Perinatal exercise improves glucose homeostasis in adult offspring

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Carter LG, Lewis KN, Wilkerson DC, Tobia CM, Tenlep SY, Shridas P, Garcia-Cazarin ML, Wolff G, Andrade FH, Charmigo RJ, Esser KA, Egan JM, de Cabo R, Pearson KJ. Perinatal exercise improves glucose homeostasis in adult offspring. Am J Physiol Endocrinol Metab 303: E1061–E1068, 2012. First published August 28, 2012; doi:10.1152/ajpendo.00213.2012.—Emerging research has shown that subtle factors during pregnancy and gestation can influence long-term health in offspring. In an attempt to be proactive, we set out to explore whether a nonpharmacological intervention, perinatal exercise, might improve offspring health. Female mice were separated into sedentary or exercise cohorts, with the exercise cohort having voluntary access to a running wheel prior to mating and during pregnancy and nursing. Offspring were weaned, and analyses were performed on the mature offspring that did not have access to running wheels during any portion of their lives. Perinatal exercise caused improved glucose homeostasis from an oral glucose challenge in both female and male adult offspring (P < 0.05 for both). Blood glucose concentrations were reduced to lower values in response to an intraperitoneal insulin tolerance test for both female and male adult offspring of parents with access to running wheels (P < 0.05 and P < 0.01, respectively). Male offspring from exercised dams showed increased percent lean mass and decreased fat mass percent compared with male offspring from sedentary dams (P < 0.01 for both), but these parameters were unchanged in female offspring. These data suggest that short-term maternal voluntary exercise prior to and during healthy pregnancy and nursing can enhance long-term glucose homeostasis in offspring.

Running; pregnancy; programming; mice

In 2007, 23.5 million people in the US were estimated to have diabetes, and this number is increasing (4). Interestingly, and what is often underappreciated, is that the metabolic status of an individual is decided not only by their inherited genes, nutritional intake, and physical exercise but also by maternal nutrition and obesity during pregnancy. In 1992, Hales and Barker (18) put forth the thrifty phenotype hypothesis that suggested that malnourished pregnant mothers produce smaller offspring that have a higher incidence of obesity, diabetes, and heart disease in adulthood. This hypothesis has since been modified to the developmental origins of health and disease (DOHaD) (15, 17, 18).

The DOHaD suggests that the maternal environment and fetal programming lead to a higher incidence of several diseases later in life (14, 16). A growing number of studies have been designed to provide evidence for the negative impact of DOHaD, using mice, rats, and sheep as animal models (11, 12, 31, 38). Many of these studies are directed at malnutrition through protein restriction or physical stressors that produce similar effects (8, 11, 34, 44, 45), but more recent studies are elucidating the metabolic effects of high-fat diet consumption during pregnancy on offspring (22, 38, 44, 48).

It has been known since Hippocrates and Galen that physical activity is an important component of a healthy lifestyle (33). However, knowledge about the contributions of maternal exercise during pregnancy and the long-term consequences on offspring is minimal. In both rats and mice, maternal exercise during pregnancy can improve brain physiology and cognition in the offspring (2, 23, 25). In humans, 5-yr-old children born to mothers who exercised regularly during pregnancy had improved intelligence scores and reduced body mass (7). Physical activity is already used as a treatment for gestational diabetes in humans, but long-term outcomes in offspring have not been fully investigated (10, 28, 41, 49).

Using a mouse model, we set out to explore maternal voluntary exercise as an intervention to improve offspring metabolic health. We hypothesized that voluntary exercise prior to and during pregnancy and nursing would benefit offspring metabolic health throughout their adult life. In this report, we show that maternal voluntary exercise just prior to and during pregnancy and lactation had a positive impact on glucose regulation and insulin sensitivity in sedentary adult offspring. This is exciting because it indicates that a simple, short-term, nonpharmacological intervention can improve long-term glucose homeostasis in the next generation.

