Greater Neonatal Fat-Free Mass and Similar Fat Mass Following a Randomized Trial to Control Excess Gestational Weight Gain

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Objective: The objective of this study was to determine the effectiveness of controlling maternal gestational weight gain (GWG) in the second and third trimesters on neonate body composition.

Methods: Two hundred ten healthy women with overweight (25 ≤ BMI < 30) or obesity (BMI ≥ 30) were randomly assigned to a lifestyle intervention (LI) program focused on controlling GWG through nutrition and activity behaviors or to usual obstetrical care (UC). Infant fat and fat-free mass (FFM) at birth were measured by using air displacement plethysmography (PEA POD) and by using quantitative magnetic resonance (QMR).

Results: At baseline, there were no between-group differences in maternal characteristics (mean [SD]): age: 33.8 (4.3) years, weight: 81.9 (13.7) kg, BMI: 30.4 (4.5), and gestational age at randomization: 14.9 (0.8) weeks. GWG was less in the LI group by 1.79 kg (P = 0.003) or 0.0501 kg/wk (P = 0.002). Compared with UC infants, LI infants had greater weight (131 ± 59 g P = 0.03), FFM (98 ± 45 g; P = 0.03) measured by PEA POD, and lean mass (105 ± 38 g; P = 0.006) measured by QMR. Fat mass and percent fat were not significantly different.

Conclusions: Intervening in women with overweight and obesity through behaviors promoting healthy diet and physical activity to control GWG resulted in neonates with similar fat and greater FFM.

Introduction

Intrauterine exposures may influence an individual’s long-term risk of developing obesity and related cardiometabolic diseases (1,2). The theory is that perturbations early in plastic, developmental stages can lead to worse health trajectories. This implies that strategies for ensuring the health of individuals may require early interventions, including prenatally. Mounting evidence in humans suggests that exposure to adverse prenatal environments increases the risk of developing obesity, metabolic dysfunction, and related health problems later in life (3-6). Fetal exposure to excessive

See Commentary, pg. 459.

Funding agencies: This work was supported by NIH grants U01-DK094463, U01-DK094463-Supplement (supplement to promote diversity, TTR), P30-DK026687, and T32-DK007559. The content is the responsibility of the authors and does not necessarily represent the official views of the NIH. The Lifestyle Interventions for Expectant Moms consortium is supported by the NIH through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (U01 DK094418, U01 DK094463, U01DK094416, and U01DK094466 [FICU]), the National Heart, Lung, and Blood Institute (U01HL114344 and U01HL114377), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U01 HD072834), the National Center for Complementary and Integrative Health, the NIH Office of Research Women’s Health, the Office of Behavioral and Social Science Research, the Indian Health Service, and the Intramural Research Program of the NIDDK.

Disclosure: The authors declared no conflict of interest.

Author contributions: DG, XP, JCT, and BR designed the study; DG and XP are coprincipal investigators of the Lifestyle Intervention for Two trial and were responsible for supervision of data collection; BR was responsible for obstetrical care; TTR, CP, and SG were responsible for newborn outcome measures; MH was the primary project coordinator; JC was the primary lifestyle interventionist; SL was responsible for data management; JCT was responsible for data analysis; and DG and XP had primary responsibility for final content. All authors read and approved the final manuscript.

Clinical trial registration: ClinicalTrials.gov identifier NCT01616147.

Additional Supporting Information may be found in the online version of this article.

Received: 9 August 2017; Accepted: 30 October 2017; Published online 21 February 2018. doi:10.1002/oby.22079
maternal gestational weight gain (GWG) influences long-term adiposity-related disease (4,7-12).

Many women with overweight and obesity gain more weight than is recommended during pregnancy (13), and this is a risk factor for obesity in the offspring (14,15). Several randomized clinical trials (RCTs) in the United States have evaluated the effect of behavioral and lifestyle interventions (LIs) on GWG and glycemic status, with mixed results (16-19). A large Australian RCT reported no differences in maternal GWG, the proportion of neonates who were large for gestational age (LGA), or birth outcomes, except for a reduction in neonatal macrosomia, in an LI group compared with standard care (20). A Norwegian study showed less GWG in the intervention group compared with controls (mean difference: 1.3 kg; P = 0.009) but no effect on infant birth weight or the proportion of LGA newborns (21). A meta-analysis of antenatal dietary or LI RCTs reported no statistical differences in mean GWG or LGA (22). It concluded that the uncertainty of both the effect of an antepartum intervention and its optimal intensity, along with inconsistency in maternal and infant outcome reporting, has yielded inadequate findings to assume that limiting GWG improves maternal and infant health. Therefore, whether LI during pregnancy to reduce excessive GWG lowers the risk of childhood obesity remains unknown.

A major limitation of most studies on newborn adiposity is that they have used length- and weight-based indices rather than actual measures (23) of body composition to infer normal, overweight, or obesity status. Such indices assume that a higher weight reflects additional fat mass and fail to consider the nonfat component.

