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Maternal Exercise Improves the Metabolic Health of Adult Offspring

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Abstract

The intrauterine environment can modulate the course of development and confer an enduring effect on offspring health. The effects of maternal diet to impair offspring metabolic health are well-established, but the effects of maternal exercise on offspring metabolic health have been less defined. Since physical exercise is a treatment for obesity and type 2 diabetes, maternal exercise is an appealing intervention to positively influence the intrauterine environment and improve metabolic health of offspring. Recent research has provided insight into the effects of maternal exercise on the metabolic health of adult offspring, which is the focus of this review.

Introduction

The prevalence of obesity and type 2 diabetes are increasing dramatically in the United States and worldwide, with recent projections indicating that the prevalence of type 2 diabetes is likely to increase to over 25% of the US population by 2050 [1]. Type 2 diabetes is a complex disease that arises from a combination of environmental factors and genetic susceptibility. Increasing evidence has indicated that the *in utero* environment plays an important role in the development of diseases during adulthood, and numerous epidemiological and experimental studies have indicated a relationship between the maternal nutritional environment and obesity, type 2 diabetes, and cardiovascular disease in offspring [2–15]. The classic Dutch Famine studies demonstrated that maternal under-nutrition resulted in offspring with increased obesity later in life [11], while children with low birth weight had increased risk for cardiovascular disease [12], impaired glucose tolerance, and type 2 diabetes [13–15]. Other studies have indicated that maternal over-nutrition is an important risk factor for childhood obesity [16, 17]. In fact, the detrimental effects of maternal over- or under-nutrition on adiposity and metabolism in offspring have been well established in both human [11–13, 16, 17] and animal studies [9, 18–21].

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Regular physical exercise is an important preventive therapeutic for several diseases, including type 2 diabetes. Physical exercise improves glucose homeostasis in people with type 2 diabetes due to enhanced glucose uptake and insulin sensitivity in the working skeletal muscles [22]. In response to physical training, there are also molecular adaptations that enhance glucose homeostasis. The effects of exercise to improve glucose homeostasis are likely an important mechanism to explain the strong epidemiological evidence that regular exercise prevents or delays the onset of type 2 diabetes [23, 24].

Exercise during pregnancy has beneficial effects for the mother, including reduced rates of preeclampsia, gestational diabetes, heartburn, and the likelihood for cesarean section [25]. The effects of exercise during pregnancy on fetal outcomes have been extensively investigated for many years. The majority of this work focused on fetal growth, as there is a strong association between offspring birth weight and postnatal health outcomes [2]. However, until recently, much less was known about the effects of maternal exercise on the metabolic phenotype of offspring. This is an important issue, since insults to the intrauterine environment during pregnancy are a critical factor in the development of obesity and type 2 diabetes in offspring [26] . Here, we will discuss recent findings related to the effects of maternal exercise on offspring metabolic health, how maternal exercise effects an impaired maternal diet, and if maternal exercise influences male or female offspring differently.

Maternal Exercise Improves Offspring Health

In humans, maternal physical activity has been shown to influence perinatal outcomes. Studies investigating diet and physical exercise in humans during pregnancy have shown that exercise reduces gestational weight, decreases the risk for caesarean section, and regarding offspring, results in small but significant reductions in birth weight [27–30]. In one study, vigorous weight bearing exercise throughout pregnancy in humans resulted in lower body weight of offspring at age 5, with no adverse postnatal health outcomes [27]. Maternal exercise has also been associated with lower BMI in offspring at 8 years of age [30]. Human studies, both retrospective to examine the effects of diet and exercise during pregnancy, or intervention studies introducing an exercise intervention, are incredibly important to determine the role of maternal exercise on offspring health. While these studies provide important data with regard to the health of the mother and the metabolic phenotype of the infant, it is difficult to follow the child throughout their lifespan and determine the effect of maternal exercise on offspring health. The majority of studies determining how the *in utero* environment affects offspring metabolic health in humans are the result of large epidemiological studies because the changes in health are not seen until adulthood [11–15]. As a result, rodent models have been used to investigate the effects of maternal exercise on the metabolic health of adult offspring [31–38]. While there are discrepancies amongst these studies - different strains of mice and rats were used, different durations and modalities of maternal exercise were studied – the majority of studies resulted in the overall phenotype that maternal exercise before and during pregnancy improves glucose tolerance and insulin sensitivity in adult offspring (Table 1).

Optimal Timing of Maternal Exercise Intervention - Pre- or During Gestation?

An important question when investigating the beneficial effects of maternal exercise on offspring metabolic health is determining the optimal timing of the exercise intervention to confer maximal benefits to the offspring. The majority of studies investigating the effects of maternal exercise on offspring metabolic health subjected the dams to voluntary wheel cage running or swimming 7–21 days before gestation and during gestation [33–35, 38]. While these studies established that exercise before and during pregnancy was important to observe improved glucose tolerance and insulin sensitivity in adult offspring, it was not clear whether a specific time point of maternal exercise (pre-gestation, during gestation, during lactation, or all of the above) was required to determine the effects on the metabolic health of offspring.

Multiple studies have sought to address this question [32–34, 36]. Recent work in our laboratory determined if the timing of maternal exercise pre-gestation, during gestation, or both, was important to confer the beneficial effects to the metabolic health of adult offspring [32]. Female mice were divided into four subgroups: trained (mice housed with running wheels preconception and during gestation), pre-pregnancy trained (housed with wheels preconception), gestation trained (housed with wheels during gestation), or sedentary (housed in static cages). Maternal exercise was not performed during the lactation period. Male offspring of sedentary dams had a worsening of glucose tolerance as they aged, and this effect was negated in the offspring if maternal exercise was performed before and during gestation. Maternal exercise both before and during gestation improved glucose tolerance, lowered fasting insulin, and decreased % body fat in male offspring compared to all other groups. Maternal exercise only during gestation improved glucose tolerance at a young age (8 and 12 weeks), but not during adulthood. Maternal exercise only during pre-pregnancy did not alter glucose tolerance of offspring at any age [32]. These data indicate that maternal exercise both before and during gestation is crucial to an improved glucose tolerance in the offspring.

Similar to these results, another study examined the effects of gestation-only exercise in rats on the metabolic health of adult male offspring [36]. Female rats were given open access to a wheel cage only during the gestation period. They observed no effect on glucose tolerance in the adult male offspring, but determined decreased % body fat. The male offspring from gestation-trained dams were also protected from high-fat diet induced hepatic steatosis and had increased expression of liver mitochondrial genes.

Another set of studies examined the effects of maternal exercise (voluntary wheel running) that was performed both pre- and during-gestation and throughout the lactation period [33, 34] using both a rat and mouse model. Adult male offspring (mouse) [33] and adult female offspring (rat) [34] had improved glucose tolerance and increased skeletal muscle insulin sensitivity. In these studies, each time point of maternal exercise (pre-gestation, during-gestation, and during lactation) was not independently investigated, but exercise continued throughout the pre-gestation, gestation, and lactation period.

Together these studies indicate that there are some beneficial effects in offspring if maternal exercise was performed only during gestation, but the maximal effects on offspring glucose

tolerance and health are evident if maternal exercise is performed either before and during gestation, or before and during gestation and throughout lactation [32–34, 36]. There was not an added improvement in glucose tolerance if maternal exercise was performed both before and during gestation and continued through lactation, however this has not been closely examined. Further investigation of maternal exercise only during the lactation period would allow insight into this, as well as a potential role for maternal exercise to alter the components of maternal milk that may improve glucose tolerance and metabolic health of offspring. Studies have shown that exercise does not affect the quality of breastmilk composition [39] but can alter the different components, including increasing insulin in the milk [40]. From a therapeutic standpoint, the fact that exercise only during gestation can confer some beneficial effects to the offspring is exciting and important; if these results translate to humans it would indicate that a previously sedentary woman could begin to exercise once she is pregnant and still provide some benefits to her offspring.

Influences of Maternal Exercise on Male vs. Female Offspring

There is an increasing amount of data indicating that metabolic insults and disease states differentially affect males and females. In fact, there are now strong efforts to understand the effects of interventions and treatments in both genders [41]. With respect to maternal influences during pregnancy, studies investigating the effects of maternal over-nutrition on both male and female offspring have repeatedly shown that the male offspring have a more pronounced detrimental phenotype than the female offspring [14, 42–46]. Here, we will discuss the effects of maternal exercise in chow-fed dams on the metabolic health of both male and female offspring; effects of maternal exercise in the presence of a maternal high-fat diet will be discussed at a later point.

The majority of studies investigating the effects of maternal exercise on offspring have primarily studied the male offspring [32, 36–38, 47, 48]. Studies by our lab and others have shown that maternal exercise in chow-fed dams results in increased % lean mass [33] and decreased % fat mass [32, 33], and decreased body weight [32, 36] in adult male offspring compared to offspring from sedentary dams. Male offspring from exercise-trained dams also had significantly improved glucose tolerance [32, 33, 35], reduce fasting insulin [32], improved insulin tolerance [33], and increased energy expenditure [38].

Studies that have measured the effects of maternal exercise in chow-fed dams on metabolic health of female offspring have seen a somewhat tempered phenotype compared to male offspring. Carter et al. determined that glucose tolerance was improved in female offspring from exercise-trained dams [33, 34] and that female offspring had improved insulin tolerance [33], and were more insulin sensitive when subjected to euglycemic-hyperinsulinemic clamps [34]. Interestingly, work in our laboratory determined no difference in insulin sensitivity measured by euglycemic-hyperinsulinemic clamps in female offspring from chow-fed sedentary or exercise-trained dams [31]. We also determined that female offspring from chow-fed, exercise-trained dams had reduced fasting insulin and % body fat compared to offspring from chow-fed sedentary dams [31].

