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# **Birth Weight is more important for Peak Bone Mineral Content than for Bone Density: The Peak-25 Study of 1061 Young Adult Women**

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**Disclosures:** NONE

**Mini-abstract:** Lower birth weight has a negative association with adult BMC and body composition in young adult Swedish women

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# ABSTRACT

*Purpose:* The aim of this study was to evaluate the influence of birth weight on peak bone mass and body composition in a cohort of 25-year-old women.

*Methods:* 1061 women participated in this cross-sectional population-based study, using dual energy X-ray absorptiometry (DXA) to assess BMC, BMD and body composition (total body (TB), femoral neck (FN), total hip (TH), lumbar spine L1-L4 (LS), lean and fat mass). Birth weight data was available for 1047 women and was categorized into tertiles of low ( $\leq 3180$  g), intermediate (3181–3620 g) and high ( $\geq 3621$  g) birth weight.

*Results:* Significant correlations were observed between birth weight and TB-BMC ( $r=0.159$ ,  $p<0.001$ ), FN-BMC ( $r=0.096$ ,  $p<0.001$ ), TH-BMC ( $r=0.102$ ,  $p=0.001$ ), LS-BMC ( $r=0.095$ ,  $p=0.002$ ) and lean mass ( $r=0.215$ ,  $p<0.001$ ). No correlation was observed between birth weight and BMD. The estimated magnitude of effect was equivalent to a 0.3-0.5 SD difference in BMC for every one kilogram difference in birth weight (151 g (TB); 0.22 g (FN); 1.5 g (TH), 2.5kg total body lean mass). The strongest correlations between birth weight and BMC occurred in women with the lowest birth weights, although excluding women who weighed  $<2500$  g at birth, the correlation remained significant although slightly weaker.

*Conclusions:* Women with lower birth weight have lower bone mineral content, independent of current body weight, and less lean and fat mass at the age of 25. Lower birth weight has a greater negative influence on bone mass than the positive influence of higher birth weight.

**Keywords:** BONE MINERAL CONTENT, BONE MINERAL DENSITY, PEAK BONE MASS, BIRTH WEIGHT, YOUNG ADULT, FEMALE

## INTRODUCTION

Bone mineral density (BMD) is one of the most important factors contributing to future fracture risk [1]. Bone mass after menopause depends to a great extent on the amount of bone attained during young adulthood and the rate at which bone is subsequently lost. The maximum amount, peak bone mass, plays a crucial role. It has been estimated that a one standard deviation increase in peak bone mass could reduce the risk of fracture by as much as 50% [2], since individuals who accrue a high peak bone mass are also likely to maintain a higher BMD throughout their lifetime [3]. Peak bone mass is commonly considered to be reached during the third decade of life [4, 5], albeit not uniformly at all skeletal sites. Peak is reached earlier in the hip than in the spine; estimates suggest just before age 20 in the total hip and up to the early or mid-thirties in the lumbar spine [6].

Peak bone mass is a summation of contributing factors, with genetic influence being central [7-9], although many environmental and other factors of varying importance modulate bone gains during childhood and adolescence [10-12]. Bone mass is commonly referred to as bone mineral density, an areal density measurement, while the actual mineral content (BMC) refers to the total amount of bone mineral [13-15]. However, the material properties of bone are not only related to bone mass but to all bone strength components such as size and structural bone geometry, including cortical thickness, porosity and trabecular bone morphology on one hand, and elasticity, matrix compositions and the mineral phase on the other.

There is evidence to suggest that the intrauterine environment plays an important role, modifying the genetically determined skeletal potential. Intrauterine growth restriction, other adverse stimulus in fetal life or preterm birth, reflected in low birth weight and also events immediately after birth, can potentially induce permanent effects on the skeleton [16]. It has been proposed that programming of bone mineral content within the periosteal envelope

occurs during the intrauterine and early postnatal period [17, 18]. This is later affected by other modulators contributing to BMD, bone strength and subsequently peak bone mass.

Earlier studies have indicated that birth weight is associated with bone mass, although studied in smaller populations and in various age groups. The influence of birth weight on bone mass at older ages (>60 years) is less clear [19], while studies in younger individuals indicate that birth weight effects are more pronounced for BMC than BMD [13, 20].