This RCT in women with overweight or obesity aimed to investigate whether an LI to control GWG would affect fat and fat-free mass (FFM) in infants at birth.

Methods

Study design

The LIFT (Lifestyle Intervention for Two) trial is part of the Lifestyle Interventions for Expectant Moms (LIFE-Moms) consortium (24), which consists of a collaboration of seven independent RCTs, a research coordinating unit, and the NIH as a sponsor, all with different strategies for reducing GWG in women with overweight or obesity. LIFT was a parallel-group RCT in pregnant women. We compared the body composition of newborns of mothers with overweight or obesity randomly assigned at a 1:1 ratio at the beginning of the second trimester to an LI designed to control GWG or to usual obstetrical care (UC). The primary hypothesis was that percentage of body fat would be less for neonates from LI than from UC mothers. The study was approved by the institutional review boards of St. Luke’s-Roosevelt Hospital and Columbia University and was registered with ClinicalTrials.gov (NCT01616147).

Participants

Women were recruited from hospital-affiliated private and clinic practices from February 2013 to October 2015. Eligibility criteria included age ≥18 years; BMI ≥25 at baseline measurement; singleton pregnancy; gestational age between 9 weeks and 15 weeks and 6 days that was confirmed by dating ultrasound; and intention to deliver at St. Luke’s-Roosevelt Hospital. Exclusion criteria are listed in the Supporting Information.

Study treatments

LI continued from randomization to delivery. Its goal was to maintain GWG during the second and third trimesters within Institute of Medicine (IOM)-recommended limits of 0.32 kg/wk for women with overweight and 0.27 kg/wk for women with obesity (13). LI focused on diet modification and increased physical activity along with behavioral and social support strategies delivered in individual sessions by study counselors. The intervention program was derived from the Diabetes Prevention Program (25) and the Action for Health in Diabetes (Look AHEAD) (26) curricula, with the focus modified from weight loss to GWG control as recommended by 2009 IOM guidelines (13). The experienced nutritionist providing the counseling was trained on the nutritional needs of pregnant women to provide counseling appropriate for controlling GWG while assuring adequate nutrition. For details, see the Supporting Information.

UC involved a single 20- to 30-minute “introduction” immediately following randomization. This covered basic nutrition for pregnancy as given in www.choosemyplate.gov and in American Academy of Nutrition and Dietetics guidelines. Thereafter, participants were invited to attend UC group meetings once every 8 weeks through delivery. The topics covered related to health during pregnancy and were similar to those covered in the LI group sessions, but with less focus on calorie counting.

Baseline and follow-up assessments

for mothers

There were three core visits for all mothers during pregnancy: the baseline visit that immediately preceded randomization occurred between 12 weeks and 15 weeks and 6 days and corresponded approximately to the beginning of the second trimester of pregnancy. The second core visit occurred at 24 weeks to 27 weeks and 6 days when participants had a 2-hour 75-g oral glucose tolerance test using the International Association of Diabetes and Pregnancy Study Groups criteria (27). This prenatal visit corresponded to the end of the second trimester. The final prenatal core visit occurred between 35 weeks and 36 weeks and 6 days at approximately the end of the third trimester. At all visits, body weight was measured to the nearest 0.1 kg (BWB-800; Tanita Corp., Arlington Heights, Illinois), and height was measured at baseline to the nearest 0.5 cm by using a stadiometer (Seca 222; Seca Deutschland, Hamburg, Germany). Baseline weight was measured at or before randomization and no later than 15 weeks and 6 days’ gestational age. Weight measured in the second trimester was adjusted (−0.45 kg for women at 14 weeks or −0.91 kg for women at 15 weeks). No adjustment was made when weight was measured in the first trimester (on or before 13 weeks and 6 days). Baseline BMI was calculated by using baseline weight and measured height. All women were asked to complete an automated self-administered 24-hour dietary assessment from which the 2010 Healthy Eating Index (HEI) was calculated, an index of diet quality validated in pregnant women (28).

Infant study assessments

Anthropometric and body composition measurements were performed prior to hospital discharge, between 1 and 4 days after birth for term infants or at 36 weeks’ postmenstrual age for preterm infants. Body weight was measured on a calibrated scale (PEA POD; COSMED USA Inc., Concord, California), infant length was
measured on a length board (Ellard Instrumentation Ltd., Monroe, Washington), and head circumference was measured by using a tape measure with a tensiometer (Glulick II, model 67020; Performance Health Technologies, Inc., Trenton, New Jersey). Skinfold thicknesses of the triceps, subscapula, iliac crest, and midthigh were measured in duplicate by using calipers (Harpenden, model HSB-BI; BATY International, Burgess Hill, UK), and the average was reported. When the results of the two duplicate skinfold measurements differed by more than 0.5 mm, a third measurement was acquired. The PEA POD system measures body composition through the measurement of body volume by air displacement plethysmography (PEA POD), as previously described (29). Infants were undressed and wore a standard tight-fitting hat (Allentown Scientific Associates, Inc., Allentown, Pennsylvania) to minimize air trapped in the hair. Body volume and mass by PEA POD were used to estimate body density using Fomon’s gender-specific equations (30), from which fat, the primary outcome, and FFM were derived. In our laboratory, repeated PEA POD tests performed twice on the same day on 29 infants gave coefficients of variation of 6.6% for percent fat, 6.5% for fat, and 1.1% for FFM.

Quantitative magnetic resonance (QMR) is a nonimaging technique (EchoMRI-Infants, Houston, Texas) that uses an electromagnetic field to detect the hydrogen atoms of fat, lean tissue, and water (31,32). Once excited by radiofrequency pulses, these protons have different relaxation times relative to the tissue (lipid or fat) or medium (e.g., water) in which they are embedded. The processed signal is obtained from the whole body at once. The total water signal by QMR comes from protons primarily found in proteins (lean tissues) and to a lesser degree in fat molecules. The greater absolute value for total water compared with total lean mass for QMR reflects the contribution from fat to the total water measure. In our laboratory, the coefficients of variation in 14 newborns measured three times by QMR with repositioning between scans were 5.3%, 2.5%, and 1.6% for fat mass, lean mass, and total body water (TBW), respectively. Secondary infant outcomes were QMR measures of fat, lean, and TBW, skinfold thicknesses at four sites, head circumference, length, and body weight.

Safety monitoring
The safety alerts were maternal weight loss, high blood pressure, contraindications to physical activity, suicidality/depression, incidental findings, and fetal growth. Adverse events included intrauterine growth restriction and smallness for gestational age, defined as weight below the 10th percentile. Serious adverse events included death, life-threatening condition, hospitalization, disability/permanent change, congenital anomaly, and medical intervention. Serious adverse events were reported within 24 hours of ascertainment by LIFE personnel to a designated NIH monitor for review by the Data Safety Monitoring Committee of LIFE-Moms.

Statistical analysis
Ninety infants per group has a power of 0.80 to detect a mean difference between groups in infant body fat of 1.8%, with an SD of 4.3% using a t-test. Fifteen additional women were enrolled per group to compensate for dropouts. Group baseline mean and SD were calculated for continuous variables and compared by using t-tests. For categorical variables, the number and percentage in each cell were calculated for each group. We used χ² tests to compare the distributions of the two groups. The group mean and SD of the outcome variables were calculated, and analysis of covariance was used to compare the adjusted means. The covariates were the mother’s age and BMI at baseline and the infant’s gestational age and sex. The adjusted difference, standard error (SE) of the difference, and P value for each outcome variable are provided. Although randomization balances groups with respect to the distributions of the independent variables (covariates), analysis of covariance is required to calculate the appropriate standard error of the difference between groups. Unadjusted differences are also presented. Statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc.) and Stata version 12 (StataCorp LLC). Significance was set at P < 0.05, two-tailed.

Results

Study participants
Figure 1 shows enrollment, randomization, and retention through infant delivery. Of the 9,412 women who were ineligible, 7,453 (79.2%) were ineligible because of BMI ≥ 25.0 kg/m². Randomization occurred between 12 weeks and 13 weeks and 6 days for 10.5% of women and between 14 weeks and 15 weeks and 6 days for 9.5% of women, from February 2013 to October 2015. Baseline group characteristics were similar (Table 1) for all demographic variables. The incidence of gestational diabetes mellitus was 10.3% for the LI group and 6.1% for the UC group (P = 0.28). Mothers who developed gestational diabetes mellitus were under the care of their obstetrician.

Intervention adherence
Adherence was measured by participant attendance at bimonthly visits and weekly food and exercise logs. The attendance of LI women was good, with median attendance at 87.5% of visits through the end of the second trimester (<27 weeks) and at 72% of visits through the end of pregnancy. Adherence to submitting weekly food logs was moderate, with a median rate of 67.5% in the second trimester and 51.1% overall. Adherence to submitting weekly exercise logs had a median rate of 52.5% in the second trimester and 34.2% overall. The exercise class attendance rate was extremely poor at 9.7%.

Maternal outcomes
A total of 210 women were randomly assigned, with 97 of 105 women (92.3%) in the LI group and 99 of 105 women (94.3%) in the UC group having body weight measures at baseline and at the end of pregnancy and having a live birth with infant weight measured.