Maternal Exercise Affects Function of Multiple Tissues in Offspring

Interestingly, while the improved glucose tolerance phenotype is more pronounced in male offspring than female offspring [31–33], the tissue responsible for the improved glucose tolerance has been more thoroughly investigated in female offspring. Work in our laboratory measured glucose clearance *in vivo* in skeletal muscle (tibialis anterior, soleus, gastrocnemius, and extensor digitorum longus). There was no difference in rates of basal or insulin-stimulated glucose clearance in skeletal muscles from offspring of sedentary or exercise-trained dams [32]. Another study in male offspring revealed increased expression of hepatic *Pgc1α* and a reduction in the presence of hepatic steatosis, indicating that maternal exercise may exert beneficial effect on offspring through adaptations to the liver. It is important to note, however, that in this study the dams only exercised during gestation and there was no improvement in glucose tolerance observed in male offspring [36].

In female offspring, studies have indicated that maternal exercise causes adaptations to the skeletal muscle [33, 34], adipose tissue [33], and liver [31, 34]. In vitro glucose uptake was measured in isolated soleus muscle and parametrial adipose tissue from female offspring. There was no difference in basal glucose uptake among groups, but insulin-stimulated glucose uptake was significantly increased in both the soleus and parametrial adipose tissue in offspring from chow-fed exercise-trained dams compared to offspring from chow-fed sedentary dams [33]. This indicates an important role for skeletal muscle and adipose tissue to mediate the improved glucose tolerance in female offspring from exercise-trained dams. Another study, this time in rats, determined an increase in skeletal muscle glucose uptake after euglycemic-hyperinsulinemic clamps in female offspring from chow-fed exercise-trained dams [34].

Other studies have examined the role of the liver in female offspring in response to maternal exercise. While both studies demonstrate an increase in hepatic insulin sensitivity and reduced hepatic glucose production, the data are slightly conflicting. In rats, the offspring from chow-fed sedentary and exercise-trained dams underwent euglycemic-hyperinsulinemic clamps. Female offspring from exercise-trained dams had increased glucose infusion rates, improved whole-body glucose turnover, and decreased hepatic glucose production [34]. We performed a similar euglycemic-hyperinsulinemic clamps experiment in mice, and determined that there was no effect of maternal exercise on glucose infusion rates or whole-body glucose turnover in offspring from exercise-trained dams [31]. While these data were perplexing in light of previous experiments, it is possible that the different species used (rats vs. mice) were partly responsible for the conflicting results. Further investigation on the effects of maternal exercise on the liver of female offspring revealed increased insulin sensitivity in isolated hepatocytes and expression of genes involved in hepatic metabolism. We measured glucose production in isolated hepatocytes and expression of hepatic genes involved in mitochondrial biogenesis, fatty acid metabolism, and Krebs cycle activity. Basal, insulin-suppressed, and glucagon-stimulated glucose production in isolated hepatocytes was significantly lower in female offspring from chow-fed, exercise-trained dams compared to offspring from chow-fed, sedentary dams. Several hepatic genes involved in mitochondrial biogenesis, fatty acid metabolism, and Krebs cycle activity were also significantly higher in offspring from chow-fed exercise-trained dams

compared to chow-fed sedentary dams [31]. Together these data indicate that maternal exercise affects the skeletal muscle, adipose tissue, and liver in female offspring, and adaptations to one or all of these tissues likely contribute to an improved metabolic response.

The age of the offspring investigated and the intensity of the maternal exercise may also play an important role in which tissue is affected by maternal exercise. The studies described above measured skeletal muscle glucose uptake and methylation in adult offspring in response to voluntary maternal exercise [32, 36]. Other studies have examined the effects of maternal treadmill exercise at various intensities before and during gestation in rats. When female rats were subjected to 4 wks of submaximal exercise (55% maximal aerobic speed), their male offspring had lower fasting glucose and pancreas weight, and a smaller islet cell size compared to offspring from sedentary dams at the time of weaning (3–4 wks of age) [48]. However, at 7 months of age, male offspring from submaximally exercise-trained dams had a worsened glucose tolerance and impaired muscle insulin sensitivity compared to offspring from sedentary dams. This is in contrast to previous studies [32, 36] that determined improved glucose tolerance in adult male offspring after voluntary maternal exercise.

Controlled, low-intensity treadmill exercise for 4 wks prior to and during gestation improved skeletal muscle insulin sensitivity at 12 wks of age in the male offspring. At this time point there was no change in glucose tolerance or fasting glucose or insulin [47]. It is not clear if this increased skeletal muscle insulin sensitivity would persist as the offspring age, but it is important to note that in this case, the skeletal muscle phenotype preceded the improvement in whole-body glucose tolerance. This study also used a controlled maternal exercise (treadmill) [47] as opposed to voluntary wheel running [32, 36], which could potentially contribute to the different phenotypes observed in offspring. It is clear that the modality and intensity of the exercise are important factors in determining the offspring phenotype, but it has not been established why a more intense maternal exercise could have potentially detrimental effects in adult offspring. The effect of a more intense exercise training regiment on female offspring has also not yet been examined. More studies are needed to identify the optimal training paradigm to confer the beneficial effects of maternal exercise to offspring and to fully elucidate the mechanisms responsible for the improvement in metabolic health in response to maternal exercise, as well as to delineate the different responses in male and female offspring.

Maternal Exercise Increases Physical Activity of Offspring

An interesting question is whether maternal physical activity increases either activity or physical performance in offspring. This is a difficult question to address in humans because of the environmental factor; if the parents are physically active, it is likely that the offspring are in an active environment and continually exposed to activity. In the rodent studies discussed above, examining the effects of maternal exercise to alter offspring metabolic health, all offspring studied were maintained sedentary throughout their lifespan.

A recent study [49] used a rodent model to determine if maternal exercise increased voluntary physical activity in offspring. Female mice were given open access to a wheel cage one wk prior to gestation and throughout their gestation period. In contrast to previous

studies, there were no effects determined on offspring body weight or composition during adulthood [31–34]. At 3, 10, and 23 wks of age, offspring from sedentary and trained dams were placed in metabolic cages and activity and energy expenditure. At 10 wks of age, female offspring from exercise-trained dams had increased activity and energy expenditure compared to offspring from sedentary dams. At 43 wks of age, female offspring were given open access to a wheel cage to determine voluntary exercise over a 3 wk period of time; offspring from exercise-trained dams had a greater % body fat loss, likely due to an increased amount of exercise. This study raises several important points, particularly that minimal maternal exercise (1 wk prior to gestation and during gestation) can increase the volition of exercise on offspring. It is somewhat surprising that this effect was only observed in female offspring instead of male offspring, particularly because the metabolic phenotypes are more pronounced in the male offspring during adulthood. Determining if the amount or intensity of maternal exercise directly impacted the amount of voluntary exercise completed by the offspring will be of interest, and future studies will focus on investigating the mechanism for maternal exercise to increase voluntary exercise in adult offspring. Regardless, these data demonstrate the importance of the early environment to effect activity in offspring. If these data are translatable to humans, it will provide further support for maternal exercise to confer benefits to adult offspring and another potential mechanism for maternal exercise to protect against offspring obesity.

Maternal Exercise and Dietary Interventions

It is well established that maternal obesity and a maternal high-fat diet are major factors in the development of obesity and diabetes in offspring as they age, initiating a vicious cycle that likely contributes to the current rise in rates of obesity and diabetes [2, 11, 13, 14, 18–20, 45, 50–53]. Similarly, models of maternal under-nutrition result in offspring with increased obesity during adulthood [11] and an increased risk for development of cardiovascular disease [12] and type 2 diabetes [13–15]. Thus an essential question with regards to maternal exercise intervention is if maternal exercise can negate the detrimental effects of a maternal high-fat diet (Table 2).

Maternal Exercise Negates the Detrimental Effects of a High-Fat Diet

To determine the effects of maternal exercise on offspring metabolic health in the presence of a maternal high-fat diet, multiple studies investigated the effects of placing dams on a high-fat diet while simultaneously giving them open access to voluntary wheel running for 2–3 weeks prior to and during gestation [31, 32, 35]. All offspring were sedentary and chow-fed and studied into adulthood.

Male offspring from high-fat fed sedentary dams had marked glucose intolerance as they aged and this was completely negated in offspring from high-fat fed exercise-trained dams [32]. In fact, offspring from high-fat fed exercise trained dams had improved glucose tolerance compared to offspring from chow-fed sedentary dams at 52 weeks of age. Male offspring from high-fat fed exercise-trained dams also had lower fasting insulin, reduced body weight and % body fat, and improved insulin tolerance compared to offspring from high-fat fed sedentary dams. These data demonstrate that a maternal high-fat diet, even for a

short period of time, has a detrimental effect on offspring metabolic health. Importantly, maternal exercise can prevent these deleterious effects in adult male offspring.

Studies investigating the effects of a maternal high-fat diet and exercise in female offspring also showed a striking effect for maternal exercise to counteract the effects of a maternal high-fat diet [31, 35]. Similar to male offspring, a maternal high-fat diet impaired glucose metabolism in adult female offspring and maternal exercise reversed that effect [31, 35]. Female offspring from high-fat fed exercise-trained dams had lower fasting insulin, body weight, and % body fat compared to offspring of high-fat fed sedentary dams. Insulin tolerance was also improved in offspring from high-fat fed exercise-trained dams compared to offspring from high-fat fed sedentary dams [31].

The tissue likely contributing to the improved glucose tolerance in response to maternal exercise in the presence of a maternal high-fat diet was investigated in female offspring. Laker et al. [35] examined the role of *Pgc1α*-promoter methylation and saw that it was hypermethylated in skeletal muscle of female offspring from sedentary high-fat fed dams, but maternal exercise reduced the hypermethylation to that of offspring from chow-fed dams. Expression of genes involved in glucose metabolism were also significantly increased in skeletal muscle of offspring from high-fat fed exercise-trained dams. There was no effect of maternal exercise or high-fat diet to alter *Pgc1a* methylation in the liver or skeletal muscle of male offspring [35].

Our laboratory investigated the effects of maternal exercise in the presence of a maternal high-fat diet on liver function in female offspring. We measured glucose production in isolated hepatocytes and found that offspring from high-fat fed sedentary dams had impaired basal, insulin-suppressed and glucagon-stimulated glucose production, but offspring from high-fat fed exercise-trained dams had glucose production similar to that of offspring from chow-fed dams. Expression of hepatic genes involved in mitochondrial biogenesis, fatty acid metabolism, and Krebs cycle activity were significantly reduced in offspring from high-fat fed sedentary dams, but offspring from high-fat fed exercise-trained dams had gene expression similar to that of offspring from chow-fed sedentary dams [31]. Together these data indicate that maternal exercise negates the detrimental effects of a maternal high-fat diet in both male and female offspring. It is important to note that in the studies discussed, the maternal high-fat diet was over a relatively short time course (2–3 weeks prior to gestation). Even with this mild intervention, offspring from high-fat fed dams had significantly worsened glucose tolerance, and this effect was reversed in the presence of maternal exercise.

As stated above, these studies all examined the effects of maternal exercise that began simultaneously with the presence of a maternal high-fat diet on offspring health [31, 32, 35]. While important, a more translational approach would be to examine the effects of maternal exercise in an already obese model and determine if this could negate or reverse the detrimental effects of maternal obesity on offspring metabolic health. A recent study investigated this using a rat model; female rats were placed on a high-fat diet for 6 wks and then given open access to a running wheel where they could complete voluntary exercise and maintained a high-fat diet for 4 wks prior to conception [54]. Male offspring from high-fat

fed dams who were exercise-trained had lower circulating leptin and triglycerides and decreased fat mass at 5 wks of age compared to male offspring from high-fat fed sedentary dams. Female offspring were not investigated, and offspring were not followed later than the 5 wk time point. These data are intriguing, indicating that maternal exercise could at least partially negate the detrimental effects of maternal obesity and could have a tremendous impact on the human population if translatable. More investigation is needed to determine if maternal exercise in an already obese mother can affect offspring metabolic health into adulthood.

Maternal Exercise Abolishes the Impaired Metabolic Response to Maternal Protein-Restriction

A maternal low-protein diet is one of the most well-studied models of early growth restriction. It is associated with elevated systolic blood pressure, increased fasting insulin and impaired glucose tolerance in offspring compared to offspring from dams fed a normal diet [55]. Recent studies investigated the effects of maternal protein-restriction in the presence of exercise both before and during gestation [56–58] in rats on male offspring. Adult female Wistar rats were subjected to a controlled, moderate- to low-intensity exercise training regiment on a treadmill for 4 wks prior to gestation and maintained on the same program throughout the gestation period. After conception the dams were further subdivided into a group that received a normal protein (17% casein) diet or a low protein (8% casein) diet and remained on that diet through gestation and lactation.

Offspring from low protein fed, sedentary dams had decreased growth rates [56, 58], decreased reflex maturation [58], increased abdominal circumference, elevated fasting glucose and cholesterol, impaired glucose tolerance, and decreased plasma leptin [57] compared to offspring from normal protein fed, sedentary dams. Maternal exercise, however, attenuated the effects of a low protein diet. Offspring from low protein fed, exercise trained dams have increased growth rates [56, 58], improved reflex maturation [58], lower abdominal circumference, decreased fasting glucose and cholesterol, improved glucose tolerance [57] compared to offspring from low protein fed, sedentary dams. Maternal exercise did not completely normalize the effects of a maternal low-protein diet, but it did improve growth rates and most metabolic markers. These data indicate that maternal exercise could be a therapeutic option for disorders associated with perinatal under-nutrition [57]

Maternal Exercise vs. Maternal Under-Nutrition

To this point, there have been no studies investigating the effects of maternal exercise in an under-nutrition model or any type of dietary energy restriction. It is important to note, however, that exercise is a model of voluntary energy expenditure and results in an opposite phenotype to that of a dietary energy restriction, with improvements in glucose tolerance and adiposity. There has not been a mechanistic link established between these phenotypes, but future investigations focused on why energy restriction vs. energy expenditure result in contradicting metabolic phenotypes could be an important approach.

Maternal Exercise Prevents Obesity in Offspring Fed a High-Fat Diet

While numerous studies have examined the effects of maternal exercise to negate the detrimental effects of an impaired maternal diet on offspring metabolic health, a few recent studies have examined the effects of maternal exercise to protect or preserve the metabolic health of the offspring when the offspring are fed a high fat or high sucrose diet.

