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Original Article

Fat free mass mediates the association between birth weight and aerobic fitness in youth

Running head: Birth weight, fat free mass and aerobic fitness

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

Abstract

Objective: To investigate whether birth weight acts as a biological determinant of later aerobic fitness, and whether fat free mass may mediate this association.

Methods: The European Youth Heart Study (EYHS) is a population based cohort of two age groups (10 and 15 years) from Denmark, Portugal, Estonia and Norway. Children with parentally reported birth weight >1.5kg were included (n=2,749). Data was collected on weight, height, and skin fold measures to estimate fat mass and fat free mass. Aerobic fitness (peak power, watts) was assessed using a maximal, progressive cycle ergometer test. Physical activity was collected in a subset (n=1,505) using a hip-worn accelerometer and defined as total activity counts/wear time, all children with >600 minutes/day for ≥3 days of wear were included.

Results: Lower birth weight was associated with lower aerobic fitness, after adjusting for sex, age group, country, sexual maturity and socio-economic status (ß=5.4, 95%CI 3.5, 7.3 W per 1kg increase in birth weight, p<0.001). When fat free mass was introduced as a covariate in the model, the association between birth weight and aerobic fitness was almost completely attenuated (p=0.7). Birth weight was also significantly associated with fat free mass (ß=1.4 95%CI 1.1, 1.8, p<0.001) and fat free mass was significantly associated with aerobic fitness (ß=3.6, 95%CI 3.4, 3.7, p<0.001). Further adjustment for physical activity did not alter the findings.

Conclusion: Birth weight may have long-term influences on fat free mass and differences in fat free mass mediate the observed association between birth weight and aerobic fitness.

Introduction

High levels of aerobic fitness are recognised to have wide ranging health benefits not only in terms of direct benefits observed in childhood, such as lower obesity risk (1) and improved metabolic function (2), but also in terms of reduced disease risk in later life (3). There is evidence suggesting that development in early life may act as a biological determinant of aerobic fitness. It is recognised that very low birth weight infants have compromised physical performance in later life, including aerobic fitness (4, 5). Furthermore, birth weight appears to be associated with childhood aerobic fitness across the spectrum of 'normal' birth weight ranges, with higher birth weight infants showing greater aerobic fitness in childhood (6) (7), and in later life (8). Birth weight has also been associated with body composition, with higher birth weight being associated with increased fat free mass in childhood (9-12) and late adulthood (13, 14).

Aerobic fitness, usually expressed in terms of maximal oxygen uptake (L O_2/min) or endurance performance measures such as peak power output (Watts/min), is influenced by the nature of the test, habitual physical activity levels (15) and body composition (16). For example, absolute maximal oxygen uptake (VO_{2max}), expressed in liters per minute, is higher in larger, obese individuals compared to normal weight individuals due to differences not only in fat mass but also in fat free mass (16, 17). It is therefore suggested that aerobic fitness should be expressed relative to body size. Various options exist when normalising maximal aerobic capacity for differences in body size (18). Usually, aerobic fitness is normalized for body weight by dividing maximal oxygen uptake or peak watts by body weight (19) or fat free mass (20).

Previous studies investigating associations between birth weight and aerobic fitness (6, 7) (21) have used different methods to assess aerobic fitness and different procedures for normalizing aerobic fitness data for differences in body size and composition. Therefore, evidence for an association between birth weight and aerobic fitness has not always been consistent. Furthermore, the type of exercise test used will also influence maximal aerobic capacity, for example some tests such as shuttle run tests are more influenced by body weight compared to non-weight bearing tests, such as cycle ergometry.

The aim of this study was to examine whether birth weight acts as a biological determinant of aerobic capacity in youth, and whether this association is mediated by differences in body size and body composition, specifically whether fat free mass may mediate the associations between birth weight and later fitness. We also investigated whether these associations were independent of objectively measured habitual physical activity in youth. To address this, we used a non-weight bearing maximal cycle ergometry exercise test in a large population-based cohort study of children and adolescents from four European countries,

Methods

Participants

The European Youth Heart Study (EYHS) is a mixed longitudinal, population-based cohort study comprising of two age groups of 9 and 15 year old children from Denmark, Portugal, Estonia and Norway (22), which aimed to examine the nature, strength, and interactions between personal, environmental, and lifestyle influences on CVD risk factors in children. Selection was based on clusters at school level, with a minimum of 20 schools in each area, with children being randomly selected from each school. The overall response rate was 73% (22). The present study is based on those children from Denmark, Portugal, Norway and Estonia, for whom data was available on maternally reported birth weight and aerobic fitness. A small number (n=12), were excluded as they were classified as very low birth weight (<1.5kg) giving a final dataset of n=2,749 with complete data on birth weight, aerobic fitness and body composition. Data on objectively measured physical activity was available for a subset of the population (n=1,505). Data on parental socio-economic status (SES) was collected via self report questionnaire and categorised based on a mean of income and parental educational status. Written informed consent was obtained from the child’s parental (or legal guardian) and the study complied with ethical procedures within each country.

