ORIGINAL RESEARCH

Birth Weight and Cardiorespiratory Fitness Among Young Men Born at Term: The Role of Genetic and Environmental Factors

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***Background*—**Preterm delivery and low birth weight are prospectively associated with low cardiorespiratory fitness (CRF). However, whether birth weight, within the at-term range, is associated with later CRF is largely unknown. Thus, the aim of the current study was to examine this issue and whether such association, if any, is explained by shared and/or nonshared familial factors.

***Methods and Results*—**We conducted a prospective cohort study, including 286 761 young male adults and a subset of 52 544 siblings born at-term. Objectively measured data were retrieved from total population registers. CRF was tested at conscription and defined as the maximal load obtained on a cycle ergometer. We used linear and nonlinear and fixed-effects regression analyses to explore associations between birth weight and CRF. Higher birth weight, within the at-term range, was strongly associated with increasing CRF in a linear fashion. Each SD increase in birth weight was associated with an increase of 7.9 (95% CI, 7.8–8.1) and 6.6 (95% CI; 5.9–7.3) Wmax in the total and sibling cohorts, respectively. The association did not vary with young adulthood body mass index.

***Conclusions*—**Birth weight is strongly associated with increasing CRF in young adulthood among men born at-term, across all categories of body mass index. This association appears to be mainly driven by factors that are not shared between siblings. Hence, CRF may to some extent be determined already in utero. Prevention of low birth weight, also within the at-term-range, can be a feasible mean of increasing adult CRF and health. **(*J Am Heart Assoc*. 2020;9:e014290. DOI: 10.1161/JAHA.119.014290.)**

Key Words: birth weight • body mass index • cardiorespiratory fitness • gestational age • physical fitness

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More than 20 million (15%) of all live births globally are low-birth-weight births (<2.500 g).[1] Shorter gestational age within the at-term range (ie, weeks 37 to 41),[2] and low weight births seem to be increasing worldwide[3–8] with adverse implications for infant mortality and morbidity.[9] Furthermore, the effects of birth weight on coronary heart disease and type 2 diabetes mellitus are not limited to extremes, but affects health across its entire range.[10] Historically, at-term births have been considered to be homogeneous and healthy.[11] However, recent studies and clinical guidelines have emphasized the heterogeneity of at-term deliveries,[12,13] in particular with regard to birth weight.[14] Yet, explorations of the detailed impact of birth weight on subsequent adult health among individuals born at-term are warranted.

Cardiorespiratory fitness (CRF) is an important determinant of both mortality[15–18] and morbidity,[18–21] which is associated with birth weight[22–24] and gestational age.[23,25–30] Moderate-to-high CRF may counteract the negative health effects of high body mass index (BMI).[31] CRF among youths is, however, declining globally,[32] including in Sweden.[33] Similarly, the proportion of adults with low volume oxygen max (VO_2max , a measure of CRF) has increased in Sweden between 1995 and 2017, from 27% to 46%.[34] Given current trends in CRF and its relevance for mortality and morbidity, there has been a growing interest in the determinants of CRF. Apart from physical activity and genetic factors,[19] perinatal characteristics, and birth weight in particular, are at the center of this interest.[22] Some authors have even argued that CRF might

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Accompanying Tables S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014290

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Received August 21, 2019; accepted December 16, 2019.

Clinical Perspective

What Is New?

- Birth weight is strongly associated with increasing cardiorespiratory fitness in young adulthood in a linear fashion among men born at-term.
- There are consistent positive associations between birth weight, within the at-term range, and cardiorespiratory fitness in all categories of young adulthood body mass index.
- Associations between birth weight and cardiorespiratory fitness appear to be mainly driven by factors that are not shared between siblings.

What Are the Clinical Implications?

- Clinicians should consider the developmental origins of fitness when attempting to examine the cause of compromised cardiorespiratory fitness.
- Birth weight may impact future cardiorespiratory health also within the at-term gestational age range, highlighting a need to consider birth weight as an important factor even among gestational age term-born children.
- These findings further emphasize the importance of prevention strategies to reduce low birth weights, as potential means to reduce the burden associated with low cardiorespiratory fitness.

mediate the observed association between birth weight and cardiovascular disease.[24] Despite some inconsistency,[35] birth weight has been associated with CRF in adults,[23,36] adolescents,[24,37] as well as in children.[22] There have also been studies indicating that the fetal origins of CRF may vary depending on levels of BMI.[37]

However, studies investigating the associations between birth weight or gestational age and CRF are confined to CRF comparisons between extremely or preterm births and at-term-born controls as a homogeneous comparator.[23,25,26,28–30,38]

Therefore, we here present data on the association between birth weight and CRF in young males born within the at-term range, based on objectively measured data from a total population cohort. We also investigate whether any such association is explained by shared familial factors using a family-based design, and if associations vary with BMI in young adulthood.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set require approval from Swedish National Board of Health and Welfare (Medical birth data), Swedish Defence Recruitment Agency (anthropometric and cardiorespiratory measures), Statistics Sweden (linking of parental data and covariate data), and the Regional Ethical Review Board, Stockholm. All data were used under license for the current study and will not be made publicly available by the authors of this study.

Study Design

This prospective cohort study used data from 4 different Swedish population-based registers: (1) the Swedish Military Service Conscription Registry, (2) the Medical Birth Register, (3) the Multigenerational Register, and (4) the Population and Housing Censuses from 1970 and 1990. In addition, we identified all full brothers in our cohort to facilitate within-families analysis, thereby controlling for unobserved shared environmental and genetic factors. Record linkage and identification of full brothers was performed using the unique personal identification numbers, assigned to each Swedish resident at birth. The Medical Birth Register contains validated data on >99% of all births in Sweden.[39] The study was approved by the Regional Ethical Review Board, Stockholm (Dnr: 2016/1445-31/1). The requirement to obtain informed consent was waived by the Regional Ethical Review Board, Stockholm.