RESEARCH DESIGN AND METHODS

Animals and diets. These studies were carried out at the University of Kentucky according to an approved Institutional Animal Care and Use Committee protocol. At 2 mo of age, female Institute for Cancer Research (ICR) mice were bred and produced one litter at Taconic prior to shipment to the University of Kentucky at 4 mo of age. Females were housed four mice per cage for a 2-wk acclimation.
period and then separated into two groups, sedentary or voluntary exercise, and were housed singly for the duration of the study. They were placed in light-controlled boxes (Phenome Technologies, Lincoln, IL) in an environmentally controlled vivarium between 68 and 72°F, with unlimited access to food and water under a controlled photoperiod (14:10 h light-dark). The dams (and sires) were fed Labdiet Formulab Diet No. 5008. Maternal body weight and food intake were measured once/wk throughout the breeding portion of the study. The pregnant dams in the exercise cohort had continual access to running wheels throughout pregnancy until 14 days after giving birth, at which point wheels were removed to prevent possible harm to growing pups. Litters were culled to eight or nine pups ~48 h after birth. Pups were cross-fostered from other litters from the same group if they did not have at least eight pups. Pups were weaned on postnatal day 21 onto Teklad Global 18% Protein Rodent Diet No. 2018 and were housed four to five mice per cage. The offspring themselves did not have access to running wheels during any portion of the study. Subsequent analyses were performed on the offspring from 20 and 18 different sedentary and exercised nursing dams, respectively.

Exercise. Female ICR mice were housed in cages purchased from Phenome Technologies (Lincol, IL). The mice had open access to the running wheels that were mounted within each cage. A mechanical counter was used to record wheel rotations to a desktop computer via ClockLab software (Actimetrics, Wilmette, IL). Sedentary female mice were housed in nearly identical cages that did not contain running wheels. Dams exercised ~7 days prior to and during pregnancy and up through day 14 of lactation. Male mice also had the ability to exercise for the 10-day period while they were in the female cages for mating purposes. The exercise was completely voluntary; mice were not forced in any way onto wheels. Offspring did not exercise for any portion of the study.

Oral glucose tolerance test. At 31–32 (6-h fast), 36–37 (3-h fast), and 71–72 (3-h fast) wk of age, offspring of both sexes were fasted and then given an oral gavage of n- (+) glucose (Sigma-Aldrich, St. Louis, MO) at 2 g/kg body wt. Blood glucose was measured in tail vein blood using an Ascensia Breeze 2 meter (Bayer, Mishawaka, IN) just prior to gavage (time 0) and at 15, 30, 60, and 120 min after glucose administration.

Intraperitoneal insulin tolerance test. At 33–34 (female) and 43–44 (male) wk of age, mice were fasted for 3 h. Female mice were then given an intraperitoneal injection of porcine insulin (Sigma, I-5523) at 0.75 IU/kg body wt. Male mice were given an intraperitoneal insulin injection at 1.25 IU/kg body wt. Blood glucose was measured at 0, 15, 30, 60, 120, and 180 min postinjection from tail vein prick. Female mice that became unresponsive to touch as a result of hypoglycemia were given a glucose injection (n = 2/20 for sedentary and n = 5/18 for exercise). No further glucose blood readings were taken from the glucose-injected mice, but preglucose injection values were included in the analysis. No male mice became unresponsive during the procedure.

In vitro soleus muscle glucose uptake. Female offspring born to sedentary and exercise dams were fasted for 3 h at 37 wk of age (n = 6/group). Mouse soleus muscles were then quickly excised immediately after euthanasia. The tissue was immersed in Krebs-Ringer bicarbonate buffer (117 mM NaCl, 4.7 mM KCl, 24.6 mM NaHCO3, 1.2 mM KH2PO4, 1.2 mM CaCl2, and 2.5 mM MgSO4) bubbled with 95% O2 and 5% CO2. Soleus muscles from one leg were used to measure the effects of insulin. All muscles were first incubated with Krebs-Ringer bicarbonate buffer with 2 mM pyruvate for 30 min at 37°C. Soleus muscles were then rinsed and incubated with Krebs-Ringer buffer containing 1 mM 2-deoxy-D-[1,2^-3H]glucose (2D^-3H]glucose, 1.5 mCi/ml) and 7 mM D-[14C]mannitol (0.45 mCi/ml) for 10 min. Insulin (100 nm) was added to the buffer of the insulin group. Finally, soleus muscles were rinsed with plain Krebs-Ringer buffer. Tendons were removed and soleus muscles blotted dry with filter paper and digested with 250 μl of 1 N NaOH at 80°C for 10 min. After neutralizing with 250 μl of 1 N HCl, 350 μl of sample was added to scintillation liquid for dual label radioactivity counting. Glucose uptake (per gram tissue weight) was then determined after the intracellular and extracellular space was calculated, as described previously by Chambers et al. (5). Tissues from male offspring were not tested due to time constraints.

