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Low Birth Weight as a Predictor of Cardiovascular Risk Factors in Childhood and Adolescence? The PEP Family Heart Study

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ABSTRACT

Background: Low birth weight is considered a risk factor for cardiovascular disease (CVD) in later life. Because data in children and adolescents are sparse and controversial, we assessed the association of birth weight with CVD risk factors in German youths.

Methods: We categorized 843 urban children and adolescents aged 3-18 years by quintiles of birth weight and measured nine traditional risk factors in terms of body mass index (BMI), waist circumference (WC), systolic (SBP) and diastolic (DBP) blood pressure, total cholesterol (TC), LDL-C, HDL-C, Non HDL-C and triglycerides (TG). SPSS 21 was used for statistical analysis.

Results: Mean values and prevalence of nine anthropometric and lipid risk variables were equally distributed over the five birth weight groups. Though risk factors clustered between 3.0 kg and 4.0 kg of birth weight in both genders we found only one significant correlation of birth weight with TG for males and females and another one for HDL-C in males. The strongest clustering of significant regression coefficients occurred in the 2nd birth weight quintile for SBP (ß 0.018), TC (ß -0.050), LDL-C (ß -0.039), non LDL-C (ß -0.049) and log TG (ß -0.001) in males and females.

Conclusions: Overall we did not find significant associations between birth weight and nine traditional cardiovascular risk factors in children and adolescents. However, the 2nd quintile of birth weight might suggest clustering of risk factors.

Keywords: Birth weight, CVD risk factors, associations in youths

INTRODUCTION

Low gestational age at birth is independently associated with increased mortality in young adulthood.[1,2] Men with the lowest weight at birth had the highest death rates from ischemic heart disease. The risk of dying from myocardial infarction at 60 years was doubled in men with birth weight of 2500 g or less compared with birth weight of 4300 g or higher.[3] The Nurses Health Study provided strong evidence of an association between birth weight and risk of coronary heart disease and stroke in adulthood.[4] In the Aberdeen children study, birth weight was inversely associated with coronary heart disease (CHD) and stroke with an age-adjusted odds ratio of 0.62 respectively 0.38 for a 1-kg increase.[5] A systematic review of 18 studies concluded that one kg higher birth weight was associated with a 10-20% lower risk of subsequent CHD.[6] The association of low birth weight

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with cardiovascular disease (CVD) risk factors including elevated blood pressure, high BMI, and dyslipidemia is controversial.[7-28] There is growing interest in the extent to which body composition differs in infants and children born at the extremes of birth weight. The discrepancies in birth weight are primarily attributable to differences in lean body mass and only to a limited extent to fatness.[28] Preterm infants have less lean tissue but more similar fat mass.[29] Small birth weight is associated with some, but not all components of metabolic syndrome.[30]

Because data on the impact of low birth weight on the development of CVD risk factors in youths are sparse and controversial, we investigated the association of birth weight with anthropometric and laboratory risk factors in urban German children and adolescents participating in the PEP Family Heart Study.[31]

METHODS

We enrolled 843 German youths (435 boys and 408 girls) with reported birth weight and nine CVD risk factors. The 310 children (aged 3-11 years) and 533 adolescents (aged 12-18 years) were categorized according to their birth weight into quintiles for boys (group I <3050 g, group II 3050-3369.5 g, group III 3369.5 -3576 g, group IV 3576-3866 g and group V >3866 g) and for girls (group I <2940 g, group II 2940-3210 g, group III 3210-3450 g, group IV 3450-3700 g and group V >3700 g). We measured body mass index (BMI), waist circumference (WC), blood pressure (BP), total cholesterol (TC), LDL-Cholesterol (LDL-C), HDL-Cholesterol (HDL-C), non HDL-Cholesterol and triglycerides (TG) as previously described.[31-34] Cardiovascular risk factors were defined as overweight (85th - 95th percentile BMI), obesity ≥95th percentile BMI,[35] abdominal adiposity >90th percentile WC,[36] Hypertension as SBP and/or DBP >95th percentile,[37] dyslipidemia in terms of TC ≥200 mg/dL, LDL-C ≥130 mg/dL, HDL-C <40 mg/dL, non HDL-C ≥126 mg/dL, TG ≥100 mg for ages 0-9 years respectively TG ≥130 mg/dL ages 10-19 years.[32]

For statistical analysis, we used SPS 21. Pearson's correlation coefficient was used to correlate birth weight with anthropometric and laboratory variables. The independent association between birth weights with the above variables was calculated including birth weight outliers using linear regression model. Two sided $P < 0.05$ was considered significant.