Study Population

All singleton men born in Sweden from 1973 to 1987 and conscripted for military service in 1991 to 2005 were eligible for inclusion in the study. During that time period, conscription was mandatory and enforced by law, and adolescents were exempted from conscription only because of incarceration or if they suffered from a severe medical condition (eg, major congenital malformations or severe functional disability). The study period was also chosen to match the availability of perinatal data from the Medical Birth Register (available from 1973). The study population, identified via the Medical Birth Registry, consisted of 620 700 infants born at-term, of which 12 396 (2%) were excluded for incomplete birth weight, maternal age and/or parental education data, leaving 608 304 individuals with complete data in the birth registry. Out of the 608 304 individuals with available birth information, 84 728 (14%) were not conscripted. Furthermore, among the conscripted individuals (n=523 576), those with incomplete data at conscription (N=236 570, 45%) were excluded, including those who did not perform the CRF test at conscription (n=236 538). Finally, we excluded those with extreme values (n=245, 0.05%) for weight (≤40 or ≥150 kg), height (≤150 or ≥210 cm), and BMI (≤15 or ≥60 kg/m^2) at conscription in accordance with previous studies.[40] A flowchart of the deviation of the analytical sample is shown in Figure 1. In total, 286 761 (54.8%) of young adults, who were conscripted and did not have missing conscription information (n=32) nor extreme values, performed the CRF test and were therefore included in the in final analytical sample. The within-families cohort included 52 544 individuals who had 1 or more matchable full brother (Table S1).

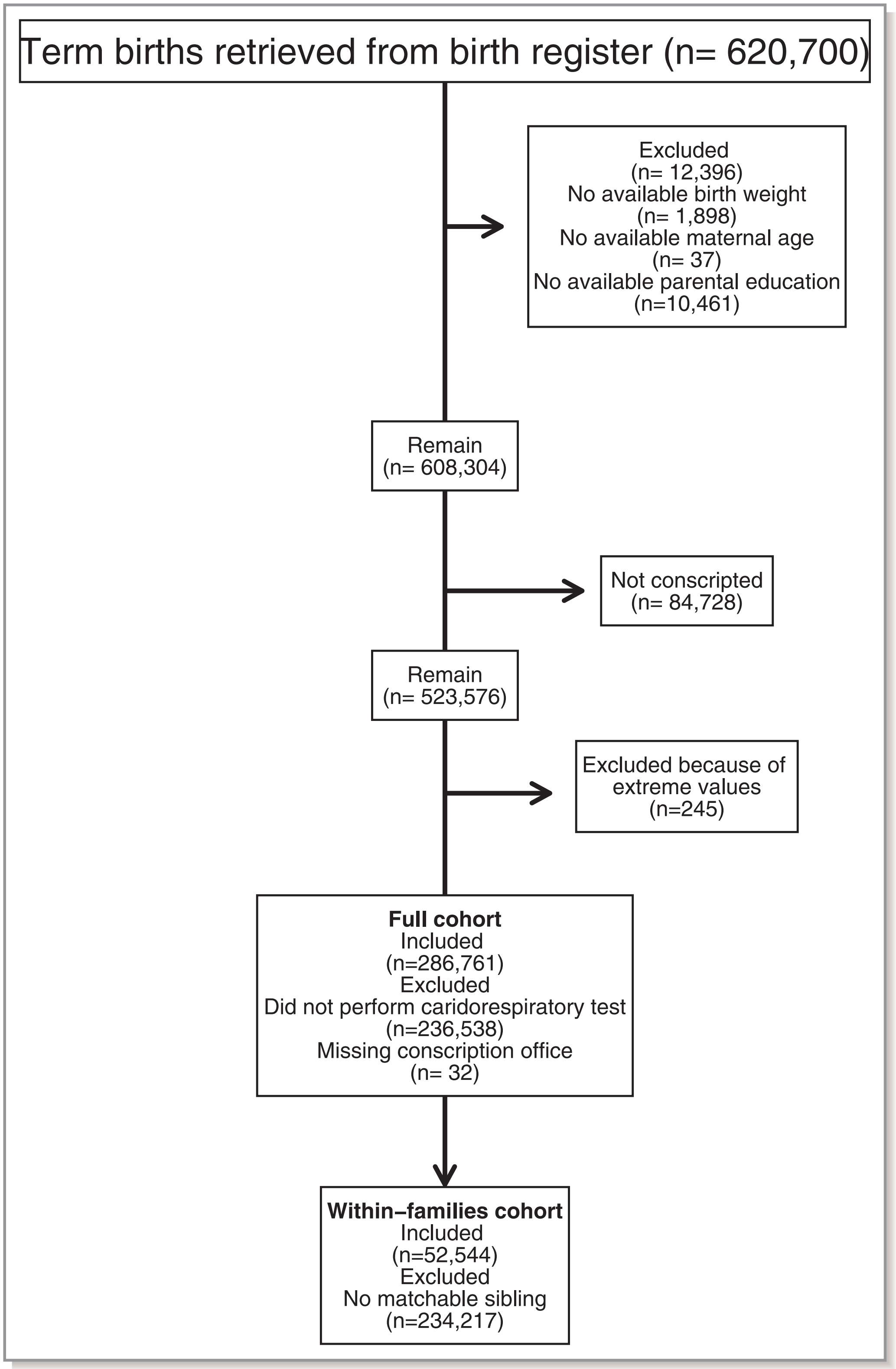

Figure 1. Flowchart of the derivation of the analytical sample.

Exposures

Perinatal variables were obtained from the Medical Birth Registry. Gestational age, in complete weeks, was estimated from the date of the last menstrual period.[41] At-term births were defined as 37 to 41 weeks[12] and birth weight was measured in grams. Birth weight values <300 and >7000 g are excluded from the Medical Birth Registry and were thus not eligible for any analysis. Birth weight *z*-scores for gestational age (specific to each completed week) were derived using the total study population as the reference. For a baby born at 40 weeks, 1 SD corresponds to ≈450 g in this study population.

Outcome: Cardiorespiratory Fitness

CRF was obtained from the Swedish Military Service Conscription Registry and was defined as the maximal load (Wmax, expressed in watts) that the conscript could manage on a cycle ergometer. Only conscripts without known diseases or injuries were allowed to perform the test. Initial resistance was determined by the conscripts' weight: 125 W for weight 70 kg, presumed average CRF. Following a 5-minute warm-up period, with a pulse ranging between 120 and 170 beats/min, the resistance was increased by 25 W per minute until exhaustion. The final work rate (Wmax) was retained and used in the analysis. Although CRF data are based on the final watts achieved, a crude estimation of the corresponding VO_2max can be calculated using the validated equation $1.76\times[\text{watts}\times 6.12/\text{body weight (kg)}]+3.5$.[42] Thus, a Wmax of 270 W for a young adult weighing 70 kg translates into ≈42 mL/min×kg, which is the cut-off proposed, from a recent meta-analysis, to identify children and young adults with increased risk for cardiovascular disease.[43]

Confounders

Weight at conscription was measured using standardized scales and height was assessed using stadiometers in a standardized manner.[44] BMI (kg/m^2) was classified according to World Health Organization categories: underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI >30).[45] Conscription center (6 centers) and age at conscription were obtained from the Conscription Registry while information regarding parental education was retrieved from the Population and Housing Censuses, where the highest education achieved by any of the parents was used as a measure of household socioeconomic position. Further potential confounders obtained from the Medical Birth Registry included hypertension at delivery,[46,47] maternal diabetes mellitus at delivery,[48,49] cesarean section,[50] and maternal age[51,52] and parity.[52,53]

Statistical Analyses

First, we descriptively present our cohort according to high/low Wmax and high/low *z*-score birth weight (4 categories), dichotomized by their respective median. Second, we analyzed the associations between *z*-score birth weight, within the at-term range, and CRF using linear regression models. Third, we used fixed-effects regression models to control for genetic and environmental factors (fixed effects) shared by full brothers within families (50% shared genetics). Fourth, we stratified our crude and fully adjusted models on BMI categories at conscription. All SEs were estimated using the robust (sandwich) method to account for the correlation within families.

We present the associations as crude estimates and adjusted for parity (categorical), maternal age (continuous), maternal diabetes mellitus (pre-existing and/or gestational) (yes/no), maternal hypertension (pre-existing and/or gestational) (yes/no), cesarean section (yes/no), conscription office (categorical), and highest parental education (categorical). To assess departure from linearity, we fitted restricted cubic splines with 5 knots at 5, 27.5, 50, 72.5, and 95 percentiles. We graphically present the restricted cubic spline models using the command "adjustrcspline." All statistical tests were 2-sided, and we considered a *P* value <0.05 to be statistically significant. Statistical analyses were performed using Stata 14.0 (Stata Corp, College Station, TX).

Sensitivity Analyses

We performed 3 sensitivity analyses. First, we adjusted for maternal smoking in early pregnancy, as maternal smoking may be associated with offspring CRF[54] and birth weight,[55] in the subsets of the total (n=54 185) and within-family (n=4071) cohorts where these data were available (Tables S2 and S3). Second, we conducted stratified analyses according to categories of maternal BMI at commencement of pregnancy using a subset of individuals (n=44 896), as previous studies have indicated that maternal obesity plays a role in offspring CRF.[56] We categorized maternal BMI according to World Health Organization categories of BMI (Tables S4 and S5). Third, we descriptively present the characteristics of the individuals excluded at conscription and at physical tests, to highlight potential differences from the original population (Table S6). Fourth, to assess to what extent standardization of birth weight influenced our findings, we analyzed the association birth weight per 100 g with CRF and adjusted for gestational age. We also stratified by completed week of gestational age and also stratified according to Spong[12] categories of term birth. We additionally quantified a statistical interaction between birth weight and gestational age, by week of gestation and Spong[12] categories, in the association with CRF.

Results

Descriptive Statistics

Table 1 presents descriptive data for the 286 761 participants in the full cohort according to birth weight and CRF at conscription. A similar description for the within-families cohort is presented in Table S1. In the full-cohort, the mean Wmax was 303.9 W, the mean birth weight was 3598.7 g, and the mean gestational age was 39.6 weeks. The majority of covariates did not differ over exposure/outcome categories. However, we observed slightly higher occurrences of lower parental education and birth by cesarean section in the lower categories of exposure/outcome. Similarly, we observed slightly higher occurrences of university parental education (43.5% versus 38.1%) in the within-families cohort as compared with the full-cohort (Table S1).

Birth Weight and Cardiorespiratory Fitness

Table 2 presents the crude and adjusted associations between birth weight *z*-score and CRF, both for the full cohort and for the within-family cohort. Higher birth weight was associated with higher CRF, with somewhat weaker associations in the within-families cohort. In the fully adjusted model, each unit increase in birth weight *z*-score (1 SD) was associated with increases of 7.9 (95% CI: 7.8, 8.1) Wmax and 6.6 (95% CI: 5.9, 7.3) Wmax in the full and within-families cohorts, respectively.

Figure 2 depicts adjusted associations, estimated with restricted cubic spline models, between birth weight *z*-scores and Wmax for both the full and within-families cohorts. As shown, the association is overall linear, although small statistical deviation from linearity was detected in the full-cohort (P=0.022). This can, however, largely be explained by the large number of observations.

Table 3 presents the crude and adjusted association between birth weight *z*-score and Wmax, stratified by the BMI categories: underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI >30). Although there was some attenuation in the underweight category, we observed consistent positive associations between birth weight *z*-score and Wmax in all categories of BMI.

