

Introduction

Lower birth weight, as a marker of restricted foetal growth, has been consistently associated with greater risk of metabolic diseases in adult life such as cardiovascular disease (1) and diabetes (2). Evidence also suggests that these associations are detectable in childhood, with lower birth weight being associated with insulin resistance (3).

The associations between birth weight and later adiposity are more complex and it can be difficult to disentangle the influence of birth weight from that of postnatal growth (4). Higher birth weight is associated with increased body mass index in childhood (5; 6), although this will reflect greater fat free mass as well as fat mass. Studies with more detailed measures of body composition in children from developed countries suggest higher birth weight is associated with greater overall fat mass and greater fat free mass, when adjusted for current height (7). The magnitude of association appears stronger between birth weight and fat free mass than for fat mass (8). While other studies suggest lower birth weight may be associated with increased percentage fat (9) and greater central obesity when adjusted for total fat mass (10), suggesting greater metabolic risk with low birth weight.

Recent studies using objectively measured physical activity have suggested that higher levels of physical activity and aerobic fitness are associated with a favorable metabolic risk profile (11) and lower levels of adiposity in healthy children and adolescents (12).

It has also been suggested that physical activity (13) and aerobic fitness (14) may modify the associations between low birth weight and metabolic risk and that higher

levels of physical activity and improved fitness may be a useful strategy to reduce the metabolic risks associated with a compromised intrauterine growth. However these previous studies assessed physical activity levels using self reported methods in adults.

The aim of this present study was to examine whether objectively measured physical activity and aerobic fitness may modify associations between birth weight and metabolic risk in a population based cohort of healthy children and adolescents. Given that increased metabolic risk and excess adiposity may already be present at early age, it is important to understand whether higher levels of physical activity and aerobic fitness may provide benefits not only for the metabolic risks associated with low birth weight, but also for the increased risk of excess adiposity associated with higher birth weights.

Methods

Study Population

The European Youth Heart Study (EYHS) is a population based mixed longitudinal cohort study comprising of two age groups of 9 year old children and 15 year old adolescents from four European countries; Denmark, Portugal, Estonia and Norway. The aim of the EYHS was to investigate the personal, environmental and lifestyle influences on cardiovascular and metabolic disease risk factors. The study aims, population, selection criteria and methods have been described previously (15). Briefly, study participants were randomly selected based on school level groups, with at least 20 schools within each area.

The present study is based on those children and adolescents with data on maternally reported birth weight and fasting blood samples from Denmark, Portugal and Estonia (n=1,254) as fasting blood samples were not collected in the Norwegian cohort. A small number of children (n=9), who were classified as very low birth weight (<1.5kg) were excluded from the analyses as very low birth weight may be associated with other health issues and can be indicative of premature birth, as information on gestational age was not available. Data collected via parental self report was available for socio-economic status (SES), which was categorised according to the mean for parental income and educational level.

Written informed consent was obtained from a parent or guardian and the study procedures were explained verbally to all children. Ethical approval for the study was obtained from the local research ethics committees in each study region.

Anthropometry and sexual maturity

Anthropometric measures were collected whilst wearing light clothes. Trained observers evaluated sexual maturity according to Tanner stages of breast development in girls and pubic hair in boys (16), with children categorised as being pre-pubertal (Tanner stage 1), mid pubertal (Tanner stage 2) or pubertal (Tanner stages 3, 4 and 5).

Waist was measured at the mid point between the iliac crest and the lowest rib, using a metal anthropometric tape, with the mean of two measures being used for the analysis.

Weight was measured with a standard calibrated beam balance to nearest 0.1kg. Height was measured using a stadiometer (Harpenden) to the nearest 0.5cm. Body Mass Index was calculated as $BMI = \text{weight (kg)} / \text{height (m)}^2$.

Skin fold measures were taken with Harpenden skin fold callipers (Baty International, UK) according to standardized methods. Body fat percentage or fat mass was estimated using seven different child specific equations (17) and were expressed relative to height, Fat Mass Index (FMI= fat mass (kg) / height (m)²). The results from each equation were pooled to provide a mean FMI for each participant.