GWG. The GWG was 1.79 kg less in the LI group compared with the UC group (P < 0.003) (Table 2). Among the women with overweight (25.0 ≥ BMI ≤ 29.9), the between-group difference in GWG did not attain statistical significance (it was lower in the LI group by 1.32 kg, P = 0.06). Among the women with obesity (BMI > 30.0), the LI group gained 0.17 kg/wk compared with 0.25 kg/wk for the UC group (P = 0.01), and the difference in total weight gain was 2.68 kg (P = 0.007) less in the LI group. Thirty-eight percent of the UC group gained more than IOM-recommended ranges, in both the overweight and obesity categories, whereas significantly fewer women in the LI group (20% with overweight and 16% with obesity) did so (Table 2).
Trimester-specific GWG. LI women had less second-trimester GWG compared with those in the UC group, with approximately 1.0 kg less among women with overweight \((P = 0.02)\) and 2.3 kg less among women with obesity \((P < 0.001)\). GWG in the third trimester did not differ \((0.64 \text{ kg}, P = 0.09)\) between groups. The greatest impact of LI on controlling GWG occurred during the second trimester. Notably, in women with obesity, GWG was halved in LI compared with UC women \((2.31 \text{ kg vs. } 4.62 \text{ kg}, P < 0.001; \text{ Table 2})\).

Maternal diet. There were no between-group differences for any component of the HEI at baseline (Supporting Information Table S1). At 35 weeks, compared with the UC group, the LI had a higher HEI score \((P = 0.004)\), reflecting a healthier maternal diet, and a higher Solid Fats, Alcoholic Beverages, and Added Sugars Score (SoFAAS) score \((P = 0.015)\) and indicating a lower consumption of calories from those items. The change in the HEI for the LI group \((5.33, P = 0.0109)\) was greater \((P = 0.0301)\) than the change for the UC group \((-1.03, P = 0.6155)\).

Infant birth characteristics

Births occurred between August 2013 and April 2015. Infant weight, length, and skinfolds were collected on 97 of 103 (94%) live births in the LI group and 99 of 102 (97%) live births in the UC group (Figure 1). Percent fat, fat mass, and FFM measured by PEA POD were collected on 95 (93%) of the LI infants and 96 (94%) of the UC infants. QMR measures of fat mass, lean mass, and TBW were collected on 82 (81%) of the LI infants and 87 (85%) of the UC infants. Poorer compliance with the infant QMR compared with the PEA POD was due to mothers feeling less comfortable with their newborn having a test involving magnetic resonance compared with air displacement, despite no known risks.

The baseline characteristics of the infant groups were similar for all demographic variables (Table 3). Mean gestational age at birth was 39.4 ± 1.8 weeks. There was a trend for LI infants, compared with UC infants, to have a higher birth weight \((3,373 \pm 587 \text{ g vs. } 3,235 \pm 532 \text{ g}, P = 0.09)\) and birth length \((51.3 \pm 2.7 \text{ cm vs. } 50.6 \pm 2.9 \text{ cm}, P = 0.07)\).

Infant outcomes

Infant body composition. Measurements were collected between 2 and 4 days of age in 89.3% of infants, prior to hospital discharge. Infant body composition measures are shown in Table 4. Those in the LI group had a greater measured body weight of 131 g \((P = 0.03)\), a larger ponderal index \((P = 0.02)\), and a larger head circumference \((P = 0.03)\) compared with those in the UC group. Percent fat and absolute fat mass measured by PEA POD did not differ between groups, whereas the LI infants had greater FFM \((2.871 \pm 404 \text{ g vs. } 2.786 \pm 405 \text{ g}, P = 0.03)\) and adjusted difference of 98 g). Similarly, lean mass measured by QMR was greater in the LI
## TABLE 1 Maternal baseline characteristics

| Demographic characteristics | Lifestyle intervention (N = 105) | Usual care (N = 105) |
|-----------------------------|---------------------------------|----------------------|
| Age (y)                     | 33.8 ± 4.0                      | 33.8 ± 4.7           |
| Race                        |                                 |                      |
| White                       | 48 (46%)                        | 50 (48%)             |
| Black                       | 25 (24%)                        | 25 (24%)             |
| Other                       | 26 (25%)                        | 22 (21%)             |
| More than one race          | 5 (5%)                          | 8 (8%)               |
| Unknown                     | 1 (1%)                          | 0 (0%)               |
| Ethnicity                   |                                 |                      |
| Not Hispanic/Latina         | 72 (69%)                        | 80 (76%)             |
| Hispanic                    | 32 (30%)                        | 25 (24%)             |
| Unknown                     | 1 (1%)                          | 0 (0%)               |
| Marital status              |                                 |                      |
| Married                     | 78 (74%)                        | 73 (70%)             |
| Not married/living with significant other | 13 (12%) | 21 (20%) |
| Separated/divorced/widowed  | 3 (3%)                          | 1 (1%)               |
| Not married                 | 10 (10%)                        | 10 (10%)             |
| Unknown                     | 1 (1%)                          | 0 (%)                |
| Education, highest level attained categories | | |
| High school diploma or less | 4 (4%)                          | 3 (3%)               |
| College (1-3 y)/business/technical | 15 (14%) | 12 (11%) |
| College degree (bachelor’s degree) | 46 (44%) | 39 (37%) |
| Postgraduate work           | 39 (37%)                        | 51 (49%)             |
| Unknown                     | 1 (1%)                          | 0 (%)                |
| Annual family income categories |                                 |                      |
| ≤ $24,999                   | 3 (3%)                          | 7 (7%)               |
| $25,000-$74,999             | 31 (30%)                        | 29 (28%)             |
| $75,000-$149,000            | 38 (36%)                        | 35 (33%)             |
| ≥ $150,000                  | 31 (29%)                        | 34 (32%)             |
| Unknown                     | 2 (2%)                          | 0 (0%)               |
| Pregnancy information       |                                 |                      |
| Gestational age categories  |                                 |                      |
| 11-13 weeks completed (11 to < 14) | 10 (10%) | 12 (11%) |
| 14 weeks completed (14 to < 15) | 33 (31%) | 37 (35%) |
| 15 weeks completed (15 to < 16) | 62 (59%) | 55 (52%) |
| 16 weeks completed (16 to < 17) | 0 (0%) | 1 (1%) |
| Gestational age at randomization (wk) | 14.96 ± 0.72 | 14.82 ± 0.78 |
| Height (cm)                 | 164.3 ± 5.4                     | 163.5 ± 7.0          |
| Baseline weight (kg)        | 81.5 ± 12.4                     | 82.2 ± 15.0          |
| Baseline BMI (kg/m²)        | 30.1 ± 4.1                      | 30.7 ± 5.0           |
| Baseline BMI categories     |                                 |                      |
| Overweight (25.0-29.9)      | 65 (62%)                        | 60 (57%)             |
| Obesity (> 30.0)            | 40 (38%)                        | 45 (43%)             |
| Parity                      |                                 |                      |
| 0                           | 39 (37%)                        | 38 (36%)             |
| 1                           | 30 (29%)                        | 31 (30%)             |
| > 2                         | 36 (34%)                        | 36 (34%)             |