In vitro adipose glucose uptake. A separate cohort of female offspring born to sedentary and exercise dams was fasted for 3 h at 36 wk of age (n = 4/group). Glucose uptake was performed as described previously with some modifications (37). Briefly, parametral fat was removed immediately after euthanasia and cut into 5- to 10-mg sized explants. Explants were washed three times in 0.5 ml of Krebs-Ringer buffer (pH 7.4) supplemented with 1% BSA. Explants were incubated in Krebs-Ringer buffer with 1% BSA at 37°C for 30 min to establish basal conditions. Explants were then transferred to a 24-well plate containing 450 μl of Krebs-Ringer buffer with either 0 or 100 nM insulin and incubated for 15 min at 37°C under 5% CO2. The assay was initiated by the addition of 50 μl of 4.5 mM 2-deoxyglucose containing 0.5 μCi of 2^-[3H]2-deoxyglucose (57.7 mCi/mmol, NEC955A00; Perkin-Elmer). After 15 min, the assay was terminated by transferring tissue explants to ice-cold Krebs-Ringer buffer supplemented with 1% BSA, washed three times with the same buffer, blotted, weighed, and incubated in 1 N NaOH for 1 h at 65°C. Radioactivity of the NaOH extract was determined by scintillation counting. Glucose uptake is expressed per gram tissue weight. Tissues from male offspring were not tested due to time constraints.

Body composition. At 39 and 68 wk of age, total fat tissue, lean tissue, and water were measured in live, conscious male and female offspring by nuclear magnetic resonance (EchoMRI; EchoMedical Systems, Houston, TX). The EchoMRI measures adipose tissue, lean mass, and free and total water. Although many tissues contribute to the lean mass output, there are undetectable components such as bone mineral content, hair, and claws.

Statistics. Repeated-measures data were analyzed using repeated-measures analyses of variance (ANOVA), followed by Student’s t-test, unless otherwise indicated. Repeated-measures ANOVA were performed using IBM SPSS statistics 20 software. For Figs. 2, C–F, and 3, A and B, repeated-measurements data were analyzed using mixed models, a generalization of repeated-measures ANOVA that uses as many observations as are available for each specimen (rather than requiring complete data from each specimen to be included in the analysis). Mixed models expressed mean scores as functions of both time and group membership, and mean scores at any particular time point (in Figs. 2, C and D, and 3, A and B) were compared using approximate t-tests corresponding to linear contrasts, as implemented in the ESTIMATE statement of PROC MIXED in SAS. Areas under the curve (as calculated by the trapezoidal rule) and mean scores at any particular time point were compared using linear contrasts embedded in the mixed models. Figure 3, C and D, was also analyzed by mixed models with treatment replacing time as the within-subjects factor. Version 9.2 of SAS software was used for mixed-model analyses. Nonrepeated measurement data were analyzed by Student’s t-test (Fig. 4D) or Mann-Whitney rank sum test when the data failed the Shapiro-Wilk normality test (Fig. 4, A–C). These analyses were completed using SigmaPlot 11.0 software.

RESULTS

Maternal body weight and food intake. After 7 days in sedentary or exercise groups, female ICR mice were bred to male mice for 10 days to ensure a maximum number of pregnancies. During breeding, males also had access to the running wheel. Depending on day of conception, exercise dams had running wheel access for a minimum of 7 and maximum of 17 days prior to conception. Eleven of 18 exercise females conceived on the first night of mating, whereas 14 of 18
Running data (Fig. 1A) were matched so that day 29 correlates to delivery day regardless of day of conception in relation to being placed on the running wheels. Mean running distance per day increased over the first 7 days as the female mice grew accustomed to the running wheels (Fig. 1A). From days 8–17, a male mouse was also present in the cage for breeding, and running distance increased most likely due to male running. Mean running distance decreased as the female mice approached delivery on day 29 and was maintained at lower levels during lactation. Average running distance during nursing was significantly lower than average running distance prior to pregnancy ($P < 0.001$).