Fasting Insulin

Since the study population is generally comprised of healthy children and adolescents we used fasting insulin as a marker of insulin resistance. Overnight fasting blood samples were taken in the morning from the antecubital vein. Samples were divided into aliquots, separated within 30 min and stored at -80°C until transport to WHO-certified laboratories for analyses. All biochemistry was performed by one of two WHO certified laboratories. Insulin was analysed using enzyme immunoassay (microtitre plate format; Dako Diagnostics, Ely, UK) in the Bristol laboratory (Danish and Estonian samples) and by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels in the Cambridge laboratory (Portuguese samples). To provide a further marker of insulin resistance the HOMA index was calculated using the homeostasis model:

$$\text{HOMA-IR} = (\text{fasting glucose} * \text{fasting insulin}) / 22.$$

Physical Activity

Physical activity was objectively measured using a hip worn accelerometer (MTI Actigraph, Manufacturing Technology, Fort Walton Beach, FL, USA) for four days. We derived two measures of physical activity: Average activity was defined as total activity counts divided by monitor wear time and expressed as counts per minute per day (cpm). Time (min/d) spent in moderate and vigorous intensity physical activity

(MVPA) was defined as all minutes above a threshold of 2,000 counts as previously described (18). We excluded all time blocks with ten or more consecutive zero counts, assuming that the monitor was not worn and all children with <600 minutes/day for <3 days were excluded. All physical activity variables were also adjusted for total monitor wear time, to adjust for how long the monitor was worn.

Aerobic Fitness

Aerobic fitness was assessed using a progressive cycle ergometer test (19) with workloads increased every 3 minutes until the child was unable to continue even after verbal encouragement. Heart rate data was collected every 5 seconds through out the duration of the test (Polar Sport Tester, Polar Oy, Finland). A heart rate ≥ 185 beats/min at the end of the test was used as criteria for achieving a maximal test and aerobic fitness was expressed relative to fat free mass as watts/kg FFM.

Statistical analyses

All data were analysed in its continuous form and non-normally distributed variables (fasting insulin and HOMA-IR) were log transformed. Multiple linear regression analyses were performed to assess the associations between birth weight and outcome variables (FMI, waist, fasting insulin and HOMA-IR). Our initial model was adjusted for sex, age group, study location, and sexual maturation and SES. Further adjustment for adolescent height was made when waist circumference was the outcome of interest, to investigate whether associations were independent of later height. Further adjustments for height and waist were also made when insulin was the outcome of interest, to investigate whether these associations were independent of central adiposity. Models were assessed for age group by sex interaction but since inclusion of this

interaction term did not materially change the effect size for any of the models, they were excluded from the final models. We also tested for non linear associations with birth weight by entering birth weight as a quadratic term.

These models were then repeated adjusting for total physical activity (cpm) or minutes of MVPA to investigate whether these variables moderated the association between birth weight and FMI, waist and insulin. Finally the model was adjusted for aerobic fitness (watts/kg FFM). We also examined whether physical activity or fitness modified the associations between birth weight and the outcomes of interest by introducing an interaction term of birth weight * average activity, birth weight * MVPA and birth weight * fitness in the models.

All analysis was performed using SPSS (v. 14), with a significance level of $p < 0.05$.

Results

Descriptive statistics, including means and standard deviations (SD) for the study population are displayed in online supplementary Table 1. There were significant differences between age and gender groups for most physical characteristics, so all models were adjusted for sex and age group, as well as study location, SES and sexual maturation.

Birth weight and fat mass index

Higher birth weight was associated with higher FMI, with a 1 kg increase in birth weight associated with 0.49 kg FM /m² increase in FMI ($\beta=0.49$, 95% CI: 0.21, 0.80, $p=0.001$), adjusted for sex, age group, sexual maturity and SES. Further adjustment for physical activity, as either average activity or minutes of MVPA per day, had little

influence on the association between birth weight and FMI and the coefficients were materially unchanged (Table 1). Figure 1 shows FMI stratified by tertiles of birth weight and MVPA and indicates lower FMI by higher tertiles of MVPA, particularly in the 3rd tertile of birth weight, although the confidence intervals overlap and do not reach statistical significance. Further adjustment for aerobic fitness also had little influence on the association between birth weight and FMI. A formal test for interaction, showed no evidence that the association between birth weight and FMI was modified by physical activity levels or aerobic fitness. There was also no evidence for a gender*age group interaction for FMI.

Further adjustment for aerobic fitness also had little influence on the association between birth weight and FMI. A formal test for interaction, showed no evidence that the association between birth weight and FMI was modified by physical activity levels or aerobic fitness.

Similar results were observed if FMI was substituted with percentage body fat as the outcome variable, with birth weight being positively associated with percentage body fat, independently of sex, age group, country, sexual maturation and maternal BMI, with little change in the magnitude of association if further adjusted for physical activity or fitness (data not shown).

Birth weight and waist circumference

Higher birth weight was associated with a greater waist circumference in childhood, with a 1kg increase in birth weight being associated with a 0.90 cm increase in waist circumference ($\beta=0.90$, 95%CI: 0.32, 1.47, $p=0.002$), adjusted for sex, age group, sexual maturity, height and SES. Again further adjustment for physical activity, either for average activity or time spent in MVPA, made little change to the birth weight and

waist circumference association and the magnitude of association was largely unaffected. Adding further adjustment for aerobic fitness to the model showed a very slight increase in the association between birth weight and waist circumference ($\beta=0.94$, 95%CI: 0.37, 1.50, $p=0.001$) (Table 1). A formal test for interaction, showed no evidence that the association between birth weight and waist circumference was modified by physical activity or aerobic fitness.

Birth weight and insulin resistance

Birth weight was not associated with fasting insulin ($\beta=-0.005$, 95%CI: -0.055, 0.045 $p=0.844$), which again was materially unchanged following further adjustment for either total physical activity or time spent in MVPA (Table 1). However when adolescent waist circumference and height were introduced to the model, lower birth was associated with higher fasting insulin ($\beta=-0.059$, 95%CI: -0.107, -0.011 $p=0.016$) and further adjustment for physical activity or fitness had little influence on the birth weight fasting insulin association and the β -coefficients remained almost unchanged (Table 1). Substituting fasting insulin for HOMA-IR did not change the observed effect size ($\beta=-0.056$, 95%CI: -0.107, -0.006 $p=0.029$) and further adjustment for physical activity or aerobic fitness did not modify this association.

Similar results were observed when waist circumference was substituted by current body weight in the model, in that there was a significant association between birth weight and fasting insulin ($\beta=-0.058$, 95%CI: -0.106, -0.010 $p=0.018$), following adjustment for sex, age group, sexual maturity, SES and current body weight (kg). However if waist circumference was substituted with current FMI, the association between birth weight and fasting insulin was attenuated and no longer significant ($\beta=-0.032$, 95%CI: -0.080, 0.015 $p=0.184$). There was also no evidence of statistical

interaction in the association between birth weight and fasting insulin by level of physical activity or aerobic fitness.

Discussion

Current levels of physical activity and aerobic fitness did not moderate or modify the associations between birth weight and FMI, waist circumference or fasting insulin. Our findings suggest that higher birth weight was associated with increased FMI and greater waist circumference, while lower birth weight was associated with greater metabolic risk in terms of higher fasting insulin but only following further adjustment for a measure of current adiposity (i.e. waist circumference or weight).

Our results are in contrast to two previous studies which reported that higher physical activity levels or aerobic fitness may moderate the associations between size at birth and metabolic risk. Laaksonen *et al* found the associations between ponderal index (ponderal index= birth length (m)/birth weight (kg)³) were attenuated in adult men reporting >25mins/week of vigorous leisure time activity and in those classified in the 'fit' above the 40th centile for VO₂ max (≥ 28.6 ml/kg/min) (14). Erikson *et al* observed an interaction between reported physical activity levels and glucose intolerance in men, with both higher frequency and intensity of physical activity being associated with lower glucose intolerance, especially in those born below 3kg (13). There are however a number of potential reasons for the differences between the current study, and these previous reports.