Recognizing the importance of obtaining high peak bone mass, it is clearly meaningful to evaluate factors determining early skeletal development which have potential long-term effects. Birth weight, as an indicator of prenatal health, might be one such factor, enhancing or reducing the likelihood of reaching the preprogrammed maximum bone mass. Hence, studying individuals during their third decade, when by most definitions they have reached peak bone mass, should be highly informative. The PEAK-25 cohort, consisting of more than 1000 women, all at the age of 25, was designed to be as closely as possible representative of peak bone mass. The purpose of this study was to determine the influence of birth weight on bone mass and body composition parameters in young adult women.

## SUBJECTS AND METHODS

### *Subjects*

Identified through a computerized administrative registration system, 2394 Caucasian women living in the city of Malmö, Sweden, were invited to participate in this population-based sample study of 25-year-old women. The only exclusion criteria applied were current pregnancy or having been pregnant within the previous 12 months (102 subjects were excluded). In all, 1064 women attended the baseline investigation; however, an additional 3 women were later excluded since they fell outside the predetermined age range (25.00–25.99 years). The final PEAK-25 cohort hence includes 1061 Caucasian women, all 25 years old. The total response rate for the study was 49%.

The investigation included bone mineral density measurements, physical and muscle strength tests, ultrasound of the calcaneus, blood and urine sampling, and a comprehensive questionnaire. The study was approved by Lund University Ethics Committee and followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

### *Bone mass and body composition*

Bone mineral density and body composition were measured by dual X-ray absorptiometry (DXA, Prodigy, Lunar corp., GE, Madison, Wisconsin). The same device was used throughout the entire study. Bone mineral content (BMC) expressed in grams (g) and bone mineral density (BMD) expressed in grams/cm<sup>2</sup> (g/cm<sup>2</sup>) were measured in: total body (TB), femoral neck (FN); total hip (TH) and lumbar spine L1-L4 (LS). In addition, lean mass and fat mass, in kilograms (kg), were measured through the total body scan.

The precision of DXA measurements in our hands has previously been determined as 0.90% in the femoral neck and 0.65% in the lumbar spine[21].

### *Birth data*

Birth-related information was obtained from the birth database at the Swedish National Board of Health and Welfare (SNBHW). Of the participating 1061 subjects, data on birth weight (g) was available for 1047 and birth length (cm) for 1034 women. Information on gestational age was not available. Birth weight was categorized according to the World Health Organization (WHO) classification of birth weight: normal ( $>2500$  g), low (LBW; 1500–2499 g), very low (VLBW; 1000–1499 g) and extremely low (ELBW;  $<1000$  g). This classification system does not include high or very high birth weights; we therefore created such a category by applying a +2 SD cut-off which corresponds to  $\geq 4500$  g. The participants were also divided into tertiles by birth weight for statistical analysis.

### *Anthropometry*

Standardized equipment was used to assess anthropometric data including weight (kg) and height (cm). BMI was calculated according to the formula  $\text{weight}/\text{height}^2$  ( $\text{kg}/\text{m}^2$ ).

### *Questionnaire*

A comprehensive questionnaire was completed. Details regarding response-reliability have been presented (Sign Test, p-value: 0.125–1.0) [21].

### *Statistical methods*

Baseline descriptive data is reported as mean and standard deviation (SD). Exploratory data analysis using the Shapiro-Wilk test was performed for all variables to assess normality of distribution. To test for linear relationships between birth weight and the variables of interest and to determine effect sizes of birth weight on adult BMC, lean and fat mass, Pearson's correlation coefficient and simple linear regression analysis were used. To examine between-group differences, tertiles of birth weight were analyzed using ANOVA/ANCOVA, followed by pair-wise comparisons. Analyses were performed with and without adjustment for current body weight.

Statistical analysis was performed using SPSS v17.0 software (SPSS Inc., Chicago, Illinois). The level of significance was set at  $p < 0.05$ .



## RESULTS

Baseline characteristics including anthropometric, bone mineral and body composition data are shown in table 1. Mean birth weight was  $3392 \pm 537$  g and length at birth  $50 \pm 2.3$  cm. Birth weight distribution according to the WHO classification was: 95.7% normal, 3.8% low while only 0.5% fell into the very low category. None of the women weighed less than 1000 g (extremely low) at birth while 2.2% ( $n=23$ ) weighed 4500 g or more.

Current body weight and height were weakly, but significantly correlated with birth weight ( $r=0.20$ ;  $p<0.001$ ;  $r=0.28$ ;  $p<0.001$ , respectively). For length at birth, the correlation was stronger for current body height ( $r=0.35$ ;  $p<0.001$ ) than for body weight ( $r=0.22$ ;  $p<0.001$ ).