In one study, female rats were divided into a sedentary or exercise group 4 wks prior to gestation. The exercise group underwent 4 wks of low-intensity treadmill exercise and the exercise regimen continued during the gestation period [47]. After weaning, offspring were either placed on a standard chow (5.1% fat, 4.4% other sugars) diet or fed a high-fat/high-sucrose (36% fat, 16.6% sucrose) diet for 10 weeks. There was no effect of maternal exercise to effect glucose tolerance, or fasting glucose or insulin in chow fed male offspring at 12 wks of age. Maternal exercise did improve muscle insulin sensitivity in chow fed male offspring.

Offspring fed a high-fat/high-sucrose diet had increased body weight, impaired glucose tolerance, increased fasting glucose and insulin, and reduced liver glycogen compared to offspring fed a standard chow diet. Maternal exercise, however, was protective against these deleterious effects of a high-fat/high-sucrose diet. Offspring from exercise-trained dams fed a high-fat/high-sucrose diet had lower body weight, fasting glucose, and insulin, and increased liver glycogen compared to offspring from sedentary dams fed a high-fat/high-sucrose diet. Muscle insulin sensitivity was also increased in male offspring from exercise-trained dams fed a high-fat/high-sucrose diet compared to offspring from sedentary dams fed a high-fat/high-sucrose diet [47]. It is important to note that the chow diet used in this study contained only 5% fat, while most chow diets contain ~20% fat. This does not take away from the effects of maternal exercise to protect against a high-fat diet, but should be considered a low-fat diet instead of a standard chow comparison.

Other studies have examined the effects of maternal exercise during gestation [36] or during gestation and lactation [40] to protect against the offspring being overfed or fed a high-fat diet. In both cases, offspring from exercise-trained dams had an improved metabolic phenotype compared to offspring from sedentary dams when overfed [40] or fed a high-fat diet [36]. Maternal exercise improved glucose tolerance, insulin tolerance, and reduced the presence of hepatic steatosis in male offspring during adulthood when compared to offspring from sedentary dams [36, 40].

Together these data suggest that maternal exercise exerts a protective effect on offspring, even when the offspring are overfed or fed a high-fat or high-fat/high-sucrose diet. While the mechanism for this protective effect has not been established, increased muscle insulin sensitivity is likely important [47]. The length of time the offspring were overfed or fed the high-fat or high-fat/high-sucrose diet also varied in each of these studies, and only male offspring were investigated [36, 40, 47]. Future investigation will be imperative to determine how maternal exercise preserves metabolic parameters in offspring who are fed a high-fat diet, as well as to establish when during gestation maternal exercise is required, and the intensity of the maternal exercise required to maximize these benefits. In terms of human

physiology, if an ideal maximal time point and intensity of maternal exercise could be identified to confer beneficial effects to offspring to protect them from the detrimental effects of a high-fat diet, the implications on public health cannot be overstated.

Maternal Exercise and Gestational Diabetes

Gestational diabetes mellitus (GDM) is associated with both short- and long-term complications for the mother and her baby. It has been associated with disorders including hypertension, pre-eclampsia and early births, as well as an increased risk for perinatal morbidity, impaired glucose tolerance and type 2 diabetes following pregnancy [59]. Recent studies have shown that exercise interventions may provide a protective effect on maternal glycemic control, thus improving maternal and infant outcomes [28, 29, 60].

The effect of maternal exercise in women with gestational diabetes on offspring metabolic health has not been extensively investigated, likely because epidemiological studies are difficult and there is not a clear animal model to use to study gestational diabetes. One study examined the effects of maternal exercise in diabetic rats and determined a beneficial effect on metabolic health of the offspring. Rats were given streptozotocin (STZ) to induce diabetes and 14 days later subjected to 14 days of pre-gestation exercise on a treadmill or kept sedentary. Offspring from exercise-trained diabetic dams had improved glucose tolerance at 4 weeks of age compared to offspring from sedentary diabetic dams [61]. It is important to note that in this study, all offspring nursed with euglycemic foster moms and the offspring were only studied at 4 weeks of age. Regardless, maternal exercise in a diabetic dam improved glucose tolerance in offspring. More studies are needed to fully understand the effects of maternal exercise in a diabetic mother on the metabolic health of the offspring.

Concluding Remarks and Future Perspectives

The intrauterine environment during pregnancy is a critical factor in the development of type 2 diabetes and obesity in offspring. Studies in both humans and rodents have shown that maternal over-nutrition and under-nutrition result in metabolic impairments during adulthood including increased rates of obesity and type 2 diabetes [2–21]. Regular exercise is an important therapeutic tool to combat obesity and improve metabolic health in the general population, but the role of maternal exercise during pregnancy on the metabolic health of the offspring has been poorly understood and human studies have been limited. Rodent models of exercise during pregnancy have been put forth to investigate these questions and have compellingly shown that maternal exercise improves the metabolic health of adult male and female offspring [31–36, 47, 56, 57]. Importantly, and with particular translatable ramifications, maternal exercise negates the detrimental effects of an impaired maternal diet on offspring metabolic health [31, 32, 35, 56–58].