RESULTS

Mean values and prevalence of anthropometric and lipid values were equally distributed over five birth weight groups of 843 children and adolescents aged 3-18 years [Table 1]. Though the majority of maximal values occurred in the 4th quintile, scatter diagrams demonstrate that risk variables cluster between 3.0 kg to 4.0 kg of birth weight as exemplified for blood pressure in Figure 1. The nearly equal distribution of the nine risk variables over the birth weight quintiles is illustrated by box plots [Figure 2].

Among the correlations of birth weight with the nine risk variables only TG in both genders and HDL-C in males were significant [Table 2a]. The age adjusted regression for birth weight and SBP is exemplified in Figure 3. Significant regression coefficients with birth weight occurred for BMI, WC and log TG in females, for HDL-C in males and for TG [Table 2b]. However, the 2nd birth weight quintile had the closest association with SBP, TC, LDL-C, non LDL-C and log TG in both genders [Table 2c].

DISCUSSION

This study describes the relationship between birth weight quintiles and blood pressure, serum lipids, BMI and WC in 843 youths. Altogether, we did not find clear associations between birth weight and CVD risk factors in children and adolescents which is consistent with published literature.[9,16,19,20] However, because five from nine regression estimates were significant for the 2nd birth weight quintile in both genders, the corresponding birth weight of 3.05-3.40 kg in males and 2.94 – 3.21 kg in females might be predictive for increased CVD risk.

Regarding lipids, a systematic review of 79 studies concluded that low birth weight does not have effects on blood cholesterol levels that would have material impact on CVD risk because 1 kg lower birth weight may be associated with only ~2.0 mg/dL higher TC. Associations with birth weight were provided for HDL-C, LDL-C and TG with heterogeneous outcome for HDL-C in terms of 34 studies without association, 6 studies with inverse and 6 studies with a positive association with birth weight, for LDL-C 23 studies without, 10 studies inverse and 1 study with a positive association and for TG 27 studies without, 15 studies inverse and 1 positive study.[19] We found significant regression coefficients between the 2nd birth weight quintile and TC (ß -0.050), LDL-C (ß -0.039), non LDL-C (ß -0.049) and log TG (ß -0.001). Another review in youths does also not provide strong evidence of a consistent relationship between birth weight and blood lipid concentrations.[20]

Though we observed significant regression coefficients in the 2nd birth weight quintile for SBP (ß 0.018) in males and females, our BP data are consistent with studies which found no association between birth weight and

Table 1: Characteristics and prevalences of 435 boys and 408 girls by quintiles of birth weight; #maximal values