Birth weight was correlated with BMC at all measured sites. The strongest correlations were observed for TB-BMC ( $r=0.24$ ;  $p<0.001$ ), TH-BMC ( $r=0.17$ ;  $p<0.001$ ) and FN-BMC ( $r=0.16$ ;  $p<0.001$ ) (figure 1) and remained significant after adjustment for current body weight. The estimated effect sizes for a 1 kg change in birth weight on BMC parameters are presented in table 3 and were equivalent to a 0.3–0.5 SD difference. The largest effect size was observed for TB-BMC (151 gram, 95% CI 114–188). Birth weight was not significantly correlated to BMD at any site after adjustment for current body weight (table 2).

Birth weight correlated with the body composition parameters lean and fat mass, with lean mass also remaining significant after adjustment for current body weight (unadjusted  $r=0.29$ ;  $p<0.001$ , adjusted  $r=0.21$ ;  $p<0.001$ ) (table 2). The estimated effect size for lean mass was 2.5 kg for every kilogram increase in birth weight, an almost 0.5 SD difference (table 3). Fat mass correlated negatively with birth weight after adjustment for current body weight ( $r=-0.21$ ;

$p < 0.001$ ), but showed a weak positive correlation ( $r = 0.10$ ;  $p = 0.002$ ) when unadjusted. This is reflected in the small effect size ( $< 0.2$  SD).

To further determine the magnitude of the association between birth weight, adult bone mass and body composition, the participants were categorized into tertiles of birth weight; low ( $\leq 3180$  g), intermediate (3181–3620 g) and high ( $\geq 3621$  g). The quantitative results are shown in table 4. Low birth weight was associated with shorter stature at age 25 and lower body weight including reduced values of all its contributing components (BMC, lean and fat mass) ( $p$ -values  $< 0.001$ – $0.005$ ). The differences between the birth weight categories was most pronounced when low and high tertiles were compared and was evident for BMC at all sites: low vs. high TB-BMC ( $-7.2\%$ ), FN-BMC ( $-5.3\%$ ), TH-BMC ( $-6.0\%$ ) and LS-BMC ( $-6.3\%$ ) (figure 2). The contribution of low birth weight to BMC was also evident from comparison of low vs. intermediate tertiles, while there was no difference between intermediate and high (table 4). In contrast, differences in BMD between birth weight tertiles were less pronounced (low vs. high; FN-BMD ( $-2.8\%$ ), TH-BMD ( $-2.1\%$ )). Additionally, women in the low birth weight tertile had  $7.3\%$  ( $p < 0.001$ ) lower lean mass values than those in the high birth weight tertile.

In order to establish whether the observations from this study were driven only by individuals with the lowest birth weights, those in WHO categories low (LBW) and very low (VLBW) birth weight ( $n = 45$ ) were excluded from the analysis. With their removal, the mean birth weight increased by  $\sim 2\%$ , from 3392 g to 3450 g. The results were largely similar, with the correlation between birth weight and BMC remaining but slightly weaker (TB-BMC ( $r = 0.14$ ;  $p < 0.001$ ), FN-BMC ( $r = 0.08$ ;  $p = 0.02$ ), TH-BMC ( $r = 0.09$ ;  $p = 0.004$ ) and LS-BMC ( $r = 0.09$ ;  $p = 0.003$ )). As before, no association was evident for BMD. The correlations between birth

weight and lean mass ( $r=0.23$ ;  $p<0.001$ ) and fat mass ( $r=-0.22$ ;  $p<0.001$ ) were also largely unchanged. Separate analysis of the women in the low and very low birth weight categories identified a correlation only with total hip BMC ( $r=0.31$ ;  $p=0.046$ ), although this may be a function of the small sample number.

## DISCUSSION

This study illustrates the long-term influence of birth weight on components of bone and body composition in young adult women, particularly BMC and lean mass. Women with low birth weights had lower BMC at all measured sites as adults, while BMD was largely unaffected. Furthermore, low birth weight was also associated with lean and fat mass. The findings were most pronounced for those with the lowest birth weight, whereas the difference between those in the intermediate and high birth weight categories was negligible. Since women at the age of 25 closely represent maximal bone mass, this study indicates that prenatal life may have implications for the attainment of peak bone mass.

