Changes in genetic and environmental effects on growth during infancy 1–3


ABSTRACT

Background: Accelerated infant growth is a possible explanation for the relation between birth weight and adult diseases.

Objective: The aim of this study was to estimate the heritability of infant growth and to examine whether the genetic contribution changes with increasing or decreasing birth weight and gestational age.

Design: Growth (change in weight z score) was analyzed in 522 infants from the East Flanders Prospective Twin Survey for age windows of 0–1, 1–6, 6–12, and 12–24 mo. Structural equation modeling was performed to estimate the relative importance of additive genetic, shared environmental, and unique environmental sources of variance.

Results: We showed no genetic contribution to growth in the 0–1-mo growth period. However, at later ages, the heritability of growth was high at 94% (95% CI: 90%, 96%) from 1 to 6 mo, 85% (95% CI: 80%, 89%) from 6 to 12 mo, and 86% (95% CI: 77%, 91%) in the 12–24-mo growth period. Nevertheless, in the last age window, a model without genetic factors was also statistically plausible.

Conclusions: This study shows that genetic factors are not important in early infant growth (0–1 mo), whereas heritability is high after 1 mo. Because many (nutritional) interventions are aimed at influencing early postnatal growth, to target long-term health, these interventions may be most successful if implemented in the first month of postnatal growth.

INTRODUCTION

Birth weight is inversely associated with risk of many diseases in adulthood, including hypertension (1), type 2 diabetes (2), and ischemic heart disease (3). One of the proposed mechanisms that could explain these associations is accelerated postnatal growth (4), which is more common in small-for-gestational-age infants (5). Although many negative long-term effects of accelerated postnatal growth have been shown, there is debate about the relative importance of growth in infancy compared with growth in childhood (6, 7). Accelerated growth in these 2 age windows has been linked to unfavorable cardiovascular risk profiles in childhood and adulthood and to cardiovascular events in adulthood (8–14). Multiple studies implied that there may be a very early neonatal critical growth window (15–17). Because of the above results, it is important to understand the regulation of infant growth, especially to inform future counseling approaches and, possibly, (nutritional) interventions in infant growth.

Cross-sectional heritability studies of postnatal anthropometric measures in infancy and childhood showed increasing heritability estimates with age (18, 19). However, cross-sectional studies that compare heritability estimates of anthropometric measures for different age groups do not provide an optimal description of the actual growth process that has long-term negative effects. Two studies (20, 21), both of which were preceded by earlier works (22, 23), analyzed infant growth velocity by using genetically sensitive designs and longitudinal data. In the Fels Longitudinal Study, heritability estimates of 0.66 (0–6 mo), 0.55 (0–12 mo), and 0.82 (0–24 mo) were shown for weight change by using pedigree data (20). A twin study that was based on a population from Amsterdam, Netherlands, showed heritability estimates of
weight velocity at the age of 1 y of 0.57 (girls) and 0.63 (boys) (21). However, to our knowledge, there is no reported study of the potentially important early neonatal age windows.

The advantage of the twin approach is the possibility of estimating the relative importance of genetic and environmental factors in infant growth in terms of heritability. A crude analysis of heritability, however, may not give a true picture of the underlying etiology if heritability depends on certain environmental factors. For example, we expect light babies to be more vulnerable to the influence of the environment (such as nutrition) than heavy babies. The lowest perinatal mortality in twins occurs in infants born between 37 and 38 wk of gestation (24, 25), and therefore, this gestational age can be considered as an optimal start for postnatal growth. Thus, we expected infants born around this gestational age to be minimally dependent on the environment. An understanding of the effects of birth weight and gestational age on the regulation of infant growth by genetic and environmental effects may assist in tailoring research, counseling, and possibly interventions in infant growth to specific subgroups in which attaining a health benefit is more likely.

In the current study we estimated the heritability of infant growth and examined whether the genetic contribution varied with birth weight and gestational age by using a twin sample from the East Flanders Prospective Twin Survey (EFPTS).

SUBJECTS AND METHODS

The study sample consisted of live-born twin pairs of white ethnic background selected from the EFPTS, Belgium. The EFPTS started in 1964 and records all multiple births in the Belgian Province of East Flanders and is a population-based survey. Details of the selection process of the subset used in this study were described previously (26). The sample consisted of 424 young adult twin pairs (804 individuals; mean age: 25 y) who were born between 1964 and 1982 and participated in a prenatal programming study in which weights in the first 2 y of life were collected. Informed consent was obtained, and ethical approval was given by the Ethics Committee of the Faculty of Medicine of the Katholieke Universiteit Leuven.