Sensitivity Analysis

Table S3 presents the linear associations between birth weight *z*-score and Wmax additionally adjusted for maternal

Table 1. Sample Characteristics of the Full Cohort by Exposure (Birth Weight) and Outcome Level (CRF, Wmax), Sweden, Born Between 1973 and 1987 and Conscripted Between 1991 and 2005

	Full Cohort	High Wmax and High Birth Weight *z*-Score*	High Wmax and Low Birth Weight *z*-Score*	Low Wmax and High Birth Weight *z*-Score*	Low Wmax and Low Birth Weight *z*-Score*
	N=286 761	N=79 675	N=65 227	N=63 558	N=78 301
Gestational age (wk), mean (SD)	39.6 (1.1)	39.6 (1.1)	39.6 (1.1)	39.5 (1.1)	39.6 (1.1)
Birth weight (g), mean (SD)	3598.7 (483.8)	3971.7 (345.6)	3272.6 (301.3)	3931.7 (331.9)	3220.4 (327.4)
Wmax (W), mean (SD)	303.9 (48.9)	345.1 (29.9)	339.5 (25.9)	266.7 (29.6)	262.7 (31.5)
BMI (kg/m^2) at conscription, mean (SD)	22.3 (3.0)	23.1 (2.8)	22.8 (2.7)	21.8 (3.1)	21.5 (3.0)
Age at conscription, mean (SD)	18.3 (0.4)	18.3 (0.4)	18.3 (0.4)	18.3 (0.4)	18.3 (0.4)
Maternal age at birth, mean (SD)	27.5 (4.9)	28.0 (4.8)	27.1 (4.7)	27.8 (5.0)	26.9 (4.9)
Maternal parity, median (IQR)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)
Maternal diabetes mellitus at pregnancy, n (%)	979 (0.3)	343 (0.4)	142 (0.2)	295 (0.5)	199 (0.3)
Birth by cesarean section, n (%)	23 895 (8.3)	6006 (7.5)	5478 (8.4)	5158 (8.1)	7253 (9.3)
Maternal hypertension at pregnancy, n (%)	221 (0.1)	52 (0.1)	64 (0.1)	34 (0.1)	71 (0.1)
Parental highest level of education, n (%)					
Primary education	36 771 (12.8)	8170 (10.3)	6962 (10.7)	9393 (14.8)	12 246 (15.6)
Secondary education ≤2 y	95 395 (33.3)	23 834 (29.9)	20 076 (30.8)	22 870 (36.0)	28 615 (36.5)
Secondary education >2 y	45 319 (15.8)	12 533 (15.7)	10 777 (16.5)	9772 (15.4)	12 237 (15.6)
University level	109 276 (38.1)	35 138 (44.1)	27 412 (42.0)	21 523 (33.9)	25 203 (32.2)

BMI indicates body mass index; CRF, cardiorespiratory fitness; IQR, interquartile range.
*Gestational-age-specific birth weight *z*-scores estimated using the total study population as the reference.

Table 2. Linear Association Between Birth Weight Standardized by Gestational Age and CRF (Wmax).

Full Cohort				
	Crude		Adjusted*	
	Estimate (B)	95% CI	Estimate (B)	95% CI
BW *z*-score	7.9	7.7, 8.1	7.9	7.8, 8.1
Within-Families Cohort				
	Crude		Adjusted†	
	Estimate (B)	95% CI	Estimate (B)	95% CI
BW *z*-score	4.9	4.3, 5.6	6.6	5.9, 7.3

BW indicates birth weight; CRF, cardiorespiratory fitness; Wmax, maximal load, expressed in watts.

*Adjusted for parity, maternal age, maternal diabetes mellitus, maternal hypertension, cesarean section, conscription office, and highest parental education.

†Adjusted for same as above, excluding highest parental education.

smoking at the commencement of pregnancy. The associations in this subanalysis of 54 185 and 4071 young adults in the full and within-families cohorts, respectively, were similar to those in the full data set.

Table S5 presents linear associations between birth weight *z*-score and Wmax, stratified on maternal BMI categories at commencement of pregnancy. The associations between birth weight *z*-score and Wmax did not differ by maternal BMI categories.

Table S6 presents the descriptive differences between characteristics of the individuals excluded at conscription and at physical tests. We observed that those conscripted had higher occurrences of high parental education. For instance, among those who conscripted, 37.2% had parents with university level education while 30.1% of those not conscripted had the same level of parental education. There were no major differences in birth characteristics between those conscripted and not conscripted. At physical tests, there were only minor differences between those who performed the physical tests and those who did not.

Table 4 presents linear associations between birth weight per 100 g and Wmax adjusted and stratified for completed weeks of gestational age. We found a statistically significant interaction between week of gestation and birth weight (*P*=0.001) and Spong[12] categories of term birth and birth weight (*P*=0.031). However, the stratified analysis only marginally varied over weeks and categories and was overall consistent with our main analysis of standardized birth weight.

Discussion

Main Findings

In this population-based study of 286 761 male participants, higher birth weight, within the at-term range (ie, weeks 37–41), was found to be prospectively and positively associated with CRF in young adulthood (age range from 17 to 25) across all categories of BMI. Our family-based analyses support that this association is mainly driven by factors that are not shared between brothers. The present study, showing that low birth weight, within the at-term range, is associated with reduced CRF in young adulthood, provides important evidence to this emerging field. To the best of our knowledge, this is the first study that has examined associations of variations in the levels of CRF in young adulthood across different birth weights within the at-term range, and also the first including family-based analyses, which provide a unique opportunity to explore whether this association is explained by shared family factors.

Underlying Mechanisms

Explanations for the protective and enduring effect that birth weight seems to have on CRF could be that low birth weight is associated with abnormal development that triggers adaptations in tissues and organs, ultimately resulting in permanent physiological alterations such as lower capillary density and fewer alveoli.[57] These factors may in turn result in long-lasting impairments in cardiac function and performance (ie, VO$_2$max).[58]

Similar to the observed association with CRF, high birth weight has been associated with a greater lean body mass and not fat mass,[59] which is further supported by studies on birth weight and muscular strength.[60,61] Notably, contrary to the potential protective effects of a higher birth weight, high birth weight has also been associated with offspring obesity,[62] although this association has been suggested to be confounded both by a parental obesogenic environment and the strong genetic component of obesity.[62] Notably, recent genetic analysis has suggested that associations between birth weight and subsequent blood pressure may be a function of confounding by genetic factors rather than intrauterine programming.[63]

Similar to the association between birth weight and blood pressure, a common genetic cause of both low birth weight and low CRF cannot be excluded. CRF has a strong genetic component with a reported heritability of 27% to 55%.[64] However, results from the within-families analysis, where ≈50% of the genetic factors (ie, those shared between siblings) are held constant, only differed marginally from those based on the full cohort. Assuming minor differential measurement error and minor confounding from nonshared factors,[65] shared factors (including both genetic and environmental) most likely only explain part of the observed associations between birth weight, within the at-term range, and CRF. Differences in upbringing between children born small and adequate for gestational age may also partly explain the observed associations. For example, parents may choose to restrict low birth weight children's participation in vigorous

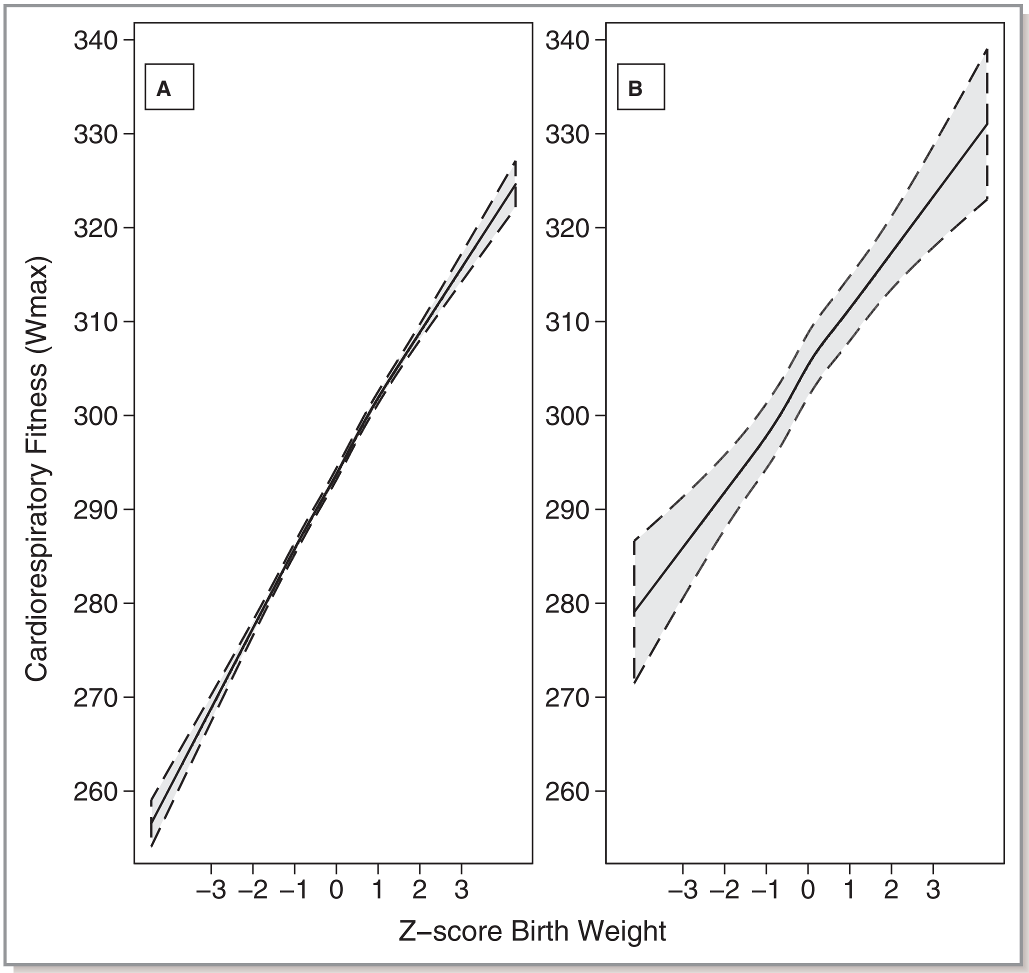

Figure 2. Adjusted associations, estimated with restricted cubic spline models, between birth weight *z*-scores and cardiorespiratory fitness (maximal load, expressed in watts [Wmax]) for the full-cohort (**A**) and the within-families cohort (**B**) (95% CI, dashed line).

physical activity because of perceptions of frailty. This notion is supported by studies based on self-reported physical activity.[38] However, studies objectively assessing physical activity with accelerometers have not shown an association with preterm birth, despite differences in CRF.[30]

Variations in perceived physical capacity may affect the performance on a cycle ergometer test. Differences in perceived physical capacity and perceived physical ability between low birth weight and normal birth weight young adults have previously been described.[66]

We demonstrated that birth weight is associated with CRF regardless of levels of BMI, suggesting that BMI does not explain the observed association, contrary to what has been previously hypothesized.[37] Finally, we demonstrated that the observed association did not vary by maternal BMI, highlighting the importance of birth weight regardless of maternal obesity.[56]

Table 3. Linear Associations Between Birth Weight *Z*-Score, Within the At-Term Range, and CRF (Wmax) Stratified by BMI Categories at Conscription

		Crude		Adjusted*	
BW *Z*-Score	N	Estimate (B)	95% CI	Estimate (B)	95% CI
BMI <18.5	14 966	4.0	3.3, 4.7	3.9	3.3, 4.6
BMI 18.5–24.9	229 379	7.1	6.9, 7.3	7.0	6.8, 7.2
BMI 25–29.9	35 603	7.3	6.7, 7.8	7.3	6.8, 7.9
BMI 30+	6803	5.9	4.8, 7.0	6.0	4.9, 7.1

BMI indicates body mass index; BW, birth weight; CRF, cardiorespiratory fitness; Wmax, maximal load, expressed in watts.
*Adjusted for parity, maternal age, maternal diabetes mellitus, maternal hypertension, cesarean section, conscription office, and highest parental education.

Implications of the Findings

Our findings are potentially of public health significance. CRF in adolescence is strongly associated with all-cause[44] and cardiovascular mortality.[20] In the same population as reported

Table 4. Linear Association Between Birth Weight in Increments of 100 g and CRF (Wmax), Adjusted for or Stratified by Gestational Age in Weeks and Term Categories

	Adjusted*		Adjusted†	
	Estimate (B)	95% CI	Estimate (B)	95% CI
BW per 100 g	1.73	1.69, 1.77	1.74	1.70, 1.78
	Crude		Adjusted‡	
	Estimate (B)	95% CI	Estimate (B)	95% CI
BW per 100 g, by completed wks of gestational age				
Wk 37 (n=15 182)	1.69	1.52, 1.85	1.69	1.52, 1.86
Wk 38 (n=37 278)	1.75	1.64, 1.86	1.75	1.64, 1.85
Wk 39 (n=72 950)	1.88	1.80, 1.96	1.87	1.79, 1.95
Wk 40 (n=94 344)	1.70	1.63, 1.77	1.72	1.65, 1.79
Wk 41 (n=67 007)	1.63	1.55, 1.71	1.64	1.56, 1.72
BW per 100 g, by Spong categories of term birth				
Early term (n=52 460)	1.67	1.59, 1.76	1.66	1.57, 1.75
Full term (n=167 294)	1.75	1.69, 1.80	1.75	1.70, 1.80
Late term (n=67 007)	1.63	1.55, 1.71	1.64	1.56, 1.72

BW indicates birth weight; CRF, cardiorespiratory fitness; Wmax, maximal load, expressed in watts.

*Adjusted for gestational age.

†Adjusted for gestational age, parity, maternal age, maternal diabetes mellitus, maternal hypertension, cesarean section, conscription office, and highest parental education.

‡Adjusted for same as above, excluding gestational age.

here, although born earlier, CRF has been linearly associated with reduced risk of cardiovascular events and mortality.[20] The 8-unit increase in Wmax for each SD increase in birth weight *z*-score reported here translates into ≈1.34 increase in metabolic equivalent.[42,67] Interestingly, a 1 metabolic equivalent higher CRF has been associated with a 13% (odds ratio 0.87, 95% CI: 0.84, 0.90) and 15% (odds ratio 0.85, 95% CI: 0.82, 0.88) reduction in all-cause mortality and cardiovascular disease, respectively in meta-analysis of 33 studies,[68] an effect of similar magnitude as a 7-cm reduction in waist circumference or a 5 mm/Hg reduction in systolic blood pressure.[68] Since ≈15% of all live births are low birth weight births, providing adequate prenatal care may be an effective means of improving adult health not only through prevention of establishing harms associated with low birth weight[69] but also via bettered CRF.

Comparison With Previous Research

Studies investigating the associations between birth weight or gestational age and CRF have mostly been confined to CRF comparisons between extremely low birth weight, or preterm births, and at-term birth being used as a homogeneous comparator.[23,25,26,28–30,38] However, similar associations between birth weight and CRF as those observed before[70] have been reported in another Swedish study.[23] However, the Swedish study did not explore whether the associations could be explained by factors shared within-families, nor did it perform any investigation into the influence of maternal BMI and maternal smoking.[23] In contrast, findings from a smaller cohort with repeated measures of CRF observed an association between birth weight and CRF at age 12 years, but the association was not observed in the re-test at age 15 years.[24] Contrary to the observed attenuation by age,[24] the results demonstrated here highlight that an association between birth weight and physical fitness persist into young adulthood.

Strengths and Limitations

The strengths of this study lie in the population-based design and the long-term follow-up, where prospectively collected data at birth could be linked to outcome at ages 17 to 25 years. We were also able to adjust for perinatal and other major determinants (birth delivery aspects, parental education, parity, etc) of CRF, and the within-families analysis enabled us to disentangle whether associations were driven by shared or nonshared factors. Additionally, both exposure and outcome (ie, CRF and birth weight) were measured using objective and standardized procedures. Furthermore, the use of a young cohort with little pre-existing disease decreases the risk of reverse causation (ie, low CRF because of disease), but also provides support for early prevention of chronic disease. Finally, by studying at-term gestational age, we are able to rule out potential confounding by prematurity.