Anthropometry

Standard anthropometric data was collected on weight and height, whilst wearing light clothes. Weight was measured with a standard calibrated beam balance to 0.1kg and height was measured to the nearest 0.5cm using a Harpenden stadiometer. Body Mass Index (BMI) was calculated as weight (kg) / height $(m)^2$. Data was also collected on sexual maturity based on Tanner stages (23), using breast development in girls and pubic hair in boys, by trained observers, with children classified into three categories as being pre-pubertal (Tanner stage 1), mid-pubertal (stage 2) or post-pubertal (stages 3, 4 and 5).

Skin fold measures were taken using Harpenden skin fold callipers (Baty International, UK) according to standardized methods (24), which were repeated either twice or three times, with the average of the closest two measurements being used. Age and sex specific equations were used to estimate percentage body fat from the sum of the triceps and subscapular measurements (25). Fat mass (FM) was calculated as FM=fat percentage/100 x body weight (kg) and fat free mass (FFM) was calculated as FFM=body weight (kg) – FM (kg).

Peak Aerobic Fitness

Aerobic fitness (Peak Watts) was assessed using a maximal, progressive cycle ergometer test (26). Heart rate data was collected every 5 seconds throughout the duration of the test (Polar Sport Tester, Polar Oy, Finland). Initial work loads were 25W for 9 year olds weighing less than 30 kg and 30W for those weighing >30 kg. The initial workloads for 15 year olds were 40W and 50W for girls and boys respectively. Work loads were increased every three minutes, until the child was unable to continue even with verbal encouragement. Peak heart rate ≥185 beats/min at the end of the test was used as criteria for achieving a maximal test.

Physical Activity

Physical activity was objectively measured, in a subset of the population (n=1,505), using a hip-worn accelerometer (MTI Actigraph) for four days as previously described (2). Total physical activity was defined as total activity counts divided by monitor wear time and expressed as counts per minute (cpm). All children with >600 minutes/day for ≥3 days were included in this analysis.

Statistical analyses

Descriptive statistics are given as means and standard deviations. Independent t-tests were used to investigate potential differences between those with maternally reported birth weight and those excluded because birth weight data was not available. Two-way ANOVA was used to test for differences between sex and age groups.

To check for a non-linear association between aerobic fitness (peak Watts) and body weight or fat free mass, both exposure and outcome variables were log transformed and regressed, to investigate whether body weight or fat free mass required allometric scaling.

Multiple linear regression analyses were performed to assess the associations between birth weight (kg) and aerobic fitness (Peak Watts), adjusted for sex, age group, sexual maturation, country and SES.

We then investigated whether birth weight was associated with fat free mass, adjusted for sex, age group, sexual maturation, country and SES. To this model we introduced height as a covariate, to investigate whether associations between birth weight and later fat free mass were influenced by later height.

In order to investigate whether fat free mass acts as a mediator in the association between birth weight and aerobic fitness, further regression models were used according to the methods suggested by Baron and Kenny (27). The final regression model investigated the association between birth weight and aerobic fitness (peak Watts), adjusting for fat free mass. The coefficients for both birth weight and fat free mass (mutually adjusted) are displayed to illustrate whether fat free mass completely or only partially mediates the associations between birth weight and aerobic fitness in youth.

In a sub-sample (n=1,505) with data on objectively measured physical activity, we introduced physical activity (cpm) as a covariate, to investigate whether the association between birth weight and aerobic fitness was independent of physical activity in youth.

To examine whether the association between birth weight and aerobic fitness were similar in each sex, age group, and country, formal interaction terms (birth weight x sex, birth weight x age group, birth weight x country) were entered into the models.
All regression analyses were performed using SPSS (v. 14) and a significance level was 0.05.

