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Effects of Maternal and Paternal Exercise on Offspring Metabolism

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Abstract

Maternal and paternal obesity and type 2 diabetes are recognized risk factors for the development of metabolic dysfunction in offspring, even when offspring follow a healthy lifestyle. Multiple studies demonstrate that regular physical activity in mothers and fathers has striking beneficial effects on offspring health, including preventing the development of metabolic disease in rodent offspring as they age. Here we review the benefits of maternal and paternal exercise to combat the development of metabolic dysfunction in adult offspring, focusing on offspring glucose homeostasis and adaptations to metabolic tissues. We discuss recent findings on the roles of the placenta and sperm in mediating the effects of parental exercise on offspring metabolic health and discuss mechanisms hypothesized to underlie these beneficial changes. Given the worldwide epidemics of obesity and type 2 diabetes, translation of these findings to humans would provide hope that regular exercise during the reproductive years may limit the vicious cycles of increased metabolic risk being propagated across generations.

A. Introduction

In 2019 the worldwide prevalence of type 2 diabetes was estimated to be 9.3% or 463 million people, and unfortunately, this number is expected to increase to 693 million by 2045[1]. Individual health consequences aside, the currently staggering prevalence of type 2 diabetes has already placed an enormous strain on health care systems, public health, and the global economy; burdens that will undoubtedly be exacerbated if these increases in type 2 diabetes occur as predicted. Obesity is a major risk factor for type 2 diabetes, and the two diseases share many points of overlap in their causes and outcomes, as well as their treatments. Rates of obesity and type 2 diabetes increase as people age, and although these metabolic diseases are often considered preventable, in reality they are complex and arise from a combination of genetic susceptibility and environmental factors. In recent years it has

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become well established that risk patterns for both obesity and type 2 diabetes can originate as a consequence of alterations in growth and metabolism during critical windows of prenatal and early postnatal development [2]. In addition, there is emerging evidence that the father's metabolic status can affect the health of his offspring [3]. Given that rates of obesity and type 2 diabetes are increasing among women and men of child-bearing age, it is important to understand means to reduce the risk of parental transmission of metabolic disease to their offspring.

It has long been recognized that exercise has important health benefits for individuals with type 2 diabetes, and regular physical exercise can delay or prevent the onset of this disease [4,5]. While there has been extensive investigation into the physiological effects of exercise and the mechanisms of action of exercise on the individual performing the physical activity, there has been less investigation aimed at understanding the effects of parental exercise on offspring health. In this review, we will focus on research investigating the effects of maternal and paternal exercise on offspring metabolic health in adulthood, the time in life when metabolic diseases typically surface. In addition, we will review current literature aimed at understanding the mechanisms mediating offspring phenotype in response to maternal and paternal exercise. While we provide an overview of studies in human subjects, given the generational length of rodents vs human (~2 vs 80 years) [6] and the ability to obtain tissues for molecular studies, most research into the effects of maternal and paternal exercise on the metabolic health of adult offspring have been done using rodent models, and that will be our focus here. The terminology F0 (mother or father), F1 (offspring of F0), and F2 (offspring of F1 and "grand-offspring" of F0) will be used to describe the generations studied. Intergenerational effects are defined as those mediated by direct exposure during pregnancy affecting F1 and F2 offspring (maternal exposure) (Figure 1) or exposure before mating affecting F1 offspring (paternal exposure); while transgenerational effects require persistence of the phenotype, even without direct exposures, affecting F3 offspring (maternal exposure) or F2 offspring (paternal exposure) [2].

B. Maternal Nutrition and Exercise Effects on Offspring Health

Human Studies of Maternal Nutrition and Offspring Metabolism.

During pregnancy, insults to the intrauterine environment such as maternal under-nutrition, over-nutrition and obesity are significant factors that contribute to the development of obesity and type 2 diabetes in offspring [2,7]. Currently, the prevalence of obesity in pregnant women hovers around 30% in western countries, with approximately 40% of women gaining an excessive amount of weight during their pregnancy [8]. Conversely, in poorer regions of the world like South-central and Southeast Asia and Sub-Saharan Africa, the rates of low maternal weight and maternal malnutrition range between 15 and 20% [9]. Both extremes of the maternal weight spectrum present risks to the mother and are associated with a suite of complications for offspring, with potentially life-long consequences.

Human studies exploring the effects of famine during pregnancy show that individuals exposed to maternal under-nutrition in utero have decreased glucose tolerance in their adult life [10,11] and are more prone to developing obesity and diabetes [12]. The detrimental effects of maternal over-nutrition and obesity on the metabolic health of offspring have been

similarly well-established [13–17]. Maternal obesity during pregnancy in humans is associated with numerous health outcome in offspring including: increased risk of certain structural, congenital abnormalities in infants [16]; increased BMI, waist circumference and adiposity in early childhood [17]; and increased risk of developing diabetes during adulthood [15]. Thus, a poor maternal nutritional environment can impact the intrauterine milieu in a manner that results in numerous effects that are metabolic in nature and are present throughout the lifetime of the offspring.

Human Studies of Maternal Exercise and Offspring Metabolism.

The effects of exercise during pregnancy on maternal and fetal outcomes have been extensively investigated in humans, with a wealth of research showing that exercise during pregnancy is safe and beneficial to both the mother and fetus (e.g. reviews [18,19]). As shown in Table 1, which summarizes four different meta-analysis studies, both aerobic and strength training reduce the risk of excessive gestational weight gain, gestational diabetes and hypertension in mothers [18–21]. As in all human exercise studies, it should be noted that there are limitations on the accuracy of daily exercise data by self-report questionnaires, although this has been improved in recent years with wearable devices.

Given that exercise is one of the most effective and commonly recommended interventions for the treatment of conditions like obesity and diabetes, it stands to reason that exercise during pregnancy may be similarly efficacious in preventing the intergenerational inheritance of metabolic dysfunction (Figure 2). Most of the human studies investigating offspring health have focused on responses during infancy. Beginning with birth itself, maternal exercise during pregnancy is associated with increased rates of full-term delivery, normalized birth measures, and a reduced risk of macrosomia [22,23]. Maternal aerobic exercise during pregnancy can also improve newborn neurobehavioural ability [24] and contribute to improved offspring cardiac autonomic health [25]. Maternal aerobic exercise during pregnancy has been shown to improve infant capacity for movement, suggesting that children from exercised mothers may be more physically active; therefore reducing their risk of developing obesity during infancy [26].

Studies in obese women found that reduced sedentary behaviour during pregnancy decreased infant adiposity as measured by skinfold thickness [27,28]. Another report showed that moderate intensity maternal exercise during pregnancy decreased the risk of offspring developing obesity in early childhood as assessed by BMI [29]. Similarly, maternal exercise was shown to decrease adiposity in neonates at 6 months postpartum [27]. A recent study using randomized controlled trials reported that aerobic physical activity in combination with a healthy diet during pregnancy decreases subcutaneous fat in neonates 48 hours after birth [28]. In contrast to these reports, the initiation of an exercise intervention during pregnancy in otherwise sedentary women resulted in offspring with increased total body fat compared to controls [30]. The reason for this discrepancy is not clear, although the authors stated that larger studies are needed to investigate the timing of exercise during pregnancy and that there should be follow-up into adolescence, which will better predict the risk of obesity in adulthood [30]. This is an important point, as the onset of type 2 diabetes and other metabolic diseases typically occur in adulthood. The effects of maternal exercise on the

metabolic health of adult offspring have not been studied in humans; understandable as the long human generation times make it is difficult to carry out randomized controlled trials investigating effects of maternal exercise across the entirety of the F1 lifespan. Therefore, rