Is restricted fetal growth associated with later adiposity? Observational analysis of a randomized trial

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ABSTRACT
Background: Several recent “developmental origins” studies have reported increased long-term risks of adiposity, especially truncal adiposity, among children born small for gestational age (SGA).

Objective: We assessed the effects of SGA birth and weight gain in early infancy on adiposity at age 11.5 y.

Design: From a cluster-randomized breastfeeding promotion trial in 17,046 Belarusian children, we measured height, weight, waist and hip circumferences, triceps and subscapular skinfold thicknesses, and bioimpedance measures of percentage body fat at age 11.5 y. Children born SGA (birth weight <10th percentile) and those born large for gestational age (LGA; >90th percentile for gestational age) were compared with those born appropriate for gestational age (AGA).

Weight gain from birth to 6 mo was categorized as high (≥0.67-SD increase in weight-for-age), low (<0.67-SD decrease in weight-for-age), or normal. Multilevel statistical models accounted for clustered measurement and controlled for maternal weight and maternal education, geographic region, urban compared with rural residence, and the child’s exact age at follow-up.

Results: Children born SGA had a significantly lower BMI, percentage body fat, and fat mass index than did those born AGA, with a dose-response effect across 2 subcategories of SGA (P < 0.001 for all comparisons). No difference was observed in waist-to-hip ratio, although the subscapular-to-triceps skinfold ratio was slightly but significantly (P < 0.001) higher in children born SGA. Differences among the study groups continued to increase since the previous follow-up at 6.5 y. SGA infants with catch-up growth in the first 3–6 mo had growth and adiposity measures intermediate between those born SGA without catch-up and those born AGA. Opposite effects of similar magnitude were observed in children born LGA.

Conclusion: The 11.5-y-old Belarusian children born SGA were shorter, were thinner, and had less body fat than their non-SGA peers, irrespective of postnatal weight gain. The Promotion of Breastfeeding Intervention Trial was registered at www.isrctn.org as ISRCTN-37687716. Am J Clin Nutr 2014;100:176–81.

INTRODUCTION
Restricted fetal growth, often studied by using its proxy—small-for-gestational-age (SGA) at birth, has been robustly associated with high blood pressure, type 2 diabetes, and coronary artery disease in later life (1). Several recent epidemiologic studies have reported that SGA birth is also associated with greater adiposity (percentage body fat and fat mass), obesity, and particularly truncal obesity, in later childhood and adulthood (2–7), which suggests that increased adiposity may be on the causal pathway between restricted fetal growth and long-term adult chronic disease outcomes. These associations have also been reported to be amplified, or even caused, by rapid catch-up growth in early infancy (8–10).

This evidence regarding obesity contrasts with the results of studies published in the 1970s to 1990s that involved the long-term follow-up of infants born SGA. Those studies consistently showed long-term reductions in height, weight, BMI, and skinfold thicknesses, all of which suggest a reduced risk rather than an increased risk of obesity (11–15). The reasons for these discrepancies between older studies and more recent ones may reflect, at least in part, the evolution of the obesity epidemic since the 1980s. Moreover, the reported associations from recent studies are likely to be confounded by the well-documented socioeconomic patterning of obesity in high-income countries (16–18). Thus, it is pertinent to examine more recent evidence in settings where the socioeconomic pattern, and thus the potential for confounding, is not as strong as in many Western countries today. Such an examination would provide useful evidence bearing on the biological link between restricted fetal growth, later adiposity, and adult chronic disease.
In this study, we took advantage of a large cohort of children who participated in a randomized trial of a breastfeeding promotion intervention in the Republic of Belarus to study these relations. This nontraditional study setting of a former Soviet-bloc country, with socioeconomic patterns in overweight and obesity that differ from those in the West (19), provided a unique opportunity to study relations among fetal growth, early infant growth, and later growth and adiposity. In addition to the setting, the study also benefits from a large sample size, high rate of follow-up, and research-standard anthropometric and body fat measurements at ages 6.5 and 11.5 y and the measurement of and control for socioeconomic status and maternal and paternal height and BMI. No previous analyses have been published from this study bearing on associations between fetal and/or infant growth and later childhood adiposity.

SUBJECTS AND METHODS

This study is an observational analysis of children who participated in the Promotion of Breastfeeding Intervention Trial (PROBIT)—a cluster-randomized trial of a breastfeeding promotion intervention in the Republic of Belarus. The original design of PROBIT (20), and the anthropometric methods and results at 6.5 (21) and 11.5 (22) y, were previously published. Briefly, the clusters were maternity hospitals and one affiliated polyclinic (outpatient clinic where children receive routine health care) per hospital. These clusters were randomized to a control intervention (continuation of the breastfeeding practices and policies in effect at the time of randomization) or an experimental intervention based on the Baby-Friendly Hospital Initiative, which was developed by the WHO and UNICEF to promote and support breastfeeding, particularly among mothers who choose to initiate breastfeeding.

The trial recruited 17,046 infants from 31 maternity hospitals and polyclinics; all of the infants were born in 1996–1997 and enrolled during their postpartum stay. All infants were healthy, singleton, term (≥37 wk gestational age), weighed ≥2500 g at birth, were initially breastfed, had a 5-min Apgar score of ≥5, and had no maternal or infant contraindications to breastfeeding or conditions that would be expected to interfere with breastfeeding. The trial conformed to the Consolidated Standards of Reporting Trials guidelines for the design, analysis, and reporting of cluster-randomized trials. As previously reported, the 2 randomized groups were similar in baseline sociodemographic and clinical variables, including maternal age, vocation, number of other children at home, the proportion of mothers who had breastfed a previous child for ≥3 mo, cesarean delivery, maternal smoking during pregnancy, birth weight, gestational age, and 5-min Apgar score.

Follow-up interviews and examinations at 6.5 and 11.5 y of age were performed by 1 or 2 pediatricians (depending on volume) at each of the 31 polyclinics. The training and quality-assurance procedures at both the 6.5- and 11.5-y follow-up visits were described in detail previously (21, 22). In addition to the anthropometric measurements repeated at 6.5 y, the 11.5-y follow-up also included measurement of percentage body fat, fat mass, and fat-free (lean) mass, measured by foot-to-foot bioelectrical impedance with the use of the Tanita TBF 300 GS body fat analyzer. This measure of body fat has been found to correlate extremely highly with body fat mass measured by dual-energy X-ray absorptiometry in school-age children (23).

SGA birth was defined as a birth weight <10th percentile for gestational age and sex, derived from a Canadian population-based reference (24). (No such reference is available for Belarus.) Similarly, large-for-gestational-age (LGA) birth was defined as birth weight >90th percentile of the same reference.

To exclude implausible measurements, we eliminated all those that were ≤–4 SD (n = 0–2, depending on outcome measurement) or >4 SD (n = 3–117) from the mean. Bivariate relations were then examined between birth weight for gestational age [by using the 3 categories of SGA, appropriate for gestational age (AGA), and LGA] and growth and adiposity outcomes. Because infants weighing <2500 g at birth were excluded from PROBIT, the most severely growth-restricted infants were not included in the trial. To examine a possible dose-response relation, however, we subdivided the SGA group into approximately equal groups according to severity based on the birth weight-for-gestational-age z score. Those <5th percentile for gestational age and sex were considered moderate SGA, whereas those from the 5th to <10th percentiles were denoted as mild SGA. Statistical differences in the anthropometric outcomes among the 4 groups (2 subgroups of SGA, AGA, and LGA) were assessed by using ANOVA.

In addition, we wished to assess whether any effects of SGA or LGA birth that may have already been manifest at age 6.5 y remained unchanged, were amplified, or diminished between 6.5 and 11.5 y. We therefore examined differences between the 3 main study groups with respect to the change in growth and adiposity measures between 6.5 and 11.5 y. To minimize the effect of children with implausible growth trajectories resulting from measurement or recording error, we excluded a priori children whose measurements were ≤–4 SD (n = 0–24) or >4 SD (n = 10–232) from the mean at either age and those in whom the change from the 6.5- to 11.5-y measurements was negative for height (n = 11) or weight (n = 25); in whom the decrease exceeded 10% of the 6.5-y value for waist (n = 42) or hip (n = 8) circumference, or in whom the decrease exceeded 20% of the 6.5-y value for triceps (n = 1168) or subscapular (n = 698) skinfold thickness.

Multivariable statistical analyses were based on the MIXED procedure in SAS (version 9.2; SAS Institute Inc), which accounts for the clustered measurement of the outcomes and adjusts for the potentially confounding covariates, including maternal and paternal height and BMI, geographic region, urban compared with rural residence, maternal education, and the child’s exact age at follow-up. Although we previously reported no effects of the breastfeeding promotion intervention on growth or adiposity outcomes at 6.5 or 11.5 y of age (21, 22), we wished to examine whether the intervention may have helped prevent overweight or obesity in children born SGA or LGA. We therefore examined whether breastfeeding [either as randomized, ie, in intention-to-treat analyses, or as fed (exclusive breastfeeding for 3 mo, defined as yes or no) interacted with SGA or LGA birth with respect to the growth and adiposity outcomes at 11.5 y of age.