Boys	GROUP I <3050 g	GROUP II 3050-3369.5 g	GROUP III 3369.5-3576 g	GROUP IV 3576-3866 g	GROUP V >3866 g
n	97	97	80	80	81
Age (year)	13.0 (3.0)	13.4 (3.2)	13.0 (3.3)	12.9 (2.8)	12.9 (3.5)
Height (cm)	158.0 (15.9)	162.0 (16.7)	160.3 (18.9)	162.6 (14.7)#	161.6 (20.1)
Weight (kg)	50.0 (17.0)	54.1 (16.9)	52.3 (18.5)	54.0 (16.3)	54.7 (20.3)#
BMI (kg/m²)	19.4 (3.6)	20.0 (3.3)	19.6 (3.7)	19.9 (3.2)	20.1 (3.7)#
Overweight (%)	8.5	8.5	9.8	11.5	10.4
Obese (%)	5.1	6.9	3.8	6.0	4.9
WC (cm)	70.4 (10.8)	72.1 (10.1)	71.4 (11.0)	72.2 (9.4)	72.4 (11.2)#
WC >90th percentile (%)	8.0	11.2	7.7	11.7	11.0
SBP (mmHg)	111.3 (13.4)	113.3 (13.7)#	111.9 (14.8)	111.6 (13.2)	111.8 (13.1)
DBP (mmHg)	71.8 (8.5)	70.8 (7.5)	71.4 (9.9)	72.8 (8.4)#	70.9 (8.6)
Hypertension (%)	8.2	8.2	3.8	7.5	3.8
Total cholesterol (mg/dL)	153.6 (28.3)	153.2 (29.8)	158.0 (28.3)	159.1 (31.3)#	152.3 (28.2)
TC >200 mg/dL (%)	5.2	1.0	7.5	5.0	7.4
LDL-cholesterol (mg/dL)	84.4 (23.3)	87.2 (27.6)	88.5 (23.2)#	90.8 (26.8)	86.1 (25.3)
LDL-C >130 mg/dL (%)	4.1	3.1	6.3	5.0	6.2
HDL-cholesterol (mg/dL)	55.0 (10.9)#	52.5 (7.0)	55.3 (10.9)	54.4 (11.0)	53.2 (9.2)
HDL-C <40 mg/dL (%)	6.2	2.1	5.0	6.3	7.4
NonHDL-C (mg/dL)	98.5 (23.6)	100.7 (28.5)	102.7 (24.5)	104.7 (28.0)#	99.0 (24.5)
NonHDL-C >126 mg/dL (%)	4.1	2.1	6.3	7.5	4.9
Triglycerides (mg/dL)	70.8 (33.7)	67.6 (23.2)	71.0 (24.4)#	69.6 (25.4)	70.6 (27.0)
TG >100/130 mg/dL (%)	5.3	2.1	2.5	2.5	3.7
Girls	**GROUP I <2940g**	**GROUP II 2940-3210g**	**GROUP III 3210-3450g**	**GROUP IV 3450-3700g**	**GROUP V >3700g**
n	78	75	90	85	80
Age (year)	13.2 (3.2)	13.0 (3.6)	12.9 (3.1)	13.1 (3.5)	12.3 (3.4)
Height (cm)	155.3 (13.6)	152.4 (14.5)	155.5 (14.7)	156.3 (15.0)#	155.0 (15.1)
Weight (kg)	49.2 (18.1)	45.9 (13.9)	46.7 (13.1)	50.7 (14.5)#	48.7 (15.1)
BMI (kg/m²)	19.8 (5.0)	19.3 (3.5)	18.9 (2.8)	20.3 (3.6) #	19.7 (3.4)
Overweight (%)	8.5	7.2	7.8	10.5	6.5
Obese (%)	5.5	4.8	3.0	6.2	7.1
WC (cm)	70.9 (13.0)	68.6 (10.3)	68.7 (8.2)	71.2 (9.9)#	69.7 (9.9)
WC >90th percentile (%)	12.3	12.1	9.0	13.1	11.8
SBP (mmHg)	110.8 (12.3)#	105.9 (9.3)	106.5 (10.1)	107.2 (12.0)	107.3 (10.8)
DBP (mmHg)	71.7 (9.8)#	67.3 7.3)	68.1 (7.3)	69.8 (8.1)	70.4 (8.0)
Hypertension (%)	5.1	4.0	4.4	8.2	6.3
Total cholesterol (mg/dL)	162.4 (29.2)	165.6 (26.7)	169.4 (29.1)#	166.4 (30.4)	160.2 (19.4)
TC >200 mg/dL (%)	7.7	6.7	12.2	15.3	2.5
LDL-Cholesterol (mg/dL)	91.9 (25.5)	95.7 (20.9)	97.3 (23.9)#	94.5 (23.7)	91.5 (16.6)
LDL-C >130 mg/dL (%)	5.1	8.0	11.1	7.1	1.3
HDL-Cholesterol (mg/dL)	54.8 (9.6)	54.4 (8.5)	56.4 (9.3)	56.5 (9.9)#	55.2 (8.5)
HDL-C <40 mg/dL (%)	6.4	1.3	3.3	3.5	1.3
NonHDL-C (mg/dL)	107.6 (27.3)	111.2 (24.2)	112.9 (26.2)#	109.9 (26.3)	105.1 (17.3)
NonHDL-C >126 mg/dL (%)	9.0	9.3	10.0	11.8	1.3
Triglycerides (mg/dL)	79.6 (38.8)#	77.3 (32.3)	78.3 (32.5)	76.4 (31.2)	67.8 (26.2)
TG >100/130 mg/dL	12.8	4.0	10.0	4.7	2.5