Values are n (%) for categorical variables and mean ± SD for continuous variables. Differences in baseline characteristics between the treatment groups were not significant.
### TABLE 2 Maternal GWG

|                     | Lifestyle intervention, mean ± SD | Usual care, mean ± SD | Difference, difference ± SE | P    |
|---------------------|-----------------------------------|-----------------------|-----------------------------|------|
|                     | N = 97                            | N = 99                |                             |      |
| GWG (from baseline to 35-36.6 weeks) (kg) |                     |                      |                             |      |
| Overweight          | 7.89 ± 4.07                       | 9.67 ± 4.17          | −1.79 ± 0.59                | 0.003|
| Weight gain (kg)    | 9.01 ± 3.55                       | 10.33 ± 4.00         | −1.32 ± 0.70                | 0.06 |
| Per week (kg/wk)    | 0.25 ± 0.10                       | 0.29 ± 0.11          | −0.04 ± 0.02                | 0.04 |
| Obesity             | 6.07 ± 4.24                       | 8.75 ± 4.27          | −2.68 ± 0.96                | 0.007|
| Per week (kg/wk)    | 0.17 ± 0.12                       | 0.25 ± 0.12          | −0.07 ± 0.03                | 0.01 |
| GWG above the IOM guidelines (per week) |                     |                      |                             |      |
| Overweight          | 19%                               | 38%                  | 0.002                       |      |
| Obesity             | 20%                               | 38%                  | 0.03                        |      |
|                      | N = 95                            | N = 97                |                             |      |
| Second-trimester GWG| 3.54 ± 2.24                       | 4.99 ± 2.47          | −1.45 ± 0.34                | 0.0001|
| Overweight          | 4.29 ± 2.12                       | 5.25 ± 2.28          | −0.96 ± 0.41                | 0.02 |
| Per week (kg/wk)    | 0.41 ± 0.19                       | 0.52 ± 0.22          | −0.10 ± 0.04                | 0.007|
| Obesity             | 2.31 ± 1.89                       | 4.62 ± 2.71          | −2.32 ± 0.54                | 0.0001|
| Per week (kg/wk)    | 0.24 ± 0.19                       | 0.43 ± 0.23          | −0.19 ± 0.05                | 0.0001|
|                      | N = 91                            | N = 91                |                             |      |
| Third-trimester GWG | 3.98 ± 2.52                       | 4.62 ± 2.59          | −0.64 ± 0.38                | 0.09 |
| Overweight          | 4.53 ± 2.35                       | 5.18 ± 2.48          | −0.65 ± 0.46                | 0.16 |
| Per week (kg/wk)    | 0.43 ± 0.22                       | 0.48 ± 0.24          | −0.05 ± 0.04                | 0.25 |
| Obesity             | 3.02 ± 2.54                       | 3.85 ± 2.57          | −0.84 ± 0.51                | 0.17 |
| Per week (kg/wk)    | 0.28 ± 0.22                       | 0.36 ± 0.26          | −0.09 ± 0.06                | 0.13 |