Figure 1, B and C, shows maternal body weight and food intake. These data were not matched for day of delivery because the values were only measured once/week. There were no significant differences in body weight due to maternal exercise prior to or during pregnancy and lactation (Fig. 1B). Figure 1C shows the weekly food intake values divided by 7 as a measurement of daily food intake. To determine food intake while males were in the cage, food intake was divided by 2 to account for two mice in the cage. There was a significant increase in food intake prior to and during mating and pregnancy ($P < 0.001$; repeated-measures ANOVA) in the running dams at weeks 2, 3, and 4 ($P = 0.015$, $P < 0.001$, and $P < 0.001$, respectively) (Fig. 1C). There were no differences in food intake during nursing (weeks 5–7). Maternal running during pregnancy did not significantly affect pregnancy rate or litter size (Table 1). There were also no significant differences in mean pup body weight per litter on postnatal days 7, 14, or 21 (Table 1).

Glucose and insulin tolerance in offspring. The offspring born to sedentary and exercised dams (shown in Fig. 1, A–C) were then used for further analyses. There were no significant differences in body weight in female or male offspring born to sedentary or exercised dams from 3 to 76 wk of age (Fig. 2, A and B). At 31–32 wk of age, both female and male offspring born to sedentary and exercised dams were fasted and given an oral dose of glucose (2 g/kg body wt). Circulating blood glucose values were measured after the oral glucose challenge (data not shown). Overall glucose disposal was improved significantly in female and male offspring born to exercised dams compared with those from sedentary dams ($P = 0.023$ and $P = 0.005$, respectively). Oral glucose tolerance was again measured in the offspring at 36–37 wk of age. Consistent with earlier results, overall glucose disposal was improved in female and male offspring born to exercised dams ($P = 0.004$ and $P = 0.011$, respectively). The female (Fig. 2C) and male (Fig. 2D)

### Table 1. Effect of maternal exercise on pregnancy rates, litter size, and pup body weights

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sedentary (SE)</th>
<th>Exercise (SE)</th>
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<tbody>
<tr>
<td>Pregnancy rate</td>
<td>26/28</td>
<td>25/28</td>
</tr>
<tr>
<td>Subsequent analyses on litters (n)</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Pups/litter</td>
<td>11.38 (0.71)</td>
<td>10.40 (0.74)</td>
</tr>
<tr>
<td>PND 7 pup body weight, g*</td>
<td>5.67 (0.09)</td>
<td>5.42 (0.15)</td>
</tr>
<tr>
<td>PND 14 pup body weight, g*</td>
<td>9.17 (0.20)</td>
<td>8.96 (0.25)</td>
</tr>
<tr>
<td>PND 21 pup body weight, g*</td>
<td>14.55 (0.19)</td>
<td>14.14 (0.40)</td>
</tr>
</tbody>
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*Postnatal day (PND) pup body weights were calculated by averaging pup body weights/litter. Each litter average was then used to calculate the mean pup body weight/group.
offspring born to exercised dams had significantly enhanced glucose disposal after 30 min compared with offspring from sedentary dams (\(P < 0.001\) and \(P = 0.010\), respectively). In addition, male offspring born to exercised dams also had significantly lower glucose levels 60 min after the glucose dose (\(P = 0.019\)). Area under the curve was decreased significantly in female (Fig. 2E) offspring from exercised dams compared with those from sedentary dams (\(P = 0.009\)), with a similar effect observed in male (Fig. 2F) offspring born to exercised dams (\(P = 0.026\)). Oral glucose tolerance was tested for a final time in offspring at 71–72 wk of age. Again, overall glucose tolerance was improved significantly in female (\(P = 0.032\)) and male (\(P = 0.039\)) offspring from exercised dams compared with those born to sedentary dams (data not shown).