Results

Descriptive data (mean ± SD), stratified by age group and sex, are presented in Table 1. There were no differences in BMI, aerobic fitness or socio-economic status between those who provided data on birth weight (n=2,632) and those excluded because this information was not available (n=257). However, those excluded had a slightly more advanced sexual maturation (mean score of 2.0 compared to 1.9, p=0.02). The association between aerobic fitness (peak watts) and both body weight and fat free mass on a log scale was largely linear and close to 1 (ß=0.97 95% CI; 0.95, 1.00 for body weight and ß=1.15 95% CI; 1.12, 1.17 for FFM), so these variables were entered in subsequent regression models in their original form, without allometric scaling.

Lower birth weight was significantly associated with lower aerobic fitness, after adjusting for sex, age group, country, sexual maturity and SES (ß=5.4, 95%CI: 3.5, 7.3, p<0.001) (table 2) (figure 1), which equates to a difference of 5.4 watts for every 1kg difference in birth weight. There was no evidence for any effect modification by sex, age group, or country (all interaction $p \geq 0.4$), so all further analyses were performed in the whole data set, adjusting for country, sex and age group.

When fat free mass was introduced as a covariate in the model, the association between birth weight and aerobic fitness was almost completely attenuated and ceased to be significant (ß=0.3, 95%CI: -1.2, 1.8, p=0.7) (model 2, table 2, figure 2). However, fat free mass was significantly associated with aerobic fitness (ß=3.6, 95%CI: 3.4, 3.7, p<0.001), when adjusted for sex, age group, sexual maturity, SES and birth weight (Table 2). We also modelled the association between birth weight with aerobic fitness expressed as a ratio by fat free mass (watts/kg FFM) and the results were similar (ß=0.02, 95%CI: -0.02, 0.06, p=0.3) (data not shown in tables).

The association between birth weight and aerobic fitness was also materially unaltered following additional adjustment for physical activity (cpm) (Model 3, Table 2).

Birth weight was significantly associated with fat free mass (ß=1.4 95%CI 1.1, 1.8, p<0.001) adjusted for sex, age group, country, sexual maturation and SES, which equates to 1.4kg greater fat free mass in youth for a 1kg increase in birth weight. This association remained significant after additional adjustment for adolescent height (ß=0.3 95%CI 0.1, 0.6, p=0.008), suggesting that birth weight has long term influences on fat free mass independent of adolescent height (Model 2, Table 3).

Discussion

While our findings suggest that birth weight is positively associated with greater aerobic fitness in terms of peak watts, this association is almost completely attenuated when adjusted for fat free mass as a covariate in the linear regression model, or when normalising the fitness measure for fat free mass (Watt/kg FFM). Birth weight was also associated with fat free mass, independently of height in youth, suggesting that birth weight has long term influences on fat free mass. Furthermore, fat free mass was strongly associated with aerobic fitness in the cross-sectional analysis. Together, these findings suggest that fat free mass mediates the observed associations between birth weight and aerobic fitness. Objectively measured physical activity in youth did not seem to influence this association.

Previous studies have used varying methods to both assess and express aerobic fitness, which may explain some of the inconsistent findings. One of the first studies examining the associations between birth weight and aerobic fitness was conducted in adolescents in Northern Ireland (6). Aerobic fitness was assessed using a timed 20 meter shuttle run test with fitness expressed as the number of completed laps. Boreham *et al* (2001) observed a positive association between birth weight and completed laps in both boys and girls aged 12 years. These investigators did not adjust for fat free mass but following adjustment for body weight, the association in boys was attenuated and diminished in girls, which suggests that body size or fat free mass may at least in part mediate the observed association. Although the fully adjusted model, which included height, weight, body mass index (BMI=weight/height^2), as well as other potential confounders, was still significant in the 12 year old boys and girls, there was no evidence for an association in the 15 year old group for either gender in unadjusted or adjusted models, suggesting that perhaps the influence of birth weight on aerobic fitness does not persist through adolescence. We did not, however, find any evidence of an interaction with age in our study, which included both 10-year old children (age range 7.5 - 11.3 yrs) and 15-year old adolescents (age range 14.1 - 17.8 yrs).

A previous study in 9 year old children, observed a positive association between birth weight and aerobic fitness (7), using measured heart rate during a sub-maximal cycle ergometer test and expressed as power (Watts) at a heart rate of 170 beats/min (PWC_{170}). This is an absolute measure of aerobic fitness which is not scaled for body weight or fat free mass. This positive association was attenuated and no longer significant with adjustment for height or BMI, again suggesting that the observed association may be mediated via differences in body size.