At birth, weight, gestational age, sex, zygosity, and chorionicity were collected prospectively. Zygosity was determined by using sequential analysis on the basis of sex, fetal membranes, blood groups, placental alkaline phosphatase, and DNA-marker analysis.

When the twins were at adult age (February 1997 to April 2000), as part of the prenatal programming study, the parents of the twins filled out questionnaires to provide information on gestational diabetes and paternal height. Gestational diabetes was defined as the occurrence of sugar in the urine.

Growth in infancy

Of all 804 individuals, 522 subjects had data on growth available, which was collected by means of growth charts from infant- and child-welfare centers (Kind en Gezin (Child and Family)). These centers offer medical examinations throughout infancy, including weight recording. Parents and infants voluntarily visited after regular invitations.

Growth was defined as the change in body weight z score and was calculated for 4 age windows as follows: from birth to 1 mo (0–1 mo), from 1 to 6 mo (1–6), from 6 to 12 mo (6–12), and from 12 to 24 mo (12–24). The availability of growth data differed for the 4 age windows, which resulted in different subsamples in each age window. Birth weight z scores were constructed by using sex-specific Flemish singleton reference data per week of gestation from the Study Centre for Perinatal Epidemiology in Brussels (personal written communication, G Martens, June 2009) (27). Postnatal z scores were based on postnatal ages corrected for gestational age. Postnatal z scores were calculated by using the 2004 sex-specific singleton Flemish growth curves (28). Singleton reference data were used because these represent normal growth in the Belgian population. Individuals were included in the analysis if they had 2 measurements available in the age windows 0.04–0.12, 0.4–0.6, 0.75–1.25, and 1.5–2.5 y, which corresponded to 2–6 wk and 4.8–7.2, 9–15, and 18–30 mo. Linear interpolation was used to construct values at exactly 4 wk and 6, 12, and 24 mo of age. All participants who were analyzed had complete data for all other variables used in the analyses.

Statistical analysis

In a previous study in the EFPTS prenatal programming study sample, the following determinants of postnatal growth were identified: birth weight and gestational age (0–1 mo and 6–12 mo); sex, birth weight, and gestational age (0–6 mo); and chorionicity, sex, gestational diabetes, and paternal height (12–24 mo) (29). Therefore, the structural equation modeling analyses in this study were adjusted for these determinants by using determinants from 0 to 6 mo for our analyses from 1 to 6 mo. Structural equation modeling was performed to quantify the genetic and environmental contributions to the observed phenotypic variance (of growth). To estimate genetic and environmental components of the phenotypic variance, the variance was decomposed in additive genetic (A, additive effects of genes on multiple loci), common environmental (C, environmental effects shared by twins reared in the same family), and unique environmental (E, environmental effects unique to the individual) effects. This is the classic ACE model. Thus, heritability ($h^2$) was defined as the proportion of observed variance, which is explained by genetic factors ($h^2 = \text{variance due to } A/\text{total variance}$). These models assume that monozygotic and dizygotic twins share a common environment to the same extent and assume no interaction between genes or between genes and environment. A nonadditive or dominant genetic contribution model was not considered in the current study because the within-pair Pearson correlation coefficient in monozygotic pairs was not more than twice that of dizygotic pairs in a previous study in this study sample (29).

In the descriptive statistics, group differences between monozygotic and dizygotic twins were analyzed by using a $t$ test for independent samples for continuous variables and a chi-square test for categorical variables. These analyses were performed with SAS version 9.2 software with the SAS Enterprise Guide 4 software package (SAS Institute).