Because of the ongoing debate about the relative importance of fetal growth compared with growth in early infancy, we also created specific combinations of fetal and early infancy growth, with the latter based on changes in weight-for-age z score (WAZ) between birth and 3 or 6 mo. For these analyses, we compared the growth and adiposity outcomes in 5 study groups: 1) AGA infants with no major change in WAZ between birth and 3 or 6
RESULTS

The background characteristics of SGA, AGA, and LGA newborns who participated in the 11.5-y follow-up are compared in Table 1. Small but statistically significant differences were seen in place of residence and maternal education. As expected, differences between the 3 groups in maternal and paternal height and BMI were substantial and statistically significant.

The growth and adiposity outcomes at 11.5 y in children born moderately SGA, mildly SGA, AGA, or LGA are shown in Table 2. A clear dose-response relation was seen for all of these outcomes; the SGA groups had the lowest growth and adiposity values, the AGA group had intermediate values, and the LGA group had the highest values. No significant difference was observed in waist-to-hip ratio, although the subscapular:triceps skinfold ratio was slightly higher in the 2 SGA groups. The moderate SGA subgroup had larger deficits than the mild SGA subgroup.

The changes in growth and adiposity measures between 6.5 and 11.5 y in children born SGA, AGA, or LGA are provided in Table 3. Significant differences in most of these changes were observed between the 3 study groups, which strongly suggests that the significant differences seen at 11.5 y had increased since 6.5 y. Compared with those born AGA, children born SGA had smaller gains in adiposity, whereas those born LGA had greater gains, from 6.5 to 11.5 y. The subscapular:triceps skinfold ratio continued to increase in the SGA group from ages 6.5 to 11 y, whereas it continued to decrease in the LGA group. We found no evidence of interaction between breastfeeding and the fetal growth categories, based either on the randomized intervention (intent to treat) or the dichotomous characterization of exclusive breastfeeding for 3 mo (data not shown).

The results of the combined fetal growth and early infancy weight gain changes in WAZ in the 3 study groups are summarized in Table 4. The results shown in Table 4 are based on the analyses between 0 and 6 mo; the relations were similar, but slightly less consistent, when the increase in WAZ was analyzed between 0 and 3 mo. No significant interactions were observed between these combined fetal/infant growth patterns and child sex. SGA infants with normal WAZ trajectories (ie, no catch-up) were shorter and less obese at 11.5 y than were those with catch-up weight gain between 0 and 6 mo. The latter group, however, remained shorter and thinner than infants born AGA with normal weight gain in early infancy (the reference group). LGA infants had the largest anthropometric measures; those with “catch-down” weight gain showed values intermediate between the reference (AGA) group and LGA infants without “catch-down.”

How the 9 possible combinations of birth weight for gestational-age (SGA, AGA, or LGA) and WAZ gain from birth to 6 mo (low, normal, or high) contributed to the normal, overweight, and obese groups—even among those with high postnatal weight gains. LGA infants made a larger contribution to the overweight and obese groups than did their AGA peers, who

DISCUSSION

The 11.5-y-old Belarusian children who were born SGA remained shorter, remained thinner, and had less body fat (in both proportional and absolute terms) than did their AGA peers, who...
TABLE 2
Growth and adiposity outcomes at 11.5 y in children born moderately or mildly SGA, AGA, or LGA

| Outcomes                  | Moderately SGA (n = 611–624) | Mildly SGA (n = 607–621) | AGA (n = 11,425–11,554) | LGA (n = 1056–1071) | P value
|---------------------------|-------------------------------|--------------------------|-------------------------|---------------------|---------
| Height (cm)               | 146.7 ± 8.0                  | 148.1 ± 7.9              | 149.8 ± 7.7             | 152.5 ± 7.5         | <0.001  |
| Weight (kg)               | 37.9 ± 8.7                   | 38.6 ± 8.4               | 41.1 ± 9.2              | 43.9 ± 9.5          | <0.001  |
| BMI (kg/m²)               | 17.4 ± 2.8                   | 17.5 ± 2.7               | 18.1 ± 2.9              | 18.7 ± 3.0          | <0.001  |
| Percentage body fat (%)   | 15.5 ± 7.7                   | 16.0 ± 7.5               | 17.1 ± 7.8              | 18.1 ± 8.0          | <0.001  |
| Fat mass index (kg/m²)    | 2.9 ± 1.9                    | 2.9 ± 1.8                | 3.3 ± 2.0               | 3.6 ± 2.1           | <0.001  |
| Waist circumference (cm)  | 62.8 ± 7.4                   | 63.2 ± 6.8               | 64.6 ± 7.8              | 66.2 ± 8.1          | <0.001  |
| Hip circumference (cm)    | 75.4 ± 7.4                   | 76.0 ± 7.4               | 77.9 ± 7.7              | 79.8 ± 7.9          | <0.001  |
| Waist-to-hip ratio        | 0.83 ± 0.06                  | 0.83 ± 0.06              | 0.83 ± 0.06             | 0.83 ± 0.06         | 0.153   |
| Triceps SF (mm)           | 12.6 ± 5.8                   | 12.9 ± 6.1               | 13.9 ± 6.3              | 14.7 ± 6.6          | <0.001  |
| Subscapular SF (mm)       | 8.4 ± 4.9                    | 8.2 ± 4.3                | 8.9 ± 5.0               | 9.2 ± 5.1           | <0.001  |
| Subscapular:triceps ratio | 0.69 ± 0.30                  | 0.67 ± 0.22              | 0.66 ± 0.22             | 0.65 ± 0.21         | 0.002   |