These exciting studies stress the important of maternal exercise, but leave us with several important questions. One such question to address is to determine the optimal timing of maternal exercise to confer metabolic benefits to the offspring. The studies discussed above examined offspring from maternal exercise that occurred: 1) pre-gestation; 2) during gestation; 3) both pre-gestation and during gestation; 4) pre-gestation, during gestation, and

during lactation; and 5) during gestation and during lactation. Exercise only pre-gestation did not result in any beneficial effects to the metabolic health of adult offspring. Investigating the timing of maternal exercise begins to address the question as to the mechanism of action through which maternal exercise improves offspring metabolic health. Because there is no effect of pre-gestation only exercise to affect offspring health [31, 32], it is unlikely that epigenetic changes to the oocyte are the mechanism responsible. Epigenetic changes to the placenta, however, have not been investigated. Changes in *Pgc1a* methylation in the liver [36] and skeletal muscle [35] of offspring were observed in previous studies, but other epigenetic changes in tissues have not been investigated. How these mechanistic changes occur to the offspring, and how they persist into adulthood is not clear and is an important topic of future investigation to maximize the potential therapeutic benefits of maternal exercise to improve the metabolic health of adult offspring.

In addition, another important question is to determine the intensity of maternal exercise required to confer metabolic benefits to offspring. The majority of the studies discussed above utilized either voluntary wheel cage running [31–36] or low intensity treadmill exercise [40, 47, 56–58] and observed metabolic benefits in the adult offspring. However, a study that subjected the dams to a more intense exercise protocol (55% maximal aerobic speed) prior to and during gestation resulted in impaired glucose tolerance in adult offspring even though skeletal muscle insulin sensitivity was increased in offspring at 12 wks of age [48]. The reasons for the discrepancies in these data are unclear. In all of these studies, the intensity of the exercise remained constant throughout the entire training period, regardless of whether it occurred pre-gestation, during gestation, or during lactation. In rodent studies using models of voluntary maternal exercise, the amount of exercise decreases throughout the gestation period. When using a submaximal treadmill exercise protocol, the pregnant mice were exercised at a high intensity regardless of their point during gestation; it is possible that this caused a stress to the dam that resulted in a negative phenotype during adulthood in the offspring. The submaximal exercise regiment was chosen to correspond to the intensity guidelines for exercise in pregnant women around the world, and similar to the frequency recommended in the United States and Denmark [62]. It is possible that the different exercise intensities affect placental blood flow differently thus resulting in varying offspring phenotypes. It is also possible that epigenetic changes induced by exercise differ with varying intensities of maternal exercise [63] thus affecting the phenotype of the offspring. More studies are needed to fully determine the optimal intensity of exercise, particularly in humans, to determine how maternal exercise can improve metabolic health of adult offspring.

Future studies investigating exercise interventions in pregnant women will provide insight into both the mechanism through which maternal exercise improves metabolic health in offspring, as well as to how translatable the rodent model is to humans. At least two such trials are underway, one investigating an exercise intervention in overweight and obese women prior to gestation (https://clinicaltrials.gov/ct2/show/NCT03146156) and one that will provide an exercise intervention in women who are ~12 wks pregnant (https://clinicaltrails.gov/ct2/NCT02125149). Both of these studies will investigate maternal health, body weight, and insulin sensitivity as a primary outcome, but will also include measures of the placenta (mitochondrial enzyme activity and lipid metabolism) (https://

clinicaltrials.gov/ct2/show/NCT03146156) or will track the offspring for at least the first two years of life (https://clinicaltrails.gov/ct2/NCT02125149). These investigations, as well as others, will provide greater insight into the effects of maternal exercise on offspring metabolic health in humans.

In summary, maternal exercise before and during pregnancy significantly improves the metabolic health of adult male and female offspring in rodents and offsets the detrimental effects of an impaired maternal diet (high-fat or low protein). These findings, if translatable to humans, will have critical implications for the prevention of obesity and type 2 diabetes in future generations.

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TRENDS

- Maternal exercise improves metabolic health in adult male and female offspring.
- Maternal exercise negates the detrimental effects of an impaired maternal diet on offspring metabolic health.
- Maternal exercise is required before and during pregnancy to confer maximal beneficial effects to offspring.

OUTSTANDING QUESTIONS

- Could maternal exercise negate the effects maternal obesity on offspring metabolic health?
- Does maternal exercise in mothers with gestational diabetes affect metabolic health of offspring?
- Is the improved metabolic health in offspring of exercise-trained dams a result of epigenetic changes or changes to the intrauterine environment?
- What is the mechanism through which maternal exercise confers beneficial effects to adult offspring?