We then focused on the mechanism of enhanced glucose disposal in female and male offspring born to exercised dams by performing an insulin tolerance test. Blood glucose levels drop over time in response to the exogenous insulin, and the rate of disposal provides an index of insulin sensitivity. At 33–34 wk of age mature female offspring were fasted, and insulin at 0.75 IU/kg body wt was injected. Offspring from both sedentary and exercised dams had consequential lowering of blood glucose in response to insulin. Offspring born to exercised dams had significantly improved overall glucose disposal (\(P = 0.024\)) compared with those from sedentary dams, with significantly enhanced disposal at 15, 30, and 60 min postinjection (\(P = 0.005\), \(P = 0.017\), and \(P = 0.035\), respectively), suggesting that these mice were more insulin sensitive (Fig. 3A). Mature male offspring at 43–44 wk of age were fasted and injected with a higher dose of insulin to ensure glucose uptake (1.25 IU/kg body wt). Offspring born to exercised dams had overall improved glucose disposal (\(P = 0.003\), with significantly enhanced disposal at 15, 30, 60, and 120 min postinjection (\(P = 0.001\), \(P = 0.010\), \(P = 0.036\), and \(P = 0.025\), respectively) compared with offspring from sedentary dams (Fig. 3B). These data confirmed that middle-aged offspring born to exercised dams had improved insulin sensitivity compared with offspring born to sedentary dams.

2-Deoxyglucose uptake in offspring muscle and adipose. Skeletal muscle and adipose tissue are responsible for the majority of insulin-sensitive glucose uptake in vivo (36, 39). We next set out to determine which tissues were responsible...
for the enhanced insulin sensitivity observed in the mature female offspring born to exercised dams. Therefore, soleus muscle was isolated, and 2-deoxyglucose (2-DG) uptake was measured in the presence and absence of 100 nM insulin in vitro (Fig. 3C). Muscle collected from offspring born to exercised dams trended toward increased 2-DG uptake compared with muscle from sedentary dam offspring in the basal state \( (P = 0.151) \). Muscle isolated from offspring born to both sedentary and exercised dams showed significant increases in 2-DG uptake in response to insulin compared with basal uptake levels \( (P < 0.001 \text{ in both comparisons}) \). Importantly, the muscles from exercised dam offspring exhibited significantly greater glucose uptake in response to the insulin dose compared with muscle from sedentary dam offspring \( (P = 0.007) \). A similar design was used to measure 2-DG uptake into isolated adipose in a separate cohort of female offspring born to sedentary and exercised dams (Fig. 3D). The addition of 100 nM insulin to adipose explants isolated from sedentary offspring did not significantly affect 2-DG uptake \( (P = 0.225) \), which suggests a level of insulin resistance. However, adipose explants collected from offspring born to exercised dams were more sensitive and had significantly increased 2-DG uptake in response to insulin compared with their basal state \( (P = 0.002) \) as well as compared with the insulin-treated explants isolated from offspring born to sedentary dams \( (P = 0.008) \). Both skeletal muscle and adipose isolated from offspring born to exercised dams exhibited enhanced insulin sensitivity. These findings suggest that peripheral tissue insulin sensitivity is the mechanism largely responsible for enhanced glucose disposal following an oral glucose challenge.

**Offspring body composition.** Body composition was analyzed by quantitative magnetic resonance imaging (EchoMRI; Echo Medical Systems) in mature 39-wk-old female and male offspring. Fat and lean mass are expressed as a percent of body weight. There were no differences observed in female offspring (Fig. 4A) or lean content (Fig. 4C). There were also no differences in percent total water between female offspring from exercised (41.1 ± 1.2) or sedentary dams (42.3 ± 1.2). However, there were significant differences observed in male offspring body composition. Figure 4B shows that male offspring born to exercised dams had significantly reduced fat content compared with male offspring from sedentary dams \( (P = 0.004) \). In addition, Fig. 4D shows that male offspring born to exercised dams also had significantly increased lean tissue composition compared with male offspring from sedentary dams \( (P < 0.001) \).