The two previous studies investigating the influence of physical activity on the association between birth weight and metabolic risk both used self reported methods to assess physical activity levels, whereas we used an objective measure of physical activity by accelerometry. Any self-report measure will be subject to issues of recall

bias, but it should also be noted that questionnaires may capture different aspects of physical activity compared with accelerometry. Self-reported physical activity usually only considers regular, distinct activities, such as specific types of leisure time activity, whereas accelerometers measure body movement throughout the measurement period. Self report methods are unlikely to fully capture incidental activity, whereas accelerometers are limited to detecting certain movements. For example in this study the hip worn monitor may not capture cycling or activities for which the monitor was removed, such as swimming. Indeed, these two measures are only weakly correlated, typically around 0.3 in adults (20). Furthermore, the questionnaires used in the previous studies captured information on physical activity during the preceding 12 months, whereas we, for practical reasons only measured physical activity for 3 to 4 days. However, we included both weekdays and weekend days and a 4 day measurement period has been suggested to be sufficient when assessing physical activity by accelerometry in youth (21). While adiposity tends to reflect long term energy balance, fasting insulin levels can be influenced by very recent physical activity levels (22). The lack of a modifying effect of physical activity or aerobic fitness in the present study compared with previous observations may also be explained by differences in the study populations. We examined the influence of physical activity on the associations between birth weight and metabolic risk in healthy children and adolescents, whereas the two previous studies were carried out in middle-aged men (14) and older adults age 65 – 75 years respectively (13). It is possible that the beneficial effect of physical activity or aerobic fitness on the association between birth weight and metabolic risk may not be apparent until later in life when the age related increase in metabolic risk is more pronounced (2).

The finding that birth weight was positively associated with FMI is consistent with previous findings in adolescents (23). However, FMI includes an adjustment for current body size, and therefore does not preclude the possibility that postnatal growth may influence the association between birth weight and FMI. A detailed measure of body fat distribution was not available, however previous studies have also observed positive associations between birth weight and waist circumference in younger children (8).

The observed association between low birth weight and insulin resistance, was only observed following adjustment for current waist circumference or weight but this association was attenuated if adjusted for any measure of general adiposity (e.g. FMI or fat mass). This suggests that current adiposity more strongly influences insulin levels than current body size. However, it is hard to disentangle the pathways involved between birth weight and later insulin resistance, when adjusting for a measure of body size, since measures such as current weight will be influenced by both fat mass and fat free mass. A previous study investigating the associations between birth weight and insulin resistance, in the EYHS study population observed an association between lower birth weight and HOMA score, which was augmented following further adjustment for current body size (BMI or height) (3). The statistically weaker association observed in this present study, which included a subset of the EYHS population with complete physical activity data, may be explained by reduced statistical power. It is also plausible that where an association between birth weight and a metabolic outcome (e.g. insulin resistance) is only detected after adjustment for current body size it may be indicative of an association between *change* in size between birth and the later measurement, such as rapid weight gain (4). However we did not have an intermediate measure of body size or composition in earlier childhood to be able to investigate this

further. Future studies with repeated measures of body composition would be particularly valuable for investigating associations between birth weight, infant and childhood weight gain and later metabolic risk.

Although we did not detect any influence of physical activity or aerobic fitness on the birth weight metabolic risk association, there is a wide range of evidence to suggest that higher levels of physical activity may be beneficial for reducing insulin resistance and metabolic risk (12), as well as adiposity (11). Given the influence of physical activity and aerobic fitness on the association between birth weight and metabolic health in the two previous studies was in older adults, it may be difficult to detect the influence in young healthy populations. Further research in older populations or those at higher metabolic risk, using objectively measured physical activity and aerobic fitness data would be particularly useful to investigate whether increasing physical activity levels or improved aerobic fitness may reduce insulin resistance in those born small or improve body composition particularly in those born at the higher end of the birth weight spectrum who may be at increased risk of later obesity.

The following limitations should be considered when interpreting the results from the present study. Firstly we used skin fold, height and weight equations to derive FMI, which may not be as accurate as other methods, such as DXA, deuterium dilution or pletysmography. However, we estimated FMI as an individual aggregate using seven different equations to increase the accuracy of this method (17). Further, this method is more feasible to use in large population based studies, provide a more comprehensive measure of adiposity than BMI and are comparable to more detailed measures of body composition (24). Although birth weight was maternally reported and not objectively measured in this study, maternally reported birth weight correlates highly with measured birth weight (28). Unfortunately, data on gestational age data was not

available, so residual confounding by gestational age may persist, although very low birth weight infants (<1.5kg) were excluded. Lastly it should be noted that potential confounding variables included in the models (maternal BMI and SES) were self reported and may be subject to recall bias. Strengths of this study include a large population based sample of children and adolescents from three differing countries combined with an objective measure of physical activity, a maximal aerobic fitness test and fasting blood samples.

In conclusion, the results from the present study did not find evidence that physical activity or aerobic fitness can moderate or modify the associations between low birth weight and insulin resistance, or between higher birth weight and increased fat mass and greater waist circumference in healthy children and adolescents. However higher levels of physical activity are beneficial for both body composition and metabolic risk throughout the life course and the moderating effect of physical activity on the birth weight and metabolic risk association may only become apparent later in adult life or within populations at greater metabolic risk.

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Author contribution

CR analysed the data and drafted the manuscript. SAA, LBA and LBS were responsible for the data collection and organised the field work, CR, SB and UE interpreted the data, UE, SB and CR conceived the hypothesis for the study. All authors approved the final version of the manuscript.

Conflict of interest

No conflict of interest is declared by any of the authors.

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Table 1. Associations (β -coefficients, 95%CI)between birth weight (kg) and FMI, waist and fasting insulin (n=1254)

	Model 1			Model 2			Model 3			Model 4		
	β	95%CI	p	β	95%CI	P	β	95%CI	P	β	95%CI	P
Fat Mass Index	0.49	0.21, 0.80	0.001	0.49	0.21, 0.78	0.001	0.49	0.21, 0.78	0.001	0.52	0.24, 0.80	<0.001
Waist (cm)*	0.90	0.32, 1.47	0.002	0.90	0.32, 1.47	0.002	0.89	0.32, 1.47	0.002	0.94	0.37, 1.50	0.001
Insulin (log)	-0.005	-0.055, 0.045	0.844	-0.007	-0.057, 0.043	0.788	-0.008	-0.058, 0.042	0.745	-0.005	-0.053, 0.044	0.856
Insulin (log)**	-0.059	-0.107, -0.011	0.016	-0.061	-0.109, -0.013	0.012	-0.062	-0.110, -0.015	0.010	-0.058	-0.105, -0.010	0.017
HOMA-IR	-0.056	-0.107, -0.006	0.029	-0.059	-0.109, -0.008	0.024	-0.059	-0.109, -0.009	0.021	-0.054	-0.104, -0.004	0.034

(log)**

* Additionally adjusted for adolescent height

** Additionally adjusted for adolescent height and waist circumference

Model 1 - Adjusted for sex, age group, country, maturity, SES

Model 2 Adjusted for sex, age group, country, maturity, SES, monitor worn time and MVPA (mins/day)

Model 3 Adjusted for sex, age group, country, maturity, SES, monitor worn time and average physical activity (counts/min)

Model 4 Adjusted for sex, age group, country, maturity, SES, monitor worn time, total physical activity (counts/min) and aerobic fitness

(watts/kgFFM)

Figure 1. Associations between birth weight and Fat Mass Index, stratified by tertiles of time spent in moderate and vigorous activity (min/day). Data (adjusted means, 95% CI) are adjusted for sex, age group, county, sexual maturation, SES and monitor wear time.