The current study has several limitations that need to be acknowledged. First, gestational age was estimated according to last menstrual period, which may have introduced some measurement errors. However, any error introduced is likely to be nondifferential with regard to both exposure and outcome. Second, although we adjusted our association estimates for a comprehensive set of potential confounders, some residual confounding can still be present. For example, the lack of data on maternal nutrition and smoking habits (of all mothers and conscripts) could have had an impact on health outcomes after birth. However, we performed a sensitivity analysis on a subset with data on maternal smoking at the commencement of pregnancy. Moreover, some of the effect of smoking on CRF is accounted for in our models since smoking is more common in families with low parental education. Third, this study only includes young male adults, which limits the generalizability of our findings to females and older-age adults. However, previous studies have described that birth weight and CRF are positively associated in both males and females.[24,36] Furthermore, associations between gestational age and CRF in young adults born at term have been shown in both sexes,[27] indicating heterogeneity in CRF among term births in both sexes. Fourth, the within-families analysis including full-brothers only allows us to control for ≈50% of the shared genetic factors between siblings, and the segregating genes potentially affecting CRF are unlikely to be randomly distributed with regard to birth weight. Fifth, although we adjust for maternal metabolic morbidities at pregnancy (diabetes mellitus and hypertension), the prevalence of such metabolic morbidities is higher in Sweden in more recent cohorts than compared with when our data were collected,[71] which may have implications for the generalizability of our findings. Finally, adolescents who performed the cycle ergometer test at conscription had a normal ECG and were without diseases or injuries. Thus, the participants in this study are likely to have been the healthiest, which may induce selection bias and limit our generalizability to healthier populations.

Conclusions

Higher birth weight, within the at-term range, is prospectively associated with higher CRF in young male adults, across all categories of BMI, and this association appears to be mainly driven by factors that are not shared between brothers. Given the strong prospective associations between CRF in young adulthood and later life morbidity and mortality, these findings may have public health implications. They further contribute to our understanding of determinants of CRF and emphasize the importance of prevention strategies to reduce low birth weights also within the at-term range.

Acknowledgments

Berglind conceived and designed the current study and wrote and was involved in data analyses. Ahlqvist performed the statistical analyses and was involved in manuscript editing. Tynelius was involved in statistical analyses. Persson, Ortega, and Magnusson critically revised the manuscript and commented on the statistical analyses. All authors approved the final manuscript.

Sources of Funding

This work was supported by the Stockholm County Council (ALF 20180266 to Berglind). The funders had no role in the design of the study, data collection, data analysis, interpretation of findings, in the writing of the report, or the decision to submit the article for publication.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Sample Characteristics of the Within-Families Cohort by Exposure (Birth Weight) and Outcome Level (Cardiorespiratory Fitness, Wmax), Sweden, Born Between 1973-1987 and Conscripted Between 1991–2005.

	Within-families cohort	**High Wmax and High birth weight z-score***	**High Wmax and Low birth weight z-score***	**Low Wmax and High birth weight z-score***	**Low Wmax and Low birth weight z-score***
	N=52,544	N=14,737	N=12,271	N=11,545	N=13,991
Gestational age (weeks), mean (SD)	39.5 (1.1)	39.5 (1.1)	39.6 (1.1)	39.5 (1.1)	39.5 (1.1)
Birth weight (g), mean (SD)	3,627.6 (473.5)	3,992.1 (340.4)	3,302.6 (292.9)	3,956.9 (323.2)	3,257.0 (315.0)
Wmax (W), mean (SD)	309.2 (48.8)	349.8 (29.9)	344.0 (25.9)	271.6 (29.2)	267.1 (31.4)
BMI (kg/m^2) at conscription, mean (SD)	22.2 (2.8)	23.0 (2.7)	22.7 (2.5)	21.8 (2.9)	21.4 (2.8)
Age at conscription, mean (SD)	18.3 (0.4)	18.3 (0.4)	18.3 (0.4)	18.3 (0.4)	18.3 (0.4)
Maternal age at birth, mean (SD)	27.4 (4.6)	27.8 (4.5)	26.9 (4.3)	27.8 (4.8)	26.9 (4.6)
Maternal parity, median (IQR)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)
Maternal diabetes mellitus at pregnancy, n (%)	126 (0.2%)	46 (0.3%)	11 (0.1%)	45 (0.4%)	24 (0.2%)
Birth by cesarean section, n (%)	4,068 (7.7%)	1,114 (7.6%)	931 (7.6%)	887 (7.7%)	1,136 (8.1%)
Maternal hypertension at pregnancy, n (%)	35 (0.1%)	7 (<1%)	8 (0.1%)	5 (<1%)	15 (0.1%)
Parental highest level of education, n (%)					
Primary education	5,488 (10.4%)	1,200 (8.1%)	1,044 (8.5%)	1,415 (12.3%)	1,829 (13.1%)
Secondary education ≤2-years	15,851 (30.2%)	3,897 (26.4%)	3,343 (27.2%)	3,845 (33.3%)	4,766 (34.1%)
Secondary education >2 years	8,351 (15.9%)	2,279 (15.5%)	1,981 (16.1%)	1,819 (15.8%)	2,272 (16.2%)
University level	22,854 (43.5%)	7,361 (49.9%)	5,903 (48.1%)	4,466 (38.7%)	5,124 (36.6%)

BMI indicates body mass index; IQR indicates inter-quartile range; SD indicates standard deviation.

*Gestational age specific birth weight z-scores estimated using the total study population as the reference

Table S2. Subsample of Maternal Smoking at the Commencement of Pregnancy (Week 12), Sweden, Born Between 1973-1987 and Conscripted Between 1991–2005.

	Full cohort			**Within-families cohort**		
	Not smoker	**1-9 cigarettes/day**	**≥10 cigarettes/day**	**Not smoker**	**1-9 cigarettes/day**	**≥10 cigarettes/day**
N, %	37,099 (74.0%)	8,358 (16.7%)	4,657 (9.3%)	3,258 (80.0%)	566 (13.9%)	247 (6.07%)
Birth weight (g), mean (SD)	3,687.7 (475.1)	3,536.8 (463.7)	3,461.6 (474.4)	3,721.4 (453.8)	3,549.9 (437.6)	3,436.9 (419.0)
Wmax (W), mean (SD)	298.1 (41.1)	291.1 (41.0)	286.4 (41.2)	301.7 (39.9)	297.1 (38.7)	293.7 (41.3)

Table S3. Linear Association Between Birth Weight Z-Score, Within the At-Term Range, and Cardiorespiratory Fitness (Wmax) Adjusted for Maternal Smoking at the Commencement of Pregnancy (Week 12).