### TABLE 3 Infant characteristics at birth

|                     | Lifestyle intervention (N = 97)  | Usual care (N = 99) | P    |
|---------------------|---------------------------------|---------------------|------|
| Birth mode          |                                 |                     |      |
| Vaginal             | 68 (70%)                        | 68 (69%)            | 0.83 |
| Cesarean            | 29 (30%)                        | 31 (31%)            |      |
| Preterm birth       |                                 |                     |      |
| <31 weeks, 6 days   | 2 (2%)                          | 0 (0%)              | 0.17 |
| 32 weeks, 0 days to 36 weeks, 6 days | 3 (3%)               | 7 (7%)              |      |
| Full-term birth (> 36 weeks, 6 days) | 92 (95%)            | 92 (93%)            |      |
| Infant sex          |                                 |                     |      |
| Female              | 44 (45%)                        | 46 (46%)            | 0.88 |
| Male                | 53 (55%)                        | 53 (54%)            |      |
| Small for gestational age (<10th percentile) | 8 (8%)                  | 13 (14%)            | 0.26 |
| Large for gestational age (>90th percentile) | 10 (10%)                | 6 (6%)              | 0.28 |
| Gestational age (wk) | 39.4 ± 1.9                      | 39.4 ± 1.7          | 0.89 |
| Birth weight (g)    | 3,373 ± 587                     | 3,235 ± 532         | 0.08 |
| Weight-for-age z score | 0.09 ± 1.30                | −0.19 ± 1.23        | 0.13 |
| Birth length (cm)   | 51.3 ± 2.7                      | 50.6 ± 2.9          | 0.07 |
| Length-for-age z score | 0.92 ± 1.41                | 0.54 ± 1.55         | 0.07 |

Values are n (%) for categorical variables and mean ± SD for continuous variables.
The relationship between infant body composition and GWG was analyzed, with GWG included as an additional variable in the regression models. The correlations between GWG and the infant body composition variables were as follows: PEA POD: FFM ($r = 0.03$, $P = 0.67$), fat ($r = 0.04$, $P = 0.57$); QMR: FFM ($r = 0.02$, $P = 0.79$), fat ($r = 0.13$, $P = 0.09$); and TBW ($r = 0.02$, $P = 0.84$). The correlations were also calculated within each group. For the UC group only, there was a statistical trend suggesting a positive relationship between GWG and QMR fat ($r = 0.20$, $P = 0.07$). The partial correlation between GWG and the infant body composition variables was calculated by adjusting for maternal baseline age and BMI, gestational age, infant gender, and group. Only the partial correlation between GWG and QMR fat was significant ($r = 0.20$, $P = 0.01$). A similar analysis with mothers classified by GWG category (excessive or within guidelines) found no association with infant body composition. The only significant partial correlation was between GWG and QMR fat within the UC group ($r = 0.24$, $P = 0.03$).

### TABLE 4 Infant body composition at study assessment

| Lifestyle intervention, mean ± SD | Usual care, mean ± SD | Unadjusted differences, difference ± SE | P<sup>a</sup> | Adjusted differences, difference ± SE<sup>b</sup> | P<sup>c</sup> |
|----------------------------------|-----------------------|----------------------------------------|--------------|----------------------------------|--------------|
| Study weight (g) | N = 97 | N = 99 | 3,229 ± 526 | 3,108 ± 500 | 121 ± 73 | 0.10 | 131 ± 59 | 0.03 |
| Study length (cm) | 49.6 ± 2.5 | 49.4 ± 2.3 | 0.2 ± 0.3 | 0.53 | 0.3 ± 0.3 | 0.33 |
| Ponderal index (kg/m<sup>3</sup>) | 26.2 ± 1.9 | 25.6 ± 2.1 | 0.6 ± 0.3 | 0.02 | 0.7 ± 0.3 | 0.02 |
| Head circumference (cm) | 34.3 ± 1.52 | 33.97 ± 1.49 | 0.36 ± 0.22 | 0.10 | 0.38 ± 0.17 | 0.03 |

### Skinfolds

| Triceps (mm) | N = 97 | N = 99 | 4.83 ± 1.35 | 4.65 ± 1.11 | 0.18 ± 0.18 | 0.31 | 0.20 ± 0.17 | 0.26 |
| Subscapular (mm) | 4.55 ± 1.27 | 4.32 ± 1.17 | 0.23 ± 0.17 | 0.19 | 0.25 ± 0.17 | 0.14 |
| Iliac crest (mm) | 3.97 ± 0.95 | 3.91 ± 0.99 | 0.06 ± 0.14 | 0.64 | 0.08 ± 0.13 | 0.54 |
| Thigh (mm) | 5.93 ± 1.89 | 5.66 ± 1.57 | 0.27 ± 0.25 | 0.28 | 0.29 ± 0.24 | 0.22 |
| Central (mm)<sup>d</sup> | 8.52 ± 2.10 | 8.23 ± 2.01 | 0.29 ± 0.29 | 0.32 | 0.33 ± 0.28 | 0.24 |
| Peripheral (mm)<sup>e</sup> | 10.76 ± 3.09 | 10.32 ± 2.54 | 0.45 ± 0.40 | 0.27 | 0.49 ± 0.39 | 0.21 |
| Sum of skinfolds (mm)<sup>f</sup> | 19.29 ± 5.03 | 18.55 ± 4.41 | 0.74 ± 0.68 | 0.27 | 0.62 ± 0.65 | 0.20 |