Intrauterine growth restriction has implications for a range of conditions [16, 22, 23] and studies have been performed to determine the relationship between birth weight, adult bone mass and future fracture risk. With peak bone mass as a key stage in skeletal development prior to the onset of the natural process of age associated bone loss, determination of the relationship between birth weight and bone mass in early adulthood is imperative. Although numerous studies have been performed [18, 19, 24-39], only a limited number involved women around the third decade and these generally employed small sample sizes. Hence the findings of our study enhances current knowledge and supports the idea of invoking preventive measures while parental awareness may be warranted for those with or at risk of lower birth weights.

The finding of a clear positive association between birth weight and bone mineral content in total body, femoral neck, total hip and lumbar spine in 25-year-old women is in agreement with the published literature. The absence of an association with bone density after adult body weight is taken into consideration is also in general agreement with the literature [13, 20] and also specifically in women in the peak bone mass age interval [24, 27, 32]. Although

the mechanism is not fully clear, a possible explanation for these observations is that the periosteal bone envelope may be determined by the growth trajectory which determines skeletal size, which is most closely related to BMC. Within this envelope, BMD develops, modulated primarily by mechanical loading and other environmental factors [18].

The clinical relevance of the findings lie in the fact that both BMC and BMD are important determinants of bone strength and even if BMC, compared to BMD, is a poorer predictor of hip fracture, the findings have important implications none the less since increased fracture risk secondary to decreased BMC has been described [13-15, 20, 40]. The estimated effect of birth weight on BMC for each 1 kg in birth weight was equivalent to a difference of 0.3–0.5 SD, which could correspond to measurable effects on future osteoporosis risk. In their meta-analysis, Baird et al inferred that values similar to those we report could be extrapolated into an equivalent relative risk for hip fracture of 1.12 in elderly women [20].

These quantitative changes support the assumption of intrauterine programming for future skeletal development. An interesting finding from this analysis was the observation of a more pronounced association between lower birth weight and BMC than with high birth weight, with the interpretation that lower birth weight has a greater negative influence leading to low BMC than high birth weight has an influence in the opposite direction. This is also obvious from the attenuated correlations when those with WHO classified low and very low birth weight were excluded from the analyses. Analyzing these low and very low birth weight individuals separately demonstrated a significant correlation only with TH-BMC, however, the low number of individuals renders a comprehensive sub-analysis non-meaningful. Unfortunately, a clinically relevant cut-off point for birth weight as a risk factor of low bone mass, although interesting, would be difficult to identify.

Both adult lean and fat mass were associated with birth weight. Lean mass was significantly correlated with birth weight even after adjustment for current body weight. Adult lean mass is a predictor of BMC [41, 42] and in the PEAK-25 cohort it explained 23–36% of the variance in bone mineral content (data not shown). Fat mass on the other hand, showed a weakly positive correlation with birth weight, which for reasons which remain unclear were inverse after adjustment for current body weight. A possible explanation is the fact that lean mass appears to contribute more to the variance in BMC than fat mass in this age group.

A major strength of this study is that the PEAK-25 cohort was designed specifically to evaluate bone mass in women at the time of maximum accrual. The single age group and gender minimizes the confounding contribution of age and sex to bone metabolism which makes comparison of the effect size difficult in meta-analyses [20]. To the best of our knowledge this is the largest population-based study of close-to-peak bone mass in women and we report on the magnitude of the association between birth weight, bone mass and the body composition parameters lean mass and fat mass. Other strengths include the homogeneity of the individuals, who are all from the same catchment area and the fact that the birth weight data is retrieved from validated national databases. A limitation of the study is the lack of data on gestational age or other information relating to maternal phenotypes which could have provided additional data on heritable body size.

In summary, this study shows that women with lower birth weight have lower BMC at 25 years of age, independent of adult body weight, and reduced quantities of lean muscle and fat tissue. The major differences occur in subjects within the lowest birth weight bracket,

indicating that low birth weight has a more negative association on BMC than high birth weight has a positive association.

Hence, this study indicates that birth weight has a positive association with peak bone mass, with sustained skeletal effects, particularly from low bone mineral content and also lean mass, which could in the long term increase the risk of osteoporosis and fracture.

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Authors' roles: K Åkesson contributed to study conception and design, and interpretation of data and revision of the manuscript; M Callréus participated in acquisition and analysis of data and drafting, writing and revising of the manuscript. F McGuigan contributed to interpretation of data and revising the manuscript.