1 All values are means ± SDs. AGA, appropriate for gestational age; LGA, large for gestational age; SF, skinfold; SGA, small for gestational age.
2 Sample size range for study group after exclusions (see Subjects and Methods).
3 For overall differences in means, based on 1-factor ANOVA.

in turn were shorter, were thinner, and had less adipose tissue than did those born LGA. Most of these differences increased further between the ages of 6.5 and 11.5 y. Moreover, the combination of SGA and rapid growth during infancy did not increase the risk of adiposity, overall or truncal, relative to children born AGA with a normal weight trajectory in the first 6 mo of life. At 11.5 y, the children with the highest BMI, fat mass index, and percentage body fat were those who were born LGA, not those born SGA (with or without catch-up weight gain). Thus, our results are in line with those of studies published in the 1970s to 1990s, which reported that children born SGA remain smaller and thinner than their AGA (and in particular their LGA) counterparts (11–14).

On the basis of our results, this relation persists even when accompanied by rapid catch-up weight gain in the first several months of life.

The strengths of our study included its large sample size, longitudinal (birth cohort) design, high rates of follow-up, research-standard anthropometric measurements at ages 6.5 and 11.5 y, measures of body fat, and extensive assessment of and control for potentially confounding covariates. We are not aware of previous studies that have separately examined the quantitative contributions of fetal and infant growth to later childhood adiposity, nor the extent to which associations with fetal growth amplify (increase) or remain stable during the childhood years. This amplification might be the result of earlier programming of the adiposity trajectory, but it is more likely to reflect the persistent influences of environmental (diet and physical activity) and/or genetic factors over the life course.

The major limitation of our study was the exclusion of newborns weighing <2500 g (ie, those with the greatest degree of fetal growth restriction). PROBIT children are likely too young to exhibit any cardiometabolic complications related to either their fetal or postnatal growth. Nonetheless, if PROBIT children born SGA experience an increased risk of future cardiometabolic disease, our results make it clear that such increased risk is unlikely to be mediated by increased adiposity.

The contrast between our findings and those of some recent studies of the “developmental origins” of adiposity may be at least partly explained by several of those studies’ statistical adjustment for height, BMI, weight, and/or Tanner stage at the time of adiposity measurement (3–7), thus inducing (rather than reducing) bias by “adjusting” for a variable on the causal path between exposure and outcome (27). Other explanations for the disparate results may reflect the different geographic and social disparities may reflect the different geographic and social conditions of birth. For example, the developmental origins hypothesis may be more applicable to populations with higher levels of socioeconomic deprivation, where the impact of early growth deviation may be more pronounced.

The results of this study suggest that the relationship between fetal growth and childhood adiposity persists even when adjusted for catch-up growth. This finding highlights the importance of understanding the complex interplay between early life conditions and later health outcomes. Future research should focus on identifying the specific mechanisms through which fetal growth and adiposity are related, as well as the potential for interventions during pregnancy and early childhood to mitigate the impact of these associations on long-term health.
compared with some Western countries, or selective publication or citation of published studies. Moreover, the potential for confounding by unmeasured (or inadequately measured) socioeconomic factors seems less likely to bias the results of our study than those of studies from Western settings. The fact that a recent systematic review (28) and other recent studies from birth cohorts in the United Kingdom (29, 30), Taiwan (31), Sweden (32), Denmark (33), and Hungary (34) have reported results similar to ours, however, reinforces the generalizability of our findings. We do urge caution, however, in extrapolating our results to low-income settings in South Asia, Africa, or Latin America, where maternal and early infant malnutrition might affect the magnitude, and even the direction, of the associations we have observed.

We are currently examining PROBIT participants at age 16 y, and it is hoped that future follow-up into adulthood will shed additional light on the relations between fetal growth, growth in early childhood, and later obesity and cardiometabolic outcomes.

The authors’ responsibilities were as follows—MSK: wrote the first draft of the manuscript; MSK, RMM, and EO: contributed to the study design, interpretation of the results, and manuscript revisions; and NB and KV: were responsible for organizing the fieldwork and supervising the data collection; MD: carried out the statistical analysis; and MSK: had primary responsibility for the final content. All authors read and approved the final manuscript. None of the authors had any conflicts of interest concerning the topic or contents of this article.

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