BMI=Body mass index, WC=Waist circumference, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, TC=Total cholesterol, LDL-C=Cholesterol, HDL-C=Cholesterol, TG=Triglycerides

BP values in children.[21] Huxley and coworkers conclude from 55 studies reporting regression coefficients that birth weight is of little relevance to BP in later life.[9] A meta-analysis of 57 observational studies included 27

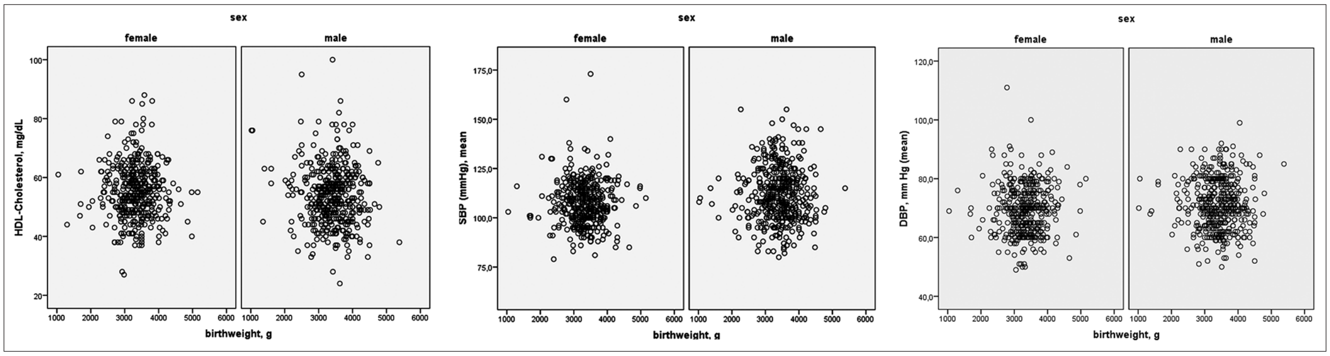

Figure 1: HDL-Cholesterol by birth weight in 435 boys and 408 girls

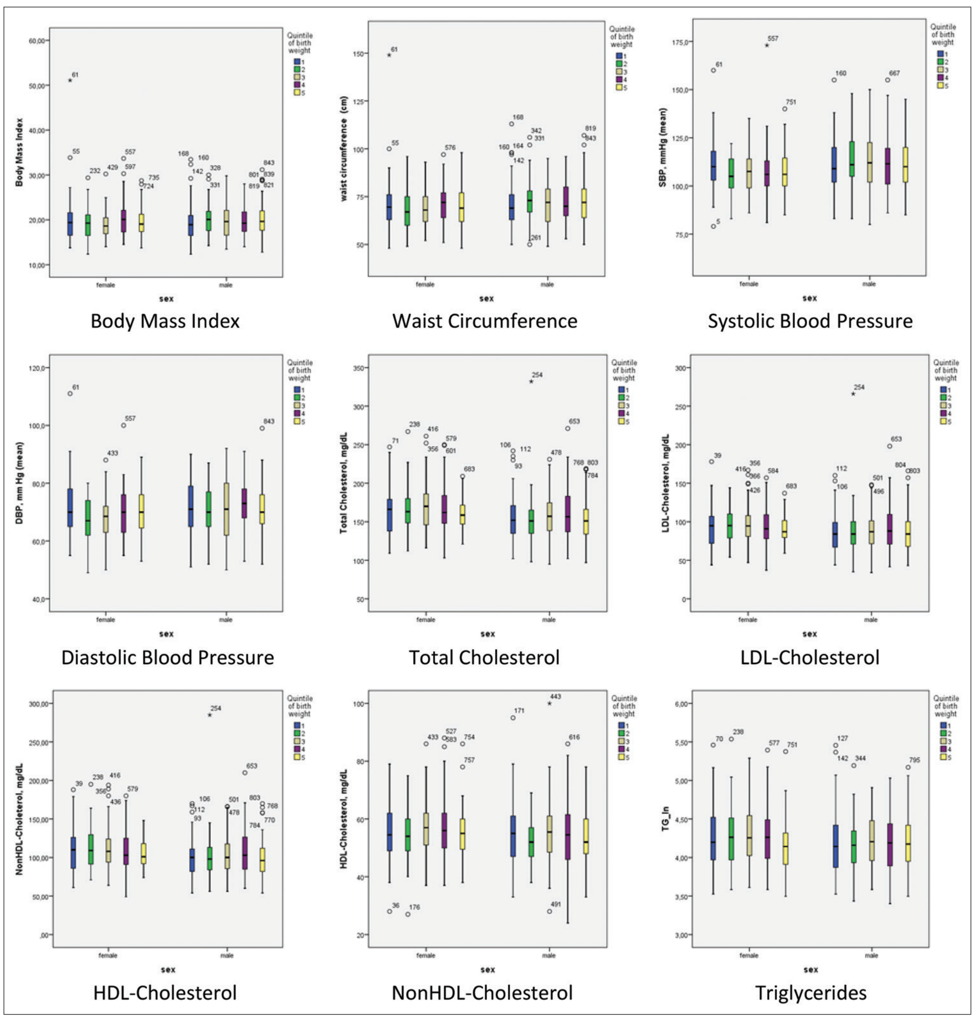

Figure 2: Distribution of Risk Factors by Quintiles of Birth Weight in 435 boys and 408 girls

studies in youth under 18 years which found combined for both genders significant ($P < 0.01$) regression coefficients -1.64 (95% CI 2,16—1.12) for SBP per kg increase in birth weight suggesting chance findings for sex differences.[15] However, a review among 0-71 years old subjects demonstrated that nearly all of the regression coefficients were inversely related typically approximately 2-3 mm Hg/kg in children among 34 studies describing a negative relationship between BP and birth weight in children and adults.[7] Elevated BP in 2.5 year-old children with a mean birth weight of 810 ± 164 g might have implications for cardiovascular health later in life[10] as low birth weight had in African American adolescents.[23] Among 149 newborns who were divided in four birth weight groups there was a positive and independent significant relationship between birth weight and SBP in terms of 1 mm Hg increase for each 125 g within the first year.[26]

Table 2: Correlations, linear regression model for all and linear regression model for five quintiles ; *$P<0.05$