With regard to structural equation modeling, the appropriate assumptions were checked first and shown to be satisfactory; there were no significant differences in means or SDs of growth between individuals categorized as twin 1 (first born member of the pair) and individuals categorized as twin 2 or between monozygotic and dizygotic twins of same sex. There were also no significant differences in means or SDs of growth between
opposite-sex twins and same-sex twins. Growth correlations in opposite-sex twins and dizygotic same-sex twins were similar. Alternative univariate nested models (ACE, CE, AE, and E models) were fitted to the raw data. A maximum-likelihood approach with accompanying Akaike’s information criterion (AIC) was used (30). The model with the lowest AIC reflected the most parsimonious model. The differences between the models were statistically tested by hierarchical chi-square tests on the basis of the $-2 \log$ likelihood. When the results of these hierarchical tests are interpreted, the best model is the model that uses the least parameters, while not being inferior to the model it is nested in. For example, if the AE model is not significantly worse than the ACE model, the AE model is preferred. Absolute values of the fit statistics (AIC and $-2 \log$ likelihood) do not provide information on the goodness of the fit. To test whether genetic and environmental factors influenced the trait to the same degree in men and women, the unstandardized path coefficients were tested for equality in men and women (quantitative differences). To assess whether it was likely that different sets of genes were involved in the determination of growth in men and women, these qualitative differences were also analyzed in a sex-limitation model. Finally, the possibility of heritability changing with increasing or decreasing birth weight or gestational age was studied by using a gene-environment interaction script (31). In these analyses the interaction between a moderator variable ($M$, birth weight or gestational age in this study) and one of the variance components ($A, C,$ or $E$) was studied. These interactions are referred to as $T$, $U$, and $V$. $T$ represents the $M \times A$ interaction, $U$ represents the $M \times C$ interaction, and $V$ represents the $M \times E$ interaction. $M$ was included in the means model to adjust for gene-environment correlation. We performed the interaction analyses on the full (ACE) model to address the possibility that $A$, $C$, or $E$ is not included in the means model to adjust for gene-environment correlation. Structural equation modeling was performed with Mx software (32). Scripts for the Mx analyses were modified from the GenomEUtwin Mx script library (33). The analyses were performed in all 4 age windows separately. All $P$ values were 2-sided and were considered statistically significant if they were $<0.05$.

RESULTS

Baseline characteristics of the study sample are given in Table 1. For weight change in the 0–1-mo growth period, there was no evidence of a genetic component, whereas common environmental sources accounted for 77% (95% CI: 68%, 84%) of the variance in the best-fitting (CE) model (Table 2). For the 1–6- and 6–12-mo growth periods, a model with only additive genetic [94% (95% CI: 90%, 96%) from 1 to 6 mo and 85% (95% CI: 80%, 89%) from 6 to 12 mo] and unique environmental [6% (95% CI: 4%, 10%) from 1 to 6 mo and 15% (95% CI: 11%, 20%) from 6 to 12 mo] sources of variance (AE) was the best fitting model. For the 12–24-mo growth period, the CE and AE models were equally suitable. Heritability (in the AE model) was similar to the previous age window at 86% (95% CI: 77%, 91%), whereas in the CE model, 83% (95% CI: 74%, 89%) of the variance was explained by common environmental factors. All best-fitting models are shown in Table 2.

Sex-limitation models did not reveal any qualitative sex differences. For the 12–24-mo growth period, a significant quantitative sex difference was detected, with the genetic contribution being more important in women. More specifically, estimates of variance components for the full ACE model in men were 3% (95% CI: 0%, 62%) for additive genetic factors, 86% (95% CI: 27%, 95%) for common environmental factors, and 10% (95% CI: 5%, 23%) for unique environmental factors. Corresponding numbers for women were 45% (95% CI: 0%, 91%), 40% (95% CI: 0%, 84%), and 15% (95% CI: 8%, 27%), respectively ($P$-difference $=0.005$).