Table 1

Characteristics of male and female offspring in response to maternal exercise

Directionality (i.e. reduced, improved) is compared to offspring from sedentary dams. Age of offspring is defined as adult (>6 months of age), youth (<12 weeks of age), or young (<3 weeks of age). Voluntary wheel running (VWR).

Gender	Species (strain)	Time of maternal exercise	Age of Offspring	Offspring Body Weight	Offspring Glucose Tolerance	Tissue Affected	Type and Intensity of exercise	Ref
Female	Mouse (C57BL/6)	Pre-Gestation	Adult	No change	Improves	_	VWR	[31]
Female	Mouse (C57BL/6)	During Gestation	Adult	No change	Improves	_	VWR	[31]
Female	Mouse (C57BL/6)	Pre & During Gestation	Adult	No change	Improves	Liver	VWR	[31]
Female	Mouse (ICR)	Pre & During Gestation & Lactation	Adult	No change	Improves	_	VWR	[33]
Female	Rat (Sprague Dawley)	Pre & During Gestation &Lactation	Adult	No change	Improves	Muscle	VWR	[34]
Male	Mouse (C57BL/6)	Pre-Gestation	Adult	No change	No effect	_	VWR	[32]
Male	Mouse (C57BL/6)	During Gestation	Adult	Reduced	No effect	Liver [36]	VWR	[32, 36]
Male	Mouse (C57BL/6)	Pre & During Gestation	Adult	Reduced	Improved	_	VWR	[32]
Male	Mouse (ICR)	Pre & During Gestation &Lactation	Adult	No change	Improved	Muscle	VWR	[33]
Male	Rat (Wistar)	Pre & During Gestation	Youth	No change	No effect	Muscle, Pancreas	Treadmill/Submaximal	[48]
Male	Rat (Wistar)	Pre & During Gestation	Adult	No change	Worsened	Muscle, Pancreas	Treadmill/Submaximal	[48]
Male	Rat (Wistar)	Pre & During Gestation	Adult	Reduced	No effect	Muscle	Treadmill/Moderate	[47]
Male	Rat (Wistar)	Pre & During Gestation	Adult	No change	No effect	_	Treadmill/Moderate	[57]
Male	Mouse (C57BL/6)	Pre & During Gestation	Adult	No change	No effect	Increased Activity	VWR	[49]
Female	Mouse (C57BL/6)	Pre & During Gestation	Adult	No change	No effect	Increased Activity	VWR	[49]

Table 2

Characteristics of male and female offspring in response to maternal exercise with a dietary intervention

Directionality (i.e. reduced, improved) is compared to offspring from sedentary dams. Age of offspring is defined as adult (>6 months of age), youth (<12 weeks of age), or young (<3 weeks of age). VWR=Voluntary wheel running.

Gender	Species (strain)	Time of maternal exercise	Maternal diet	Age of Offspring	Body Weight	Glucose Tolerance	Tissue Affected	Offspring diet	Type and Intensity of exercise	Ref
Female	Mouse (C57BL/6)	Pre-Gestation	High-Fat	Adult	No change	No change	_	Chow	VWR	[31]
Female	Mouse (C57BL/6)	During Gestation	High-Fat	Adult	No change	No change	_	Chow	VWR	[31]
Female	Mouse (C57BL/6)	Pre & During Gestation	High-Fat	Adult	Reduced	Improves	Muscle [35]; Liver [31]	Chow	VWR	[31, 35]
Male	Mouse (C57BL/6)	Pre-Gestation	High-Fat	Adult	No change	No change	_	Chow	VWR	[32]
Male	Mouse (C57BL/6)	During Gestation	High-Fat	Adult	No change	Improves	_	Chow	VWR	[32]
Male	Mouse (C57BL/6)	Pre & During Gestation	High-Fat	Adult	Reduced	Improves	_	Chow	VWR	[32, 35]
Male	Mouse (C57BL/6)	During Gestation	Chow	Adult	No change	Improves	Liver	High-Fat	VWR	[36]
Male	Rat (Wistar)	Pre & During Gestation	Chow	Adult	Reduced	No effect	Muscle	High-Fat/High-Sucrose	Treadmill/Moderate	[47]
Male	Rat (Wistar)	Pre & During Gestation	Low Protein	Adult	Reduced	Improves	_	Chow	Treadmill/Moderate	[57]
Male	Rats (Wistar)	Pre & During Gestation	High-Fat	Youth	No change	Improves	_	Chow	VWR	[54]
Female	Rats (Wistar)	Pre & During Gestation	High-Fat	Youth	No change	Improves	Muscle	Chow	VWR	[54]
Male	Rats (Wistar)	Gestation and Lactation	Chow	Young	Reduced	Improves	_	Over-fed	Treadmill/Moderate	[40]
Male	Rats (Wistar)	Gestation and Lactation	Chow	Youth	Reduced	Improves	_	Over-fed	Treadmill/Moderate	[40]