Full-cohort

	*Adjusted**		*Adjusted†*	
	Estimate (B)	**CI 95%**	**Estimate (B)**	**CI 95%**
BW Z-score	6.8	6.4, 7.1	7.2	6.8, 7.6

Within-families cohort

	*Adjusted**		*Adjusted‡*	
	Estimate (B)	**CI 95%**	**Estimate (B)**	**CI 95%**
BW Z-score	4.9	2.9 , 6.9	6.7	4.6, 8.8

BW indicates birth weight; CI indicates confidence interval.

*Adjusted for: maternal smoking.

†Adjusted for: maternal smoking, parity, maternal age, maternal diabetes, maternal hypertension, cesarean section, conscription office and highest parental education.

‡Adjusted for: same as above, excluding highest parental education

Table S4. Subsample of Maternal BMI Categories* at the Commencement of Pregnancy (Week 12), Sweden, Born Between 1973-1987 and Conscripted Between 1991–2005.

	Full cohort			
	BMI <18.5	**BMI 18.5-24.9**	**BMI 25-29.9**	**BMI ≥30**
N, %	2,978 (7.1%)	33,790 (80.1%)	4,673 (11.1%)	740 (1.8%)
Birth weight (g), mean (SD)	3,492.9 (454.5)	3,636.8 (471.9)	3,773.8 (500.1)	3,767.8 (513.5)
Wmax (W), mean (SD)	287.7 (40.7)	296.7 (41.2)	297.9 (42.0)	295.1 (41.3)

*BMI categories according to World Health Organization standard.

Table S5. Linear Associations Between Birth Weight Z-Score, Within the At-Term Range, and Cardiorespiratory Fitness (Wmax) Stratified by Maternal BMI Categories at Commencement of Pregnancy (Week 12).

		Crude		***Adjusted****	
BW Z-score	**n**	**Estimate (B)**	**CI 95%**	**Estimate (B)**	**CI 95%**
BMI <18.5	3,130	8.3	6.8, 9.8	7.8	6.3, 9.4
BMI 18.5-24.9	36,025	7.2	6.7, 7.6	7.3	6.9, 7.8
BMI 25-29.9	4,955	7.5	6.3, 8.7	7.8	6.6, 9.0
BMI 30+	786	7.1	4.5, 9.8	7.2	4.5, 9.9

BMI indicates body mass index; BW indicates birth weight; CI indicates confidence interval.
*Adjusted for: parity, maternal age, maternal diabetes, maternal hypertension, cesarean section, conscription office and highest parental education.

Table S6. Descriptive Characteristics of the Total Population Available in the Medical Birth Registry and the Stepwise Excluded Population, , Sweden, Born Between 1973-1987 and Conscripted Between 1991–2005.

	Participation in conscription		Exclusion at physical tests	
	Not Conscripted	**Conscripted**	**Incomplete conscription records***	**Analytic sample**
	N=84,728	N=523,576	N=236,815	N=286,761
Gestational age (weeks), mean (SD)	39.4 (1.2)	39.5 (1.1)	39.5 (1.2)	39.6 (1.1)
Birth weight (g), mean (SD)	3,559.6 (506.2)	3,597.1 (484.2)	3,595.2 (484.8)	3,598.7 (483.8)
Maternal age at birth, mean (SD)	27.9 (5.2)	27.8 (5.0)	28.1 (5.1)	27.5 (4.9)
Maternal parity, median (IQR)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)
Maternal diabetes mellitus at pregnancy, n (%)	484 (0.6%)	2,338 (0.4%)	1,359 (0.6%)	979 (0.3%)
Birth by cesarean section, n (%)	8,954 (10.6%)	47,749 (9.1%)	23,854 (10.1%)	23,895 (8.3%)
Maternal hypertension at pregnancy, n (%)	140 (0.2%)	601 (0.1%)	380 (0.2%)	221 (0.1%)
Parental highest level of education, n (%)				
Primary education <=10 years	16,121 (19.0%)	67,430 (12.9%)	30,659 (12.9%)	36,771 (12.8%)
Secondary education <=2-years	31,387 (37.0%)	182,793 (34.9%)	87,398 (36.9%)	95,395 (33.3%)
Secondary education >2 years	11,753 (13.9%)	78,480 (15.0%)	33,161 (14.0%)	45,319 (15.8%)
University level	25,467 (30.1%)	194,873 (37.2%)	85,597 (36.1%)	109,276 (38.1%)
Measures at conscription				
Age at conscription, mean (SD)			18.4 (0.5) (n=236,720)	18.3 (0.4) (n=286,758)
Height (cm) at conscription, mean (SD)			179.9 (6.6) (n=154,869)	180.0 (6.5) (n=286,751)
Weight (kg) at conscription, mean (SD)			73.8 (14.1) (n=154,870)	72.4 (10.8) (n=286,751)
BMI (kg/m²) at conscription, mean (SD)			22.8 (4.0) (n=154,869)	22.3 (3.0) (n=286,751)
Subsample				
Maternal smoking habits, n (%)				
Not smoker	26,232 (67.6%)	123,654 (71.2%)	83,297 (69.6%)	40,357 (74.5%)
1-9 cigarettes/day	7,406 (19.1%)	30,996 (17.8%)	22,072 (18.5%)	8,924 (16.5%)
≥10 cigarettes/day	5,173 (13.3%)	19,133 (11.0%)	14,229 (11.9%)	4,904 (9.1%)
Maternal BMI (kg/m²), mean (SD)	22.1 (3.3) (n=31,276)	21.9 (3.0) (n=144,240)	21.9 (3.1) (n=99,344)	21.9 (2.9) (n=44,896)

*No available Wmax, conscription office and/or extreme values at conscription.

n indicated where a n<N