Fig. 3. Mature female and male ICR offspring born to exercised dams show enhanced insulin sensitivity. Female and male offspring were fasted prior to an insulin tolerance test. A: blood glucose levels in female offspring from exercised dams were significantly decreased at 15, 30, and 60 min after insulin injection compared with offspring from sedentary dams. B: blood glucose levels in male offspring from exercised dams were significantly decreased at 15, 30, 60, and 120 min after insulin injection compared with offspring from sedentary dams. C: both sedentary and exercise dam female offspring muscle showed significantly increased 2-deoxyglucose (2-DG) uptake in response to 100 nM insulin treatment compared with basal uptake. In addition, muscle from offspring born to exercised dams showed significantly increased 2-DG uptake in response to insulin compared with offspring from sedentary dams. D: adipose from exercise dam offspring show significantly increased 2-DG uptake in response to insulin treatment compared with basal uptake and compared with insulin-stimulated uptake in adipose from offspring born to sedentary dams. *\( P < 0.05 \) and **\( P < 0.01 \) compared with offspring born to sedentary dams (A and B) or insulin-treated compared with basal sedentary or exercise control (C and D). ***\( P < 0.001 \) compared with insulin-treated sedentary; \( n = 20 \) for sedentary and 18 for exercise in A; \( n = 16 \) for sedentary and 14 for exercise in B; \( n = 6 \) for sedentary and exercise in C; \( n = 4 \) for sedentary and exercise in D. Error bars indicate SE.
from exercised dams had significantly increased percent total water ($P = 0.047$) compared with female offspring from sedentary dams (data not shown). Again, there were significant differences in male body composition. Males from exercised dams had significantly reduced percent fat content ($P = 0.023$) and significantly increased percent lean tissue ($P = 0.040$) compared with males from sedentary dams (data not shown). However, there were no differences in male offspring percent total water at the older age (data not shown). It appears that changes in body composition were not required for glucose tolerance improvements observed in the female offspring born to exercised dams but may play a role in changes in glucose disposal observed in male offspring.

**DISCUSSION**

We have found that maternal exercise prior to and during pregnancy and lactation can improve long-term metabolic outcomes in offspring. Glucose disposal was significantly enhanced in both female and male offspring born to exercised dams compared with those from sedentary dams. In addition, male and female offspring from exercised dams were found to be more sensitive to exogenous insulin. In female offspring, we also found that excised skeletal muscle and fat pads from offspring born to exercised dams were more sensitive to in vitro insulin stimulation compared with those from sedentary dams. Previously, exercise during pregnancy has been shown to result in acute and long-term reduction in glucose that reaches the fetus (6, 46). Changes in glucose availability during development could have long-lasting effects in that mature offspring become more sensitive to glucose changes. Consistent with our findings, Vanheest and Rodgers (47) used moderate speed treadmill running (20 m/min) in streptozotocin-induced diabetic pregnant rats and found that their offspring had improved glucose tolerance compared with offspring born to sedentary diabetic and nondiabetic dams. Although the connection is somewhat limited, this does suggest that the improvement of glucose regulation by maternal exercise will be observed in multiple species.

Previous studies by other laboratories have looked at different maternal and offspring outcomes resulting from exercise during pregnancy. In human studies, maternal exercise effects have focused mainly on pregnancies complicated by gestational diabetes. In a study of women with gestational diabetes, it was found that resistance exercise was effective in lowering the number of women who needed insulin therapy to maintain normal blood glucose levels (9). In a study of healthy pregnant women, mild physical activity was found to lower the risk of developing gestational diabetes (26). In contrast, a recent randomized control trial in women of normal body weight showed that exercise during pregnancy did not decrease the prevalence of gestational diabetes compared with sedentary controls (43). Few human studies have investigated offspring effects of maternal exercise during pregnancy. These studies have focused mainly on birth weights, body composition, and cognitive outcomes. In several studies, exercise during pregnancy reduced birth weights (7, 20). Lower birth weights were found to coincide with reduced fat mass at birth as well as reduced cord serum concentrations of growth hormones. At 5 yr of age, children from mothers who exercised during pregnancy were shown to have improved scores on general intelligence and oral language skills tests (7). Animal studies have detected neurological changes in offspring as a result of exercise during pregnancy. Maternal swimming in rats was found to increase hippocampal neurogenesis in rat pups that was then associated with improved memory in the pups (25). A similar study found that, in mice, maternal running during pregnancy and nursing resulted in a 40% increase in total granule cells in the offspring hippocampus (2). Recently, Herring et al. (19) showed that short-term exercise during pregnancy was able to reduce Alzheimer pathology in offspring in a transgenic mouse model that is predisposed to the disease.
pregnancy can clearly affect many maternal and offspring outcomes.

