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# The relationship between IGF-I and –II concentrations and body composition at birth and over the first two months

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## Abstract

**Background:** Insulin-like growth factors (IGF)-I and -II play an important role in prenatal growth. During the first two months from birth, body fat doubles, and rapid weight gain during this time increases future risk of cardiometabolic disease.

**Objective:** To determine if IGF measurements at birth associate with body composition and the trajectory of its changes in the first two months.

**Methods:** Umbilical cord IGF-I and -II concentrations were measured in term infants. Air displacement plethysmography was performed at birth and two months. Fat mass (FM) and fat free mass (FFM) were corrected for infant length (L) to $FM/L^3$ and $FFM/L^2$ respectively.

**Results:** In 601 (317 male) infants, IGF-I concentrations at birth were associated with $FM/L^3$ and $FFM/L^2$ Z-scores at birth ($R^2$=0.05 and 0.04 respectively, P<0.001), and IGF-II concentrations were associated with $FFM/L^2$ Z-scores at birth ($R^2$=0.01, P=0.02). Lower IGF-I concentrations were weakly associated with increases in $FM/L^3$ Z-scores over the first two months ($R^2$= 0.01, P=0.003).

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**Conclusion:** IGF-I concentrations at birth are associated with adiposity and lean mass at birth and inversely with the trajectory of FM accumulation over the first two months. IGF-I measurements only account for a small amount of the variance in these measures.

## Introduction

The *in utero* environment and early infant growth play an important role in the development of adult disease. Low birth weight is associated with increased risk of cardiovascular disease in adulthood(1) and offspring of mothers exposed to famine during pregnancy have shown an increased risk of obstructive airway disease(2), metabolic syndrome(3), and psychiatric disease(4, 5). Following birth, rapid early weight gain also adversely affects risk of obesity(6), insulin resistance(7), premature adrenarche(8) and cardiovascular disease(1, 6). These early-life weight changes may have additional implications for future health, as the obese phenotype often tracks from early childhood through adulthood(9).

Insulin-like growth factor (IGF)-I and –II play an important role in regulating fetal growth. Infants with IGF-I and –II signaling defects have significant prenatal growth failure(10). Regulation of IGF-I and -II *in utero* appears to be more dependent on nutrition(11) than growth hormone (GH). Infants with GH deficiency have normal size at birth(12) whereas infants with intrauterine growth restriction have reduced concentrations of IGF-I and –II(13, 14). This correlation with weight at birth is stronger for IGF-I than for IGF-II concentrations(14). Animal models also show that expression of IGF-I and –II is reduced in response to intrauterine nutritional deprivation(15).

Birth weight is often used as a proxy for adiposity, but these do not always correlate(16, 17). It is possible that IGF-I and –II concentrations are associated more closely with lean and fat mass than with birth weight. Infants born small for gestational age (SGA) have a greater deficit in body fat than in lean mass and have lower IGF-I concentrations(18), suggesting that IGF-I levels may be more closely associated with body fat than lean mass at birth. IGF-I measurement may also be useful in assessing early growth trajectories. In children born appropriate for gestational age, higher IGF-I concentrations at three months of age are associated with increased weight gain over the preceding three months(19).

There are limited data describing the association of IGF-I and -II concentrations with detailed body composition measurements at birth, or assessing the predictive value of IGF-I and –II concentrations at birth on subsequent dynamic changes in body composition. The aim of this study is to determine if IGF-I and IGF-II measurements at birth are associated with body composition at birth and with the trajectory of body composition changes in the first two months from birth.

## Methods

### Subjects

The Cork BASELINE birth cohort study (ClinicalTrials.gov NCT: 01498965) is a prospective study that recruited infants born in Cork, Ireland between August 2008 and August 2011(20). Children born between 37 and 42 weeks' gestation to low risk first-time

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mothers were eligible for inclusion in this study. Exclusion criteria were non-singleton pregnancies, known major fetal anomalies, maternal prepregnancy hypertension, diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, major uterine anomalies, cervical cone biopsy and ≥3 miscarriages. Ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

The first day of the last menstrual period (LMP) was used to determine gestational age. Ultrasound gestational age was used if performed before 16 weeks' gestation and if there was a discrepancy of more than six days between this and LMP. Ultrasound gestational age was also used if there was a discrepancy of more than ten days between LMP and the ultrasound measurement at 20 weeks' gestation.

## Body Composition assessment

Air displacement plethysmography (ADP) (PEAPOD™ Infant Body Composition System, Life Measurement Inc, Concord, CA)(21) was used to measure body composition at birth and two months of age. Standardized protocols were used to assess body composition as per manufacturer specifications. The naked infant, without umbilical cord clip, was weighed on a high precision scale and placed in a closed chamber. Pressure and volume changes in the chamber were used to calculate air displacement, and body density was determined. Age and sex specific FFM density values, and the density of fat were then used to calculate FM and FFM(22, 23).

Birth measurements were included if they occurred within the first four days from birth. In this cohort, 90% of two month measurements were taken between 49 and 86 days of age, and two month measurements were included if they occurred within this window. FM and FFM are dependent on infant size, so these measurements were adjusted for infant length in order to remove the confounding effect of size(24, 25). We have previously shown that FM/length$^3$ (FM/L$^3$) and FFM/L$^2$ are the optimal indices for this correction in the first three months from birth(16). Age-and sex-specific Z-scores for FM/L$^3$ and FFM/L$^2$ parameters have been determined from this birth cohort, and have been previously described elsewhere(16).

## Sample collection and storage

Umbilical cord samples were collected at birth. They were processed to serum within three hours of collection, and stored at −80°C until analyzed.

## Mass Spectrometry

IGF-I and –II concentrations were measured using liquid chromatography-mass spectrometry (LCMS) (Quest Diagnostics, Madison, NJ). This methodology is described in detail elsewhere(26, 27). Isotopically labeled IGF-I was added to the sample as an internal standard to correct for any analyte lost in binding protein extraction. IGF-I and –II were separated from their binding proteins by an acid ethanol extraction followed by automated online extraction and analytical chromatography using an Aria TX-4 (Thermo-Fisher, San Jose, CA). IGF-I and –II were quantified using a time-of-flight mass spectrometer using narrow mass extraction of full scan spectra. Performance characteristics of this assay have

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been previously described(26, 27). For IGF-I measurement, the interassay coefficient of variation and percent recovery were 5 and 104% at 100 ng/mL, 5.2 and 103% at 400 ng/mL, and 3.5 and 103% at 700 ng/mL. For IGF-II measurement, the interassay coefficient of variation and percent recovery were 6.1 and 102% at 200 ng/mL, 3.2 and 99% at 500 ng/mL, and 5.3 and 99% at 1,200 ng/mL.

### Statistical Analysis

Analysis of $FM/L^3$ and $FFM/L^2$ also utilized age- and sex-specific Z-scores at birth and two months. The change in Z-score between birth and two months was calculated by subtracting the age- and sex-specific Z-score at birth from the two months Z-score. Gestational age- and sex-specific Z-scores for IGF-I and –II concentrations were also used in this analysis, and the development of these reference data are described elsewhere(14). The LCMS assay cannot detect IGF-I concentrations below 16 ng/ml or IGF-II concentrations below 32 ng/ml. When samples had concentrations below these values, a concentration of 15 ng/ml for IGF-I or 31 ng/ml for IGF-II was assigned.

Linear regression analysis was used to test associations between IGF-1 and –II concentration Z-scores with body composition. When evaluating the relationship between IGF Z-scores at birth and changes in $FM/L^3$ and $FFM/L^2$ Z-scores over the first two months, partial correlations were used to correct for $FM/L^3$ and $FFM/L^2$ Z-scores at birth.

Data analyses were performed using SPSS 21.0 (IBM, New York). Mean (SD) were reported for normally distributed data and compared using Student's independent sample T-tests. Linear regression analysis was used to evaluate the relationship between continuous variables.

## Results

There were 2137 infants enrolled in the Cork BASELINE birth cohort. Of these, 105 were excluded from this study due to gestational age less than 37 weeks, 932 did not have sufficient cord blood available for IGF measurement, and a further 499 did not have body composition measurement performed both at birth and two months. Complete measurements of IGF-I and –II at birth and ADP measurements at birth and two months of age were available in 601 term infants (317 male) (Figure 1). Characteristics of these subjects are shown in Table 1. At birth, IGF-I concentration Z-Score correlated positively with IGF-II concentration Z-Score ($R^2$=0.08, $P < 0.001$).

### 1. Association of IGF-I and –II concentrations at birth with body composition at birth

Increased IGF-I concentrations were associated with higher $FM/L^3$ and $FFM/L^2$ Z-scores at birth ($R^2$=0.05, $P < 0.001$ and $R^2$=0.04, P=0.016 respectively) although these accounted for a small amount of the variance in body composition at birth (Figure 2). IGF-II concentrations at birth were associated with $FFM/L^2$ Z-score at birth ($R^2$=0.01, P=0.02) but not with $FM/L^3$ Z-score at birth ($R^2$=0.002, P=0.4).

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### 2. Association of IGF-I and –II concentrations at birth with body composition trajectory over the first 2 months

FM/$L^3$ and FFM/$L^2$ Z-scores at 2 months were not associated with IGF-I ($R^2$=0.002, P=0.3 and $R^2$ =0.001, P=0.5 respectively) or IGF-II ($R^2$=0.004, P=0.1 and $R^2$ =0.002, P=0.3 respectively) Z-scores at birth. This indicates that body composition at two months was not predicted by IGF-I or –II concentrations at birth.

Although IGF-I and –II concentrations at birth were not associated with body composition at two months, there was a weak but significant association with change in body composition over the first two months. Higher IGF-I Z-scores at birth were associated with reductions in FM/$L^3$ Z-scores ($R^2$=0.05, P < 0.001) and FFM/$L^2$ Z-scores ($R^2$=0.03, P < 0.001) between birth and two months of age. However, IGF-II concentrations were not associated with changes in FM/$L^3$ Z-scores ($R^2$=0.006, P=0.05) or FFM/$L^2$ Z-scores ($R^2$=0.003, P=0.02) over the same timeframe (Figure 3).

To control for the potential effect of FM/$L^3$ or FFM/$L^2$ at birth on growth and body composition over the subsequent two months further analyses were performed. When controlled for FM/$L^3$ Z-score at birth, higher IGF-I Z-scores at birth were associated with a reduction in FM/$L^3$ Z-score between birth and two months of age ($R^2$=0.01, p=0.003). This association was not seen with IGFII Z-scores at birth ($R^2$=0.01, p=0.07). When controlling for FFM/$L^2$ Z-score at birth, there was no association between the change in FFM/$L^2$ Z-score over the first two months with IGF-I ($R^2$=0.01, P=0.08) or –II ($R^2$=0, P=0.88) Z-scores at birth.

## Discussion

This study demonstrated the relationships between IGF-I and -II concentrations at birth and neonatal body composition in a large well-defined cohort of healthy, term infants in Ireland. Lower IGF-I concentrations at birth were associated with reduced adiposity and lean mass, while lower IGF-II concentrations at birth were associated with reduced lean mass. Despite these significant associations, IGF concentrations accounted for a small amount of the variance in these body composition parameters. IGF-I and –II concentrations at birth were not associated with body composition parameters at two months. However lower IGF-I concentrations at birth were associated with a greater increase in both adiposity and lean body mass in both sexes between birth and two months.

The relationship between IGF-I concentration at birth and adiposity is not surprising. There are strong associations between IGF-I concentrations and birth weight(14, 28) and nutritional status(11). IGF-II is an important prenatal growth factor. Chorionic villi expression of *IGF2* mRNA is associated with birth weight(29) and paternally inherited *IGF2* mutations are associated with growth restriction(30). Animal models also support this important role of IGF-II in regulating prenatal growth(31). It is possible that IGF-II is more critical to growth prior to the third trimester(32), and this may explain the small association between body composition and IGF-II concentrations at birth.

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Although IGF-I and –II concentrations at birth are not directly associated with body composition parameters at two months, there is a weak association with trajectory of accumulation of adiposity. Significant changes occur in body composition during the first three months from birth, with a two-fold increase in FM corrected for length. Lean mass remains relatively stable during this time(16). The inverse relationship between IGF-I at birth and the change in adiposity may simply reflect the early “catch up” accumulation of body fat in infants with relative intrauterine growth restriction at birth. The same inverse association was seen between change in lean mass and IGF-I concentration at birth, indicating that this “catch-up” is not limited to adiposity but also occurs in lean mass. While significant, it should be noted that IGF-I concentrations accounted for only 5% of the variance in changes in $FM/L^3$ and over the first two months, and this reduced to 1% when corrected for $FM/L^3$ at birth. This suggests that IGF-I concentrations at birth only predict a small fraction of observed subsequent body composition changes.

The consequences of this relationship may extend to the interplay between intrauterine nutritional status, the GH/IGF axis and fetal programming of postnatal growth. Pregnancies complicated by limited access to nutrition are associated with increased IGF-I concentrations in adulthood, and it is hypothesized that chronic IGF suppression *in utero* results in an irreversible “overshoot” of this axis in later life(33). Children who have rapid early weight gain have increased BMI and insulin resistance as early as eight years of age(34), and SGA children with rapid early weight gain have persistent increases in adiposity when compared with similar weight, control children who were not born SGA(35). Although the mechanisms for these persistent metabolic complications are unknown, it is possible that low IGF-I concentration at birth is a biomarker for future risk.

Strengths of this study include the large, well-defined, relatively homogenous study population. All children were term, healthy and Caucasian, making confounding factors unlikely to contribute to these findings. However, this homogeneity may limit the generalizability of our findings to other populations. The large number of children with available body composition measurement is also unique for investigating these relationships. IGF-I and –II measurement by standard radioimmunoassays can be subject to assay interference by IGF binding proteins. However, LCMS was used in this study and this technique is not subject to interference from binding proteins(26, 27). A weakness of the study is the lack of available IGF-I and –II measurements at two months, to further investigate the hypothesis that IGF-I and -II may be useful biomarkers of metabolic risk during catch-up growth. Also, this study only included term infants and it is not known if the association is similar for preterm infants. Data were not available for the entire birth cohort, and it is not known if this introduced bias to our analysis.

We conclude that IGF-I concentrations at birth are associated with adiposity and lean mass at birth and the trajectory of FM accumulation over the first two months, although this only accounts for a small proportion of the variability seen in these parameters. Although IGF-I and -II play a significant role in prenatal growth, we have found that, in a cohort of healthy term infants, IGF-I and –II concentrations at birth are not major determinants of body composition changes over the first 2 months.

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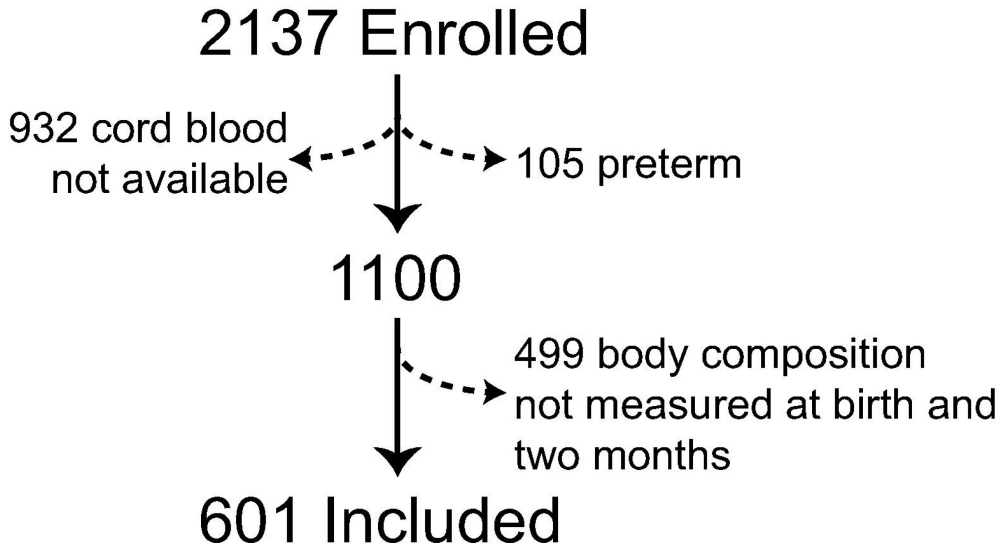


**Figure 1:**
The number of subjects recruited who 1) were born at term, 2) had umbilical cord blood samples available and 3) had body composition measurement performed at birth and two months.

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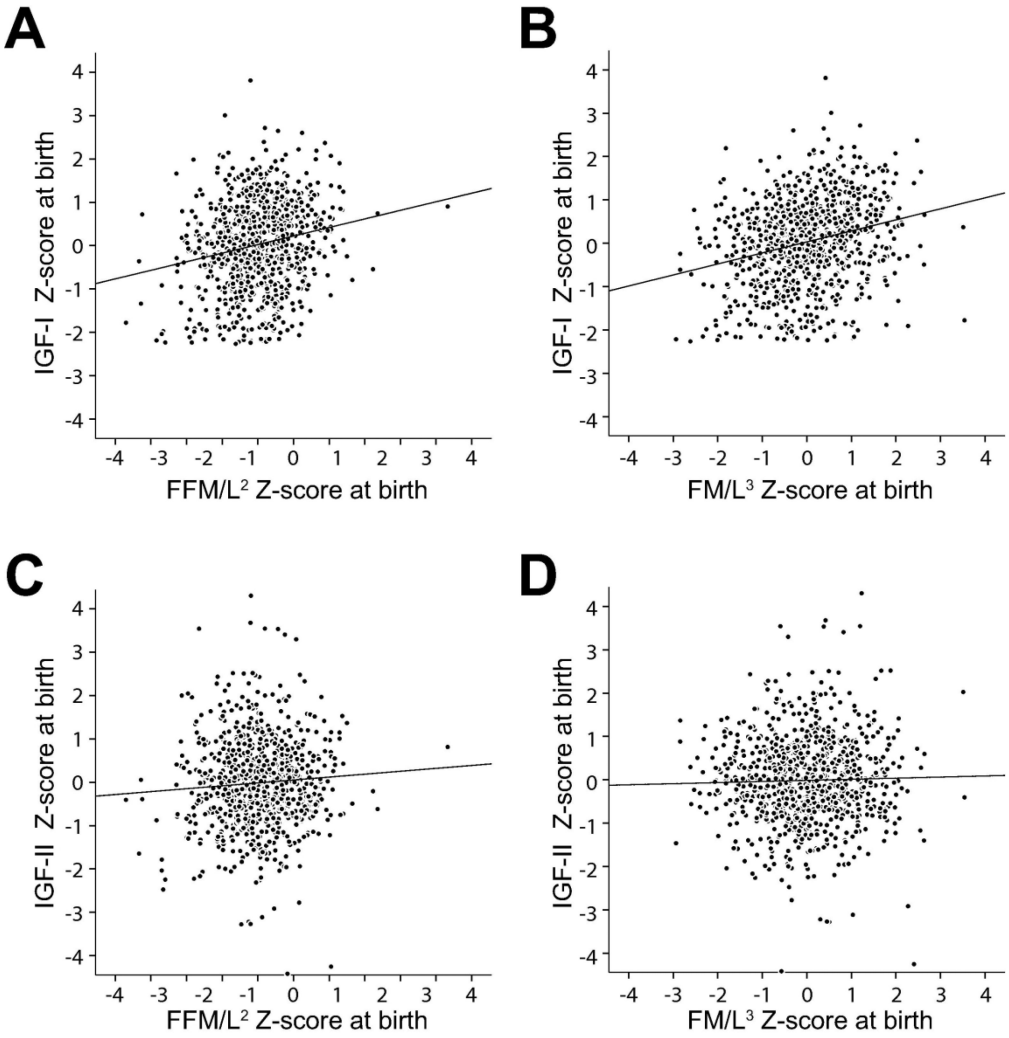


**Figure 2:**

Scatter-plot and linear regression comparing IGF-I (A and B) and –II (C and D) concentrations with age- and sex-corrected $FM/L^3$ and $FFM/L^2$ Z-scores at birth. The associations between IGF-I concentration and $FM/L^3$ and $FFM/L^2$ Z-scores and the association between IGF-II concentration and $FFM/L^2$ Z-score at birth were significant.

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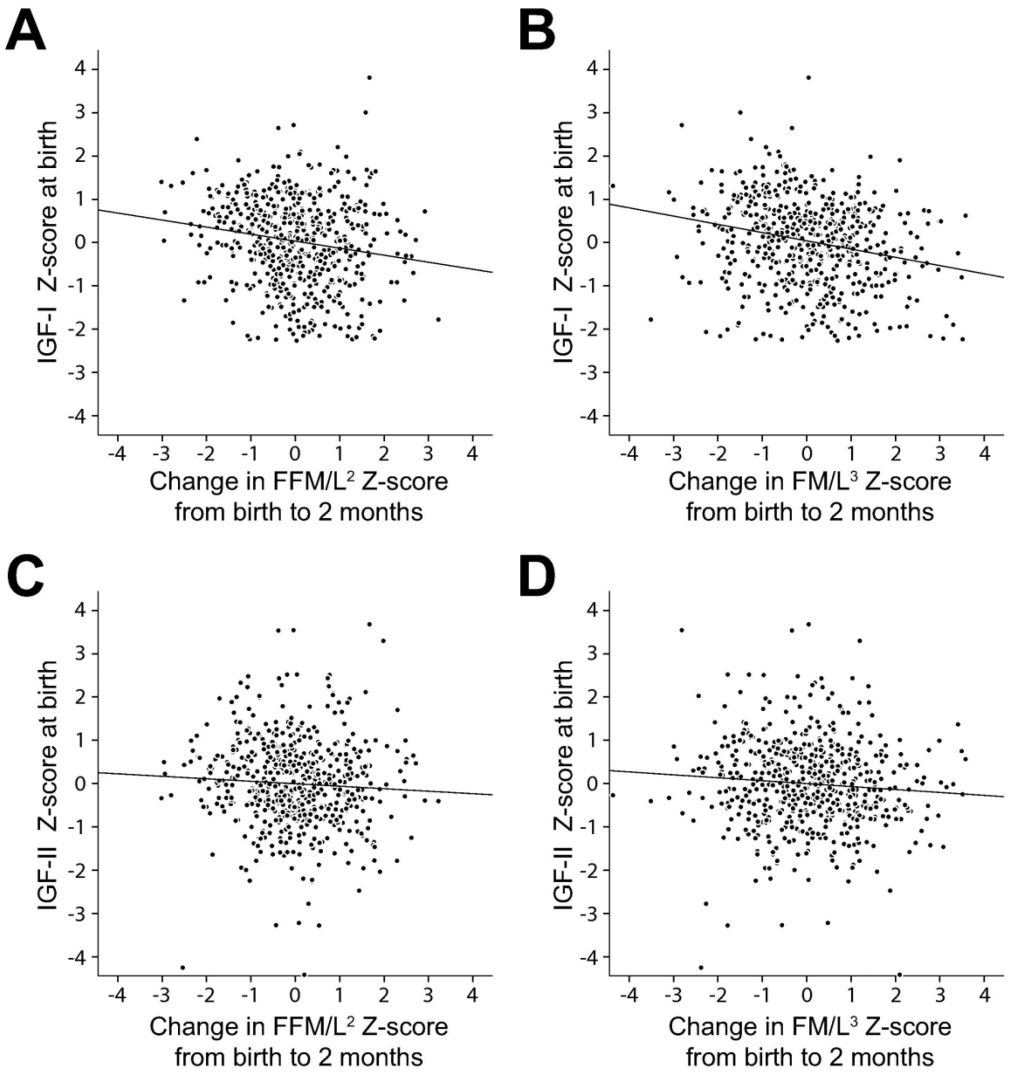


**Figure 3:**

Scatter-plot and linear regression comparing IGF-I and –II concentrations at birth with age- and sex-corrected $FM/L^3$ and $FFM/L^2$ Z-scores at 2 months.

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**Table 1:**

Characteristics of population. Unless otherwise stated, mean (SD) are presented.

| | Males | Females | All |
|---|---|---|---|
| Number, n | 317 | 284 | 601 |
| Gestational age, weeks | 40.2 (1.1) | 40.2 (1) | 40.2 (1.1) |
| Birth weight, kg | 3.57 (0.45) | 3.49 (0.45) | 3.53 (0.45) |
| Weight at 2 months, kg | 5.66 (0.68) | 5.3 (0.57) | 5.49 (0.66) |
| Length at birth, m | 0.51 (0.02) | 0.50 (0.02) | 0.50 (0.02) |
| Length at 2 months, m | 0.59 (0.02) | 0.58 (0.02) | 0.59 (0.02) |
| IGF-I, ng/ml | 49.6 (23.9) | 56.6 (24.3) | 52.9 (24.3) |
| IGF-I, Z-score | 0.07 (1) | −0.004 (1) | 0.03 (1) |
| IGF-II, ng/ml | 421.4 (98.1) | 428.5 (103.7) | 424.8 (100.8) |
| IGF-II, Z-score | 0 (1) | −0.01 (1) | − 0.004 (1) |
| $FM/L^3$ at birth, $kg/m^3$ | 2.7 (1.2) | 3.2 (1.2) | 2.9 (1.2) |
| $FM/L^3$ at birth, Z-score | 0 (1) | −0.02 (1) | −0.01 (1) |
| $FM/L^3$ at 2m, $kg/m^3$ | 5.9 (1.5) | 6.2 (1.4) | 6 (1.5) |
| $FM/L^3$ at 2m, Z-score | 0 (1) | 0.09 (1) | 0.04 (1) |
| $FFM/L^2$ at birth, $kg/m^2$ | 11.8 (0.9) | 11.5 (0.9) | 11.7 (0.9) |
| $FFM/L^2$ at birth, Z-score | 0 (1) | 0.06 (1) | 0.02 (1) |
| $FFM/L^2$ at 2m, $kg/m^2$ | 12.8 (0.8) | 12.1 (0.8) | 12.5 (0.9) |
| $FFM/L^2$ at 2m, Z-score | 0.04 (1) | 0.04 (1) | 0.04 (1) |
| Change in $FM/L^3$ Z-score from birth to 2-months | 0 (1.2) | 0.1 (1.2) | 0.05 (1.2) |
| Change in $FFM/L^2$ Z-score from birth to 2-months | 0.04 (1) | −0.02 (1.1) | 0.01 (1) |

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**Table 2:**

The relationship between sex- and gestational age-corrected $FM/L^3$ and $FFM/L^2$ Z-scores at birth and two months, with sex- and gestational age-corrected IGF-I and IGF-II Z-scores at birth. For this analysis, IGF-I and –II Z-scores are the dependent variables and $FM/L^3$ or $FFM/L^2$ measures are independent variables.

| | IGF-I Z-score | | | IGF-II Z-score | | |
|---|---|---|---|---|---|---|
| | $R^2$ | Regression coefficient (SEM) | P | $R^2$ | Regression coefficient (SEM) | P |
| $FM/L^3$ Z-score at birth | 0.05 | 0.23 (0.04) | <0.001 | 0.001 | 0.04 (0.04) | 0.4 |
| $FM/L^3$ Z-score at 2 months | 0.002 | −0.05 (0.04) | 0.3 | 0.004 | −0.06 (0.04) | 0.1 |
| $FFM/L^2$ Z-score at birth | 0.04 | 0.2 (0.04) | <0.001 | 0.01 | 0.1 (0.04) | 0.02 |
| $FFM/L^2$ Z-score at 2 months | 0.001 | 0.03 (0.04) | 0.5 | 0.002 | 0.04 (0.04) | 0.3 |
| Change in $FM/L^3$ Z-score from birth to 2 months * | 0.01 | −0.12 (0.04) | 0.003 | 0.01 | −0.07 (0.04) | 0.07 |
| Change in $FFM/L^2$ Z-score from birth to 2 months ** | 0.01 | −0.07 (0.04) | 0.08 | 0 | −0.01 (0.04) | 0.88 |

* Partial correlation controlling for $FM/L^3$ Z-Score at birth

** Partial correlation controlling for $FFM/L^2$ Z-Score at birth