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**Table 1** Baseline Characteristics Of The PEAK-25 Cohort

Variables	N	Mean	SD	Range
Age (years)	1061	25.5	0.2	25.008 - 25.999
Height (cm)	1060	168	6	149.6 - 186.5
Weight (kg)	1060	64.7	11.4	40 - 141
BMI (kg/m <sup>2</sup> )	1060	23.0	3.8	15.2 - 51.2
Weight at birth (g)	1047	3392	537	1090 - 5520
Length at birth (cm)	1034	50	2.3	30 - 56
TB-BMC (g)	1060	2592	337	1649 - 3932
FN-BMC (g)	1057	5.07	0.69	2.76 - 8.08
TH-BMC (g)	1022	32.62	4.55	20.85 - 55.83
LS-BMC (g)	1059	66.40	10.42	38.51 - 113.04
FN-BMD (g/cm <sup>2</sup> )	1057	1.053	0.123	0.746 - 1.604
TH-BMD (g/cm <sup>2</sup> )	1022	1.061	0.121	0.742 - 1.593
LS-BMD (g/cm <sup>2</sup> )	1059	1.217	0.128	0.824 - 1.868
Lean mass (kg)	1060	40.4	4.7	26.4 - 65.3
Fat mass (kg)	1060	21.2	8.4	5.5 - 69.7

**Table 2** Correlations between birth weight, BMC, BMD and body composition variables\*

Variable	Birth weight	
	r	p
TB-BMC (g)	0.16	<0.001
FN-BMC (g)	0.10	0.0018
TH-BMC (g)	0.10	0.0012
LS-BMC (g)	0.09	0.0022
FN-BMD (g/cm <sup>2</sup> )	0.05	ns
TH-BMD (g/cm <sup>2</sup> )	0.01	ns
LS-BMD (g/cm <sup>2</sup> )	-0.00	ns
Lean mass (kg)	0.21	<0.001
Fat mass (kg)	-0.21	<0.001

\* adjusted for current body weight

**Table 3** Estimates of effect size on BMC and lean mass for every kilogram difference in birth weight

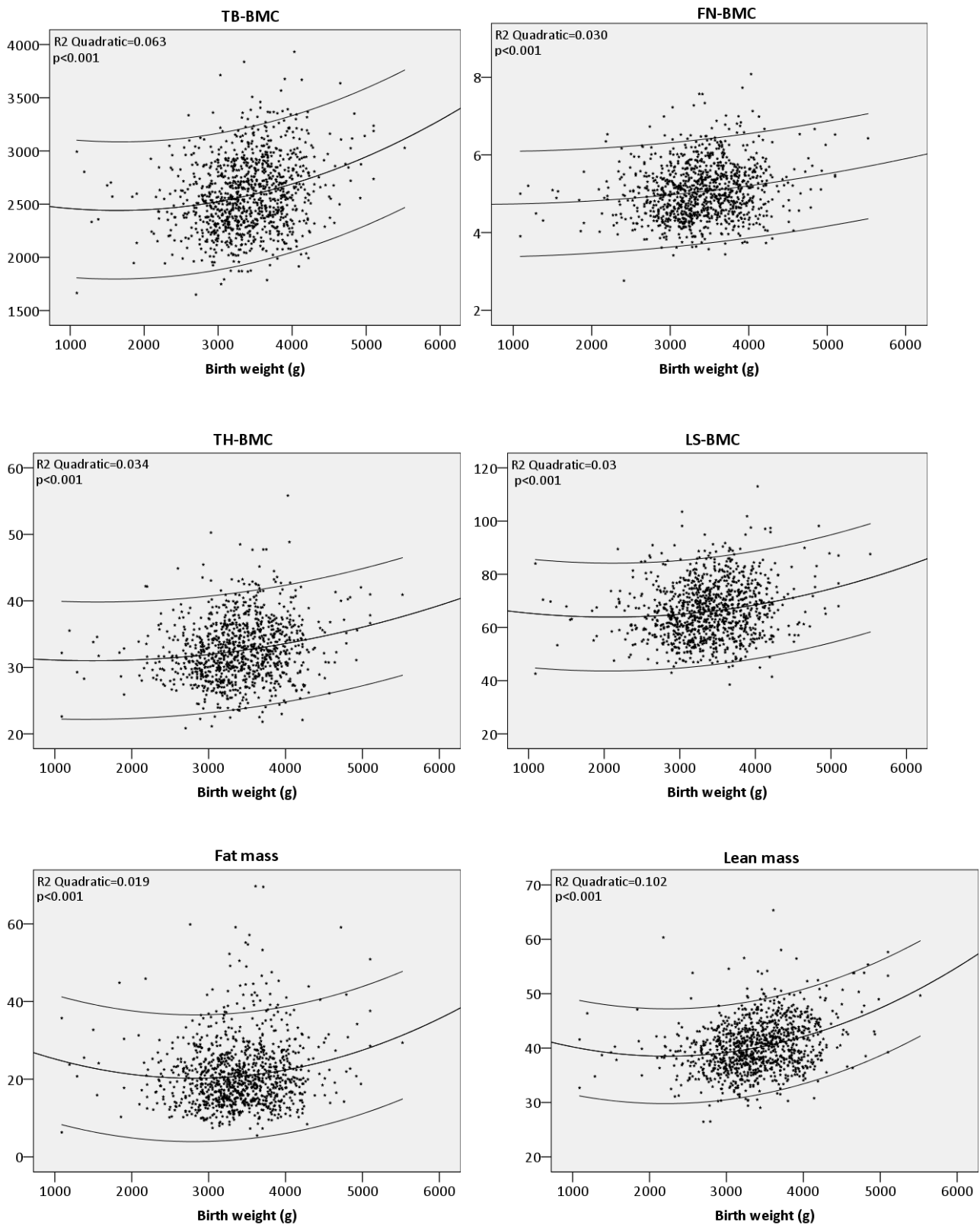
Variable	Effect Size (ß)	95% CI	p
TB-BMC (g)	151	114 - 188	<0.001
FN-BMC (g)	0.22	0.14 - 0.30	<0.001
TH-BMC (g)	1.5	1.0 - 2.0	<0.001
LS-BMC (g)	3.1	1.9 - 4.3	<0.001
Lean mass (kg)	2.52	2.02 - 3.03	<0.001
Fat mass (kg)	1.55	0.60 - 2.49	0.0013

**Table 4** Quantitative differences on bone mass and body composition variables\* of birth weight tertile

Birth Weight Tertile					% Difference Between Tertiles		
	<b>LOW</b> (≤3180 g)	<b>INTERMEDIATE</b> (3181-3620 g)	<b>HIGH</b> (≥3621 g)	Overall	<b>Low vs. Intermed</b>	<b>Low vs. High</b>	<b>Intermed vs. High</b>
<b>Variables</b>	n=349	n=351	n=347	p-value	% p-value	% p-value	% p-value
Weight (kg)	61.9	65.0	67.2	<0.001	- -	- -	- -
Height (cm)	166	168	169	<0.001	- -	- -	- -
BMI (kg/m <sup>2</sup> )	22.6	23.1	23.4	0.012	- -	- -	- -
TB-BMC (g)	2487	2608	2680	<0.001	4.6 0.002	7.2 <0.001	2.7 ns
FN-BMC (g)	4.90	5.12	5.17	<0.001	4.3 0.009	5.2 0.01	1.0 ns
TH-BMC (g)	31.43	32.96	33.42	<0.001	4.6 0.004	6.0 0.002	1.4 ns
LS-BMC (g)	63.98	66.94	68.29	<0.001	4.4 0.02	6.3 0.001	2.0 ns
FN-BMD (g/cm <sup>2</sup> )	1.031	1.065	1.060	<0.001	3.2 0.02	2.7 ns	-0.5 ns
TH-BMD (g/cm <sup>2</sup> )	1.043	1.072	1.065	0.005	2.7 ns	2.1 ns	-0.7 ns
LS-BMD (g/cm <sup>2</sup> )	1.203	1.223	1.223	ns	1.6 ns	1.6 ns	0.0 ns
Lean mass (kg)	38.8	40.5	41.9	<0.001	4.2 0.002	7.4 <0.001	3.3 0.008
Fat mass (kg)	20.1	21.3	22.1	0.005	5.6 0.003	9.0 <0.001	3.6 0.01

\*adjusted for current body weight

**Figure 1** Correlation between birth weight, bone mineral content and lean mass with quadratic curve estimation and 95% confidence interval



**Figure 2** Relationship between the birth weight tertiles for BMC, BMD and body composition variables in the PEAK-25 cohort. Values are shown as means and 95% confidence interval error bars