### TABLE 1

<table>
<thead>
<tr>
<th>Twins' characteristics</th>
<th>0–1 mo ($n = 220$)</th>
<th>1–6 mo ($n = 176$)</th>
<th>6–12 mo ($n = 280$)</th>
<th>12–24 mo ($n = 130$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monozygotic</td>
<td>Dizygotic</td>
<td>Monozygotic</td>
<td>Dizygotic</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2561 ± 465</td>
<td>2861 ± 415</td>
<td>2635 ± 412</td>
<td>2861 ± 460</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>37.1 ± 1.8</td>
<td>37.7 ± 1.5</td>
<td>37.4 ± 1.7</td>
<td>37.6 ± 1.6</td>
</tr>
<tr>
<td>Growth ($\Delta z$ score)</td>
<td>$-0.42 ± 0.8$</td>
<td>$-0.31 ± 0.6$</td>
<td>$1.25 ± 1.0$</td>
<td>$1.19 ± 1.0$</td>
</tr>
<tr>
<td>Monochorionic [%]</td>
<td>32 (55.2)</td>
<td>0 (0)</td>
<td>22 (47.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>F (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2669 ± 453</td>
<td>2613 ± 466</td>
<td>2682 ± 482</td>
<td>2624 ± 481</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>37.7 ± 2.1</td>
<td>37.8 ± 1.6</td>
<td>37.8 ± 2.3</td>
<td>37.9 ± 1.7</td>
</tr>
<tr>
<td>Growth ($\Delta z$ score)</td>
<td>$-0.41 ± 0.7$</td>
<td>$-0.31 ± 0.6$</td>
<td>$1.54 ± 0.8$</td>
<td>$1.51 ± 1.1$</td>
</tr>
<tr>
<td>Monochorionic [%]</td>
<td>36 (47.4)</td>
<td>0 (0)</td>
<td>28 (45.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>All (n)</td>
<td>134 (86)</td>
<td>108 (68)</td>
<td>108 (68)</td>
<td>190 (90)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2622 ± 460</td>
<td>2737 ± 456</td>
<td>2662 ± 452</td>
<td>2736 ± 483</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>37.4 ± 2.0</td>
<td>37.8 ± 1.5</td>
<td>37.6 ± 2.0</td>
<td>37.8 ± 1.6</td>
</tr>
<tr>
<td>Growth ($\Delta z$ score)</td>
<td>$-0.41 ± 0.7$</td>
<td>$-0.31 ± 0.6$</td>
<td>$1.42 ± 0.9$</td>
<td>$1.36 ± 1.0$</td>
</tr>
<tr>
<td>Monochorionic [%]</td>
<td>68 (50.8)</td>
<td>0 (0)</td>
<td>50 (46.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>M [%]</td>
<td>58 (43.3)</td>
<td>43 (50.0)</td>
<td>46 (42.6)</td>
<td>32 (47.1)</td>
</tr>
<tr>
<td>Member of opposite-sex pair (n, %)</td>
<td>0 (0)</td>
<td>30 (34.9)</td>
<td>0 (0)</td>
<td>24 (35.3)</td>
</tr>
</tbody>
</table>

1 Mean ± SD (all such values).
2 Comparison of monozygotic and dizygotic twins $<0.05$ (t test).
HERITABILITY OF INFANT GROWTH

TABLE 2
Variance components estimates of growth in 4 age windows

<table>
<thead>
<tr>
<th>Age Window</th>
<th>Variance components</th>
<th>Model fit</th>
<th>Compared with ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$a^2$</td>
<td>$c^2$</td>
<td>$e^2$</td>
</tr>
<tr>
<td>0–1 mo (n = 110 pairs)</td>
<td>0.16 (0.00, 0.52)</td>
<td>0.64 (0.28, 0.82)</td>
<td>0.20 (0.14, 0.30)</td>
</tr>
<tr>
<td>1–6 mo (n = 88 pairs)</td>
<td>0.85 (0.49, 0.96)</td>
<td>0.09 (0.00, 0.45)</td>
<td>0.06 (0.04, 0.10)</td>
</tr>
<tr>
<td>6–12 mo (n = 140 pairs)</td>
<td>0.52 (0.23, 0.88)</td>
<td>0.34 (0.00, 0.62)</td>
<td>0.14 (0.10, 0.20)</td>
</tr>
<tr>
<td>12–24 mo (n = 65 pairs)</td>
<td>0.26 (0.00, 0.88)</td>
<td>0.61 (0.00, 0.87)</td>
<td>0.14 (0.08, 0.22)</td>
</tr>
</tbody>
</table>

1 Results were adjusted for birth weight and gestational age (0–1 and 6–12 mo); sex, birth weight, and gestational age (1–6 mo); and chorionicity, sex, gestational diabetes, and paternal height (12–24 mo). $a^2$, $c^2$, $e^2$, proportion of variance explained by additive genetic ($a^2$), common environmental ($c^2$), and unique environmental factors ($e^2$); ACE, model that contained additive genetic, common environmental, and unique environmental factors; AE, model that contained additive genetic and unique environmental factors; AIC, Akaike’s information criterion; CE, model that contained common environmental and unique environmental factors; E, model that contained unique environmental factors; $-2LL$, $-2$ log likelihood.