Finding the mechanisms behind the observed metabolic changes in offspring due to perinatal exercise will be an important focus of future studies. This was beyond the scope of the current study given the number of possible epigenetic and sex-specific changes that are associated with developmental programming models. Developmental programming of metabolism has been observed in human and animal models of intrauterine growth restriction (IUGR). IUGR in humans and animals is known to decrease glucose disposal and insulin sensitivity in mature offspring (35, 40). Although the link between IUGR and decreases in insulin sensitivity has been known for decades, not until recently have researchers begun to investigate the mechanisms behind these metabolic derangements. Studies have found decreases in the expression and insulin-stimulated activation of many proteins involved in the insulin-signaling pathway that correlate with decreases in whole body insulin sensitivity (21, 32). Further complicating the elucidation of the mechanism is that many of the metabolic changes observed in developmental programming models do not occur until offspring are aged. Because of this, it is unclear whether offspring from sedentary dams develop a dysfunction in insulin sensitivity as they age or whether offspring from exercised dams are protected from a natural, age-related decline in insulin sensitivity. It is important to note that in the current study glucose tolerance was first tested in 3-mo-old offspring, but differences were not detected until the offspring reached 7 mo of age.

The effects of developmental programming on long-term offspring health have been shown to be specific in several studies (13, 29). A similar observation was made in this study when significant effects on the percentage of fat and lean tissue in response to maternal exercise were found only in male offspring despite an improvement in glucose tolerance in both females and males. Perhaps more important than the change in body composition in male offspring was the lack of changes in fat and lean tissue in female offspring, highlighting improved insulin sensitivity as the potential mechanism contributing to enhanced glucose uptake in these offspring. It will be necessary to determine whether increased lean tissue plays a unique role in improved glucose uptake in male offspring to elucidate divergent mechanisms between males and females.

The findings from this study are an important step in discovering potential beneficial effects of maternal exercise for offspring. Future studies will look at the mechanism through which maternal exercise improves offspring glucose homeostasis, including investigating changes in milk content and production during lactation. Experiments can be designed to focus on periods of time before, during, and/or after pregnancy, when maternal exercise is essential for beneficial effects in offspring. Furthermore, cross-fostering strategies can be used to control multiple factors.

One recent study showed that high-fat-fed male rats produced female offspring with impaired β-cell function (29), and another showed that low-protein diet consumption by male mice prior to mating affected metabolic gene expression in offspring (3). Therefore, it will be necessary to determine whether paternal exercise prior to fertilization influences the offspring outcomes observed in Figs. 2–4. One possible way to control for paternal influence would be to use artificial insemination. It is also important to address that the presence of a running wheel in the cage may serve as enrichment for the exercising dams. Although no studies have been conducted to look at maternal environmental enrichment and its effects on the metabolic health of offspring, a few animal studies have shown that it can improve maternal and offspring cognitive functions (24, 27, 42). It may be necessary in future studies to control for this as a possible confounding factor by using a controlled exercised paradigm in which there is no running wheel in the home cage. Rather, mice would be removed from the home cage daily and would exercise for a predetermined amount of time using any one of a number of exercise paradigms. This design would also control for the vast amount of running seen in the voluntary exercise paradigm.

Much work is left to be done, but our studies provide new information on the positive impact that perinatal exercise can have on offspring metabolic health in a mouse model. Such an intervention provides a realistic mechanism to improve insulin sensitivity in the next generation and positively impact insulin-resistant states.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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