### Outcomes

| PEA POD | N = 95 | N = 96 | 2.86 ± 5.34 | 3.32 ± 6.26 | −0.46 ± 0.84 | 0.59 | −0.35 ± 0.70 | 0.62 |
| Percent fat (%) | 10.86 ± 4.34 | 10.10 ± 3.90 | 0.76 ± 0.60 | 0.20 | 0.79 ± 0.55 | 0.16 |
| Fat mass (g) | 360 ± 173 | 324 ± 157 | 36 ± 24 | 0.13 | 38 ± 22 | 0.08 |
| Fat-free mass (g) | 2,871 ± 404 | 2,786 ± 405 | 85 ± 59 | 0.15 | 98 ± 45 | 0.03 |
| QMR | N = 82 | N = 87 | 2.63 ± 4.95 | 3.13 ± 5.17 | −0.49 ± 0.78 | 0.53 | −0.49 ± 0.60 | 0.42 |
| Percent fat (%) | 542 ± 189 | 509 ± 179 | 33 ± 28 | 0.25 | 32 ± 24 | 0.19 |
| Total lean mass (g) | 2,327 ± 325 | 2,211 ± 314 | 116 ± 49 | 0.02 | 105 ± 38 | 0.006 |
| Total body water (g) | 2,452 ± 334 | 2,342 ± 320 | 109 ± 50 | 0.03 | 97 ± 40 | 0.02 |

<sup>a</sup>P value for unadjusted differences.
<sup>b</sup>Covariates used in analyses were mother’s age and BMI at baseline and the infant’s gestational age and sex.
<sup>c</sup>P value for adjusted differences.
<sup>d</sup>Central is sum of subscapular and iliac crest skinfolds.
<sup>e</sup>Peripheral is sum of triceps and thigh skinfolds.
<sup>f</sup>Sum of triceps, subscapular, iliac crest, and thigh skinfolds.

 infants (2,327 ± 325 g vs. 2,211 ± 314 g, $P = 0.006$; adjusted difference of 105 g). TBW measured by QMR was greater in the LI infants (2,452 ± 334 g vs. 2,342 ± 320 g, $P = 0.02$; adjusted difference of 97 g), but total fat mass did not differ between the groups. Skinfold thickness did not differ between groups for any of the four sites. In secondary analyses, the infant body composition variables were reanalyzed by (1) excluding preterm infants, (2) substituting premenstrual age for gestational age, and (3) using infant age at testing as an additional covariate. Infant age (in days) was a significant covariate for QMR total water, PEA POD fat mass, and PEA POD FFM, suggesting that these body composition values increase with increasing age. For all three analyses, the results and the statistical interpretation of the results were identical to those in the primary analyses.
coefficient was not significant for any of the infant body composition variables ($P > 0.30$).

**Safety events**

Through the end of pregnancy, 13.3% of women in the LI group ($n = 14$) and 14.3% ($n = 15$) in the UC group ($P = 0.84$) reported serious adverse events. None was considered related to the study intervention. Maternal hospitalizations accounted for 79.3% of these. Among infants, serious adverse events were reported in 7.6% ($n = 8$) of infants in the LI group and 9.5% ($n = 10$) in the UC group ($P = 0.62$). None was considered related to the study intervention. Smallness for gestational age occurred in four LI and eleven UC infants, and intrauterine growth restriction occurred in zero LI and two UC infants.

**Discussion**

This RCT reports that an LI promoting healthy diet and physical activity to control GWG in women with overweight or obesity resulted in neonates who weighed more and had greater FFM, while not differing in the amount of fat. Our data show that the intervention impacted fetal development, although the exact mechanisms or mediators leading to the observed effects on infant body composition are unknown and were not a target of this investigation. We are unaware of any previous RCT demonstrating the efficacy of an LI on neonatal body composition.

Our methods specifically measured infant body composition. For infants in this study, 10.5% of body mass at birth is fat mass (approximately 340 g of fat) and 89.5% is FFM (Table 4). Although we hypothesized that the intervention would result in a lower percentage of infant body fat, no effect was found. Body weight and its lean component were significantly increased in LI measured by two independent methods. Head circumference, an index of greater brain growth, was similarly greater in the LI group. FFM measured by using PEA POD is the nonfat component of body weight and was 105 g higher in LI infants. Lean mass measured by QMR was 97 g higher in LI infants. QMR also measured greater TBW in the LI group. By comparison, these data show that an LI had a similar degree of impact on infant FFM (105 g) as not smoking during pregnancy (113.8 g) (33).

Our trial demonstrates that reliance only on infant body weight, length, and ponderal index would have resulted in an interpretation that LI produced larger and heavier babies, unequivocally assuming them to have greater adiposity and less lean mass per body weight measure (34). Our rigorously controlled RCT shows this assumption to be misguided, highlighting the importance of designing newborn trials with sensitive body composition measurement methods for adiposity and lean tissues.

This intervention targeting a healthier pregnancy lifestyle had an important measurable impact on neonate lean tissue. Our data were collected in the first few days of life and are largely devoid of confounding influences of the postnatal environment on body composition, such as mode of feeding (breast or formula). Whether these measurable effects are sustainable into childhood requires further investigation. We cannot attest to the clinical significance of this greater neonate lean mass, but clearly this could be of high relevance, given the strong epidemiology linking birth weight to adult health.

The effect of LI on infant body composition could not be explained by baseline maternal characteristics, which were well balanced by randomization (Table 1). Previous RCTs examined effects of interventions to reduce excessive GWG on infant outcomes. The most effective interventions appear to be those that comprehensively target maternal dietary intake and physical activity (35) as conducted here in LIFT (24). One study (36) found that the intervention group had a significantly lower median GWG compared with the control group ($7.0$ kg vs. $8.6$ kg, $P = 0.01$), whereas the intervention group offspring had a higher birth weight compared with the control group (median $3,742$ g vs. $3,596$ g). This is consistent with our finding of a higher infant weight in the LI group.

A few LIs targeting GWG (16) demonstrated an effect on neonatal weight. Healthy Moms found that an intensive intervention encouraging minimal GWG ($0 \pm 3$ kg) in women with obesity resulted in lower GWG (mean difference $= -3.4$ kg) and a lower prevalence of LGA infants at birth ($9\%$ vs. $26\%$, odds ratio $= 0.28$, 95% CI: $0.09$-$0.84$) (37). The randomized trial LIMIT found that a prenatal intervention targeting eating, activity, and behaviors with no prescribed calorie goals had no effect on reducing GWG but reduced birth weight $> 4,000$ g ($15\%$ vs. $19\%$; relative risk $= 0.81$ [0.67-0.98]) (20). By contrast, the UPBEAT trial found that a prenatal intervention designed to improve glucose tolerance but not GWG reduced GWG but had no effect on offspring LGA (38).

LIFT was not designed to identify specific mechanisms through which intervention affects neonate body composition. The LIFT hypothesis was that maternal pregnancy physiology, including glucose-insulin status, lipids, inflammation, blood pressure, and other metabolomics (39), could be improved by targeting GWG, producing an intruterine environment leading to healthier neonatal body composition. The absence of an association of infant lean mass with GWG category (excessive or within guidelines), or between degree of GWG and infant lean mass, suggests that intervention aspects other than limiting GWG may be important in development of lean mass. Prenatal behaviors (physical activity, diet) employed in LIFT could be mediators in the pathway(s) leading to the observed infant body composition, independent of GWG. However, no association was found between any infant body composition variable and the HEI. Other postulated mediators for the greater lean mass in LI neonates include possible changes in maternal or intraamniotic or placental metabolomic and inflammatory substances (secondary to the healthier diet) impacting the transfer of macronutrients to the fetus, recently reported to affect placental lipid transfer in women with obesity (40). Our intervention did not involve the first trimester of pregnancy, possibly missing an important period for fetal and neonatal fat accretion (41) and placental functioning (42). Our study highlights the need for further research to elucidate potential molecular, epigenetic, and/or biological mechanisms involved in determining fetal body composition. The demonstrated effect on neonatal body composition raises questions as to its persistence into and beyond the postnatal period.

A potential limitation of this study is that we did not measure nutritional intake (breast milk and infant formula) between birth and study measurement, which could have differed by group, thereby influencing the body composition measurements. We ensured a high degree of internal validity, with staff involved in collection of measurements blind to group assignment. We employed high-quality infant measurements with results consistent between PEA POD and...
QMR, methods employing very different technology, thereby maximizing our confidence in study findings. The generalizability of these findings to the wider patient population (external validity) is unknown. Our trial involved women with overweight or obesity only and did not include women with lower weight. The women enrolled into LIFT included a racially/ethnically diverse cohort, a large proportion of whom had high income.

Conclusion

This trial demonstrates the efficacy and safety of an LI in pregnant women with overweight and obesity that targeted the control of GWG during a highly malleable period of fetal development. It resulted in no differences in fat mass but resulted in greater lean mass in infants at birth.

Acknowledgments

We thank the LIFE-Moms consortium members for their contributions to the development and oversight of common measures and procedures across the trials; the LIFT study participants (women and infants) for enrolling in this study; the LIFT staff for their herculean efforts; Kasey Faulkner, Maryanne Holowaty, Isaiyah Janumala, Jill Johnson, Kim Kelly, Rachel Kolesky, Jennifer Patricio, Julie Roman, Elizabeth Widen, and Wen Yu; and Rebecca Gersonovitz Clifton, PhD, at The George Washington University Biostatistics Center for guidance specific to LIFE-Moms consortium outcomes and definitions.

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