a. Correlations	BMI	Waist	SBP	DBP	TC	LDL-C	HDL-C	Non HDL-C	TG
Birthweight									
r	0.62	0.041	0.006	0.011	−0.042	−0.002	−0.053	−0.028	−0.072*
p	0.071	0.238	0.858	0.74	0.22	0.952	0.128	0.421	0.038
Birthweight ♂									
r	0.047	0.04	0.002	−0.007	−0.024	0.034	−0.09	0.008	−0.04
p	0.331	0.408	0.973	0.884	0.62	0.476	0.06*	0.873	0.408
Birthweight ♀									
r	0.075	0.028	−0.021	0.013	−0.037	−0.024	0.007	−0.044	−0.089
p	0.132	0.578	0.679	0.794	0.457	0.63	0.883	0.378	0.071
b. Linear regressions (age-adjusted)	**BMI**	**Waist**	**SBP**	**DBP**	**TC**	**LDL-C**	**HDL-C**	**Non HDL-C**	**TG ln**
Birthweight all									
ß	0.00002	0.001	0.00005	0.00005	−0.002	0.00009	−0.001	−0.001	0.00005*
p	0.071	0.238	0.858	0.740	0.220	0.952	0.128	0.428	0.027
Birthweight ♂									
ß	0.00004	0.001	0.000	0.000003	−0.001	0.001	−0.002*	0.000	−0.003
p	0,146	0.176	0.762	0.906	0.544	0.515	0.032	0.914	0.226
Birthweight ♀									
ß	0.00004*	0.001*	0.0009	0.001	−0.002	−0.001	0.000	−0.002	−0.00007*
p	0.007	0.009	0.926	0.505	0.499	0.568	0.764	0.389	0.032
c. Linear regressions (age-adjusted)	**BMI**	**Waist**	**SBP**	**DBP**	**TC**	**LDL-C**	**HDL-C**	**Non HDL-C**	**TG ln**
Birthweight 1st quintile									
ß	0.000	0.000	0.003	0.000019	-0.004	0.001	−0.004*	0.000	0.000016
p	0.587	0.918	0.133	0.990	0.512	0.764	0.05	0.986	0.823
Birthweight 2nd quintile									
ß	0.000	0.007	0.018*	0.003	−0.050*	−0.039*	−0.001	−0.049*	−0.001*
p	0.807	0.209	0.01	0.568	0.011	0.021	0.879	0.007	0.004
Birthweight 3rd quintile									
ß	0.003	0.009	0.021*	0.011	−0.040	−0.024	−0.008	−0.032	0.000
p	0.089	0.073	0.007	0.056	0.057	0.156	0.273	0.083	0.062
Birthweight 4th quintile									
ß	−0.002	0.003	0.014	0.012*	−0.041	−0.028	−0.011	−0.030	0.000013
p	0.212	0.583	0.08	0.02	0.053	0.095	0.129	0.106	0.956
Birthweight 5th quintile									
ß	0.001	0.004*	0.0004	0.004	−0.02*	−0.009	−0.007*	−0.013*	−0.000061
p	0.103	0.04	0.280	0.063	0.002	0.103	0.003	0.025	0.477

BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, TC=Total cholesterol, LDL-C=Choleterol, HDL-C=Cholesterol, TG=Triglycerides

A meta-analysis of 643,902 1-75 year-old subjects from 26 countries described that high birth weight increased the risk of overweight in later life and low birth weight might indicate decreased risk of later overweight.[24]

The strengths of this study are a homogeneous setting consisting of sustained staff using the same equipment including auscultatory device and procedures including fasting blood collection in winter and laboratory methods, the representative recruitment of children and adolescents enrolled from 94% of the 54 elementary schools in one city. The weaknesses are missing or incomplete data on length and gestational age were reported from mothers. Furthermore, we did not control for confounding variables such as maternal BP, BMI and smoking status, which are correlated with low birth weight.

CONCLUSIONS

Overall we did not find relevant associations between birth weight and nine cardiovascular risk factors in children and adolescents. This is consistent with published literature. However, the 2nd quintile of birth weight might be suggested to be predictive for a higher risk for CVD.

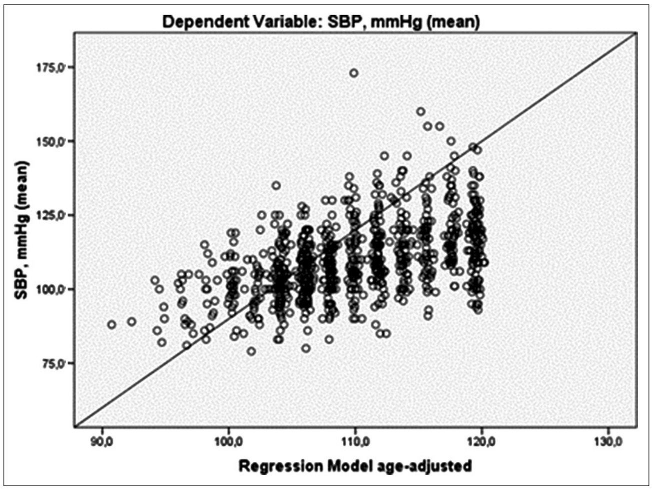

Figure 3: Regression model for linear regression between birth weight (g) and Systolic Blood Pressure in 843 children

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