We have previously observed an association between birth weight and aerobic fitness at the age of 31 yrs in a large population-based study in Finland (8). In that study, aerobic fitness was measured with a sub-maximal step test with heart rate post step test being used as a measure of aerobic fitness, which has previously been shown to correlate with $V0_{2max}$ (28). Birth weight was positively associated with aerobic fitness and this was independent of adult BMI, however a measure of body composition was not available in that population so it was not possible to address if the association was independent of fat free mass.

Results from a more recent study in adolescents, which used a 20m shuttle run test to predict $V0_{2max}$ normalized by body weight ($V0_{2max}$ ml/kg/min) did not observe an association between birth weight and aerobic fitness (21). Although not directly comparable with our results due to differences in test procedures and how aerobic fitness was expressed, both studies suggest that the association between birth weight and later aerobic capacity is mediated by differences in body size.

Our findings suggest that birth weight is associated with fat free mass in youth and that while reduced following adjustment for height there is still an independent association between birth weight and later fat free mass. This is consistent with evidence from studies with more detailed assessment of body composition, which find that higher birth weight is associated with increased fat free mass in youth (9-12) and later life independent of later height (13, 14). Taken together, these findings suggest that birth weight may have long term influences on body composition, specifically fat free mass, which may have consequences for physical performance and aerobic fitness throughout childhood and into adulthood.

The following limitations of the present study should be considered when interpreting our results. Birth weight was retrospectively maternally reported in this study and not collected at the time of birth. However, previous studies suggest that maternal recall of their offspring's birth weight is valid and correlates highly with measured birth weight (29). Since gestational age was not available in this study, we excluded individuals with very low birth weight (below 1.5kg) to avoid the results being overly influenced by very preterm infants who are known to have reduced aerobic fitness (4, 30), however it is possible that residual confounding with gestational age remains. It should also be considered that body composition was not directly measured in this study but estimated from a two compartment model using skin fold measures, however skin fold measures have been shown to be valid for large-scale epidemiological studies where more detailed measures may not be achievable in larger numbers of individuals (31). Finally, while this analysis is adjusted for potential confounders (SES) these were also parentally reported, so residual confounding may still remain. However this study also has several strengths; it comprises of a large population-based cohort across four differing European countries, as well as including a maximal exercise test to estimate aerobic fitness and objectively measured physical activity using accelerometry.

Increasing fat free mass for low birth weight individuals may well offer long term health benefits, not only in terms of improved aerobic fitness, but also in terms of reduced metabolic risk in later life as it has been hypothesised that fat free mass may mediate the associations between birth weight and metabolic diseases (12)(32). Growth during early infancy may offer a potential window to increase fat free mass (33) (11), however at present the optimum growth during early infancy, particularly for low birth weight infants, is not well understood as low birth weight associated with rapid infant weight gain is also associated with increased risk of obesity in later life (34). There may also be opportunities to increase fat free mass via resistance training, which has been shown to increase fat free mass in youth (35). Further research investigating the potential benefits of increasing aerobic fitness and physical activity in term of reducing the metabolic risks associated with low birth weight would be particularly useful given that aerobic fitness and physical activity are potentially modifiable throughout the life course.

Our findings suggest that the association between birth weight and aerobic fitness in youth is mediated via fat free mass. Birth weight may have long term influences on fat free mass, independent of later height, and these differences in fat free mass may largely explain the observed associations between birth weight and measures of aerobic fitness. Increasing fat free mass in youth may offer benefits in terms of reducing the deleterious effects of low birth weight in later life.

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No conflicts of interest are declared by the authors

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Table 1. Descriptive statistics of participants (n=2,632)

	9 year old boys n=680		9 year old girls n=678		15 year old boys n=609		15 year old girls n=665		
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**P value**
Birth weight (kg)	3.51	(0.57)	3.39	(0.54)	3.49	(0.53)	3.36	(0.51)	S***
Age (yr)	9.7	(0.4)	9.6	(0.4)	15.5	(0.5)	15.5	(0.6)	A*** S*
Sexual Maturation†	1.3	(0.5)	1.4	(0.5)	2.6	(0.5)	2.4	(0.5)	A*** AxS***
Height (m)	1.38	(0.06)	1.38	(0.06)	1.72	(0.08)	1.63	(0.07)	A*** S*** AxS***
Weight (kg)	33.4	(6.7)	32.8	(6.6)	61.7	(10.2)	55.8	(8.4)	A*** S*** AxS***
BMI (kg/m^2)	17.3	(2.6)	17.2	(2.6)	20.7	(2.8)	20.9	(2.9)	A***
Fat Mass (kg)	6.1	(4.3)	7.2	(3.6)	10.1	(6.0)	14.0	(5.3)	A*** S*** AxS***
Fat Free Mass (kg)	27.3	(3.5)	25.7	(3.8)	51.6	(6.9)	41.8	(5.0)	A*** S*** AxS***
Peak Watts (watts)	99.3	(19.9)	83.4	(17.9)	214.0	(41.7)	141.9	(31.6)	A*** S*** AxS***
Physical activity (cpm) (n=1,505)	787	(288)	643	(199)	590	(219)	474	(148)	A *

† Sexual Maturation, based on Tanner stages 1= 1 (pre-pubertal), 2=2 (mid-pubertal) and 3>=3 (post-pubertal).

ANOVA age group (A) sex (S) and interaction AxS ***p<0.001, **p<0.01, *p<0.05

Table 2. Results from multiple linear regression analysis examining the association between birth weight (kg) and maximal aerobic fitness (peak Watts) in European children (n=2,632)

	ß	**95%CI**	**p**
Model 1			
Birth weight (kg)	5.4	3.5, 7.3	<0.001
Model 2			
Birth weight (kg)	0.3	-1.2, 1.8	0.7
Fat free mass (kg)	3.6	3.4, 3.7	<0.001
Model 3			
Birth weight (kg)	0.5	-1.2, 2.3	0.6
Fat free mass (kg)	3.8	3.4, 3.8	<0.001
Physical Activity (100*cpm)	0.05	-0.01, 0.11	0.1

ß regression coefficients represent differences in childhood aerobic fitness (peak Watts) per 1kg difference in birth weight or 1kg difference in childhood fat free mass.
All models are adjusted for sex, age group, country, sexual maturity and SES.
Displayed coefficients are mutually adjusted for the other included variables in each model.

Table 3. Results from multiple linear regression analysis examining the association between birth weight (kg) and fat free mass (kg) in European children (n=2,632)

	ß	**95%CI**	**P**
Model 1			
Birth weight (kg)	1.4	1.1, 1.8	<0.001
Model 2			
Birth weight (kg)	0.3	0.1, 0.6	0.008
Height (cm)	0.5	0.5, 0.5	<0.001

ß regression coefficients represent differences in childhood fat free mass (kg) per 1kg difference in birth weight or 1cm difference in childhood height.
All models are adjusted for sex, age group, country, sexual maturity, SES.
Displayed coefficients are mutually adjusted for the other included variables in each model.

Figure 1. Association between birth weight and aerobic fitness

Adjusted for sex, age group, country, sexual maturity and socio-economic status.

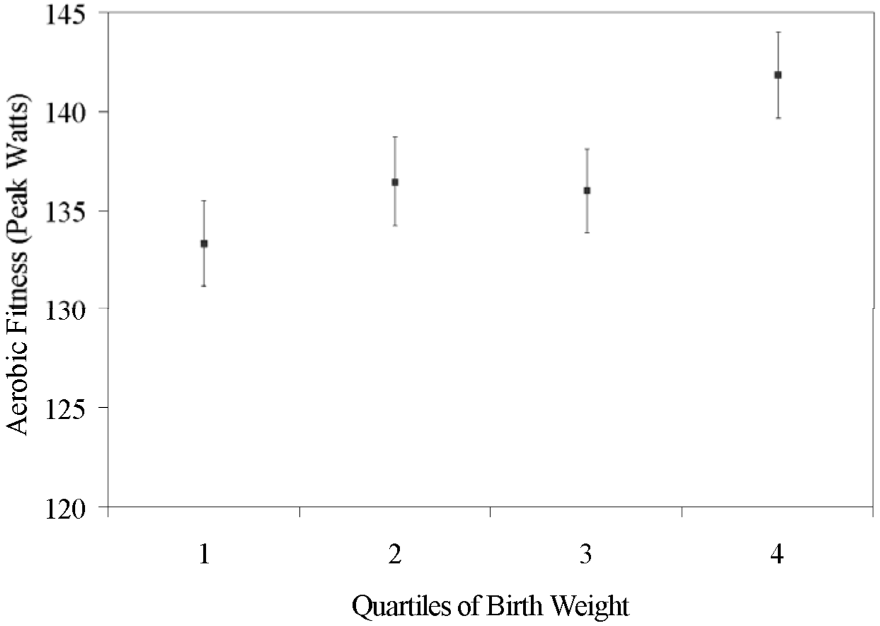

Figure 2. Association between birth weight and aerobic fitness

Adjusted for sex, age group, country, sexual maturity, socio-economic status and fat-free mass.