2 Results are given as the proportion of total growth variance and were calculated by structural equation modeling; 95% CIs in parentheses.

3 Best-fitting models.

Complete results from the gene-environment interaction analyses are available (see Table 1 under “Supplemental data” in the online issue). Accompanying variances of the best-fitting models from supplemental Table 1 (see Table 1 under “Supplemental data” in the online issue), which showed a significant interaction, are presented in Figure 1. On the $y$ axes in Figure 1, the observed growth variation (variance) is depicted, whereas on the $x$ axis, the different values for the moderator are shown. For a specific birth weight or gestational age (moderator; $x$ value), summed values of the $A$, $C$, and $E$ variances represent the total observed growth variance. For example, from 0 to 1 mo, for a birth weight of 1.75 kg, the total variance of growth was ~5.5 (summed values of $A$, $C$, and $E$). Of this 5.5, a little more than 3 was explained by $A$, and hence, the genetic variance was relatively large in postnatal growth at a birth weight of 1.75 kg. Similarly, from 0 to 1 mo, the genetic contribution to growth (growth variance because of $A$) was low around the average value of birth weight in our sample (~2.6 kg) but was also larger at the high end of the spectrum. Because growth variance that was due to $C$ and growth variance that was due to $E$ showed no interaction with birth weight in the age window from 0 to 1 mo, these lines were horizontal. For the 1–6 mo growth period, no interactions were identified with birth weight (see Table 1 under “Supplemental data” in the online issue). For the 12–24 mo growth period, no interactions were identified with birth weight (see Table 1 under “Supplemental data” in the online issue). With respect to gestational age, the unique and common environmental contributions declined with advancing gestational age for the 0–1 mo growth period (the common environment showed a steep decrease), whereas the additive genetic contribution showed a minimum of ~36 wk of gestation. For the 1–6 mo growth period, common environmental factors explained the minimal variance at a gestational age slightly larger than 37 wk, but this contribution increased sharply for shorter and longer gestation. No interactions were identified with gestational age from 6 to 12 and 12 to 24 mo (see Table 1 under “Supplemental data” in the online issue).

DISCUSSION

This study showed that genetic factors were not important in early infant growth (0–1 mo), whereas heritability was high after 1 mo. This difference was reflected in the structural equation modeling analyses, which showed no additive genetic contribution in the best-fitting model in the growth period from 0 to 1 mo and high heritability thereafter. For the 12–24 mo growth period, both the AE and CE models fitted the data. Although the AE model showed a heritability of 86%, the CE model resulted in a heritability of 0%. This discrepancy was most likely due to low statistical power in the age window from 12 to 24 mo. Nevertheless, the intrapair correlation for growth in this sample was 0.90 in monozygotic twins and 0.48 in dizygotic twins in this age window (29), which suggests a substantial genetic component.
and favors the AE model, in which case the heritability would be 86%.

These results suggested that, after 1 mo, growth was mainly determined by genetic factors, which is in accordance with earlier studies (18–21). Our heritability estimates could not be compared directly to any study because, to our knowledge, our study is the first study to examine a change in weight in consecutive age windows including in an early age window (0–1 mo). However, the Fels Longitudinal Study reported a heritability of 66% (20) for growth from 0 to 6 mo. Given our results, we speculated that this estimate was a weighted average of 2 age windows of low (0–1 mo) and high (1–6 mo) heritability.

We used postnatal ages adjusted for gestational age to calculate \( z \) scores at the age of 1 mo. In infants with gestational age <36 wk, this may have resulted in negative adjusted ages. Because a \( z \) score for a negative age was calculated by using birth weight reference values (because references for negative ages do not exist), this may have been a suboptimal method, and this may have contributed to the unexpected growth pattern from 0 to 1 mo, during which period the average \( z \) score decreased (Table 1). To avoid this problem, growth can be expressed in grams per kilogram per day, as suggested by Patel et al (34). Therefore, we performed an extra analysis with this method of expressing growth and also showed that AE was the best model from 0 to 1 mo, with even lower estimates of A in the ACE model [0% (95% CI: 0%, 30%)].

To our knowledge, our study is the first study to examine the importance of genetic factors under different circumstances (varying gestational age and birth weight) in early postnatal growth. We speculated that heavier babies were born after more optimal intrauterine conditions, and hence, we expected their postnatal growth to show less dependence on the environment (such as nutrition). We showed that the genetic contribution from 0 to 1 mo was, on average, low but may have been of importance at the birth weight extremes. This may have also indicated that a larger birth weight does not render the infant’s growth independent of the environment. As regards gestational age, the optimal gestational age of 37–38 wk of gestation was expected to result in less dependence on the environment. This pattern was clearly shown from 1 to 6 mo but not from 0 to 1 mo when the relative importance of genetic factors only increased from 36 wk of gestation onwards. The interaction analyses may have been underpowered because of our moderate sample size, and therefore, these results should be interpreted and extrapolated with caution.

There is an increased interest in early postnatal growth because it has been linked to adverse cardiometabolic outcomes later in life. Variations in growth may lead to lasting epigenetic differences (35, 36) and/or to a reprogramming of hormonal axes that regulate food intake and metabolism, for example via leptin (37). Therefore, the modification of postnatal growth is a potential target for the prevention of adult cardiometabolic disease. Nutritional changes have their effect through the environment and may, therefore, be more successful in age windows in which the environment is of importance; according to our study, this age window would be 0–1 mo. Two recent studies underlined the
importance of early postnatal growth compared with later growth with respect to obesity and cardiometabolic risk profiles (38, 39). Given the results of the varying genetic contribution with increasing or decreasing birth weight and gestational age, interventions aimed at influencing growth from 0 to 1 mo to target long-term health might be most successful in infants of average (twin) birth weight and in infants of low gestational age.

One of the strengths of this study was the assessment of growth over time in 4 consecutive age windows and the inclusion of correction methods for factors that are known to influence growth in this sample. However, the extrapolation of growth studies from twins to singletons should be done with caution. Twins do not show the same growth patterns as singletons, and it is debated whether they show the same relations between birth weight and cardiometabolic risk factors (40, 41). Furthermore, twins do not have the same average birth weight and gestational age as singletons, and their prenatal environment is different from that of singletons. Even within a pair of monochorionic twins, the prenatal environment may differ. Although we presented a sample size of several hundreds, it is likely that some of our analyses were underpowered; especially in the age window from 12 to 24 mo, in which the least data were available. This was also illustrated by our wide CIs, the sometimes small statistical differences between different models, and because we did not detect (a biologically plausible) C in all windows (Table 2). Our limited power should be kept in mind when our results are interpreted. Finally, our data represented growth in weight, and therefore, this study could not clarify whether our models would also be appropriate for growth in length or growth in BMI.

In conclusion, this study provides evidence that genetic factors are not important for postnatal growth before 1 mo of age but are very important after 1 mo of age. Because many (nutritional) interventions are aimed at influencing early postnatal growth, to target long-term health, these interventions may be most successful if implemented shortly after birth.

The authors’ responsibilities were as follows—CD, RV, and RJL: designed and conducted research; CD, RV, RJL, and MPZ: provided essential materials; RNT, MG, and TF: analyzed data; RNT, MG, ALM, and MPZ: wrote the manuscript; WJG, LJZ, AJH, and CDS: provided significant advice; RNT: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. The funding sources had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. None of the authors had a conflict of interest.

REFERENCES


4. RNT, MG, and TF: analyzed data; RNT, MG, ALM, and MPZ: wrote the manuscript; WJG, LJZ, AJH, and CDS: provided significant advice; RNT: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. The funding sources had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. None of the authors had a conflict of interest.

5. The authors’ responsibilities were as follows—CD, RV, and RJL: designed and conducted research; CD, RV, RJL, and MPZ: provided essential materials; RNT, MG, and TF: analyzed data; RNT, MG, ALM, and MPZ: wrote the manuscript; WJG, LJZ, AJH, and CDS: provided significant advice; RNT: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. The funding sources had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. None of the authors had a conflict of interest.
36. Tosh DN, Fu Q, Callaway CW, McKnight RA, McMillen IC, Ross MG, Lane RH, Desai M. Epigenetics of programmed obesity: alteration in IUGR rat hepatic IGF1 mRNA expression and histone structure in rapid vs. delayed postnatal catch-up growth. Am J Physiol Gastrointest Liver Physiol 2010;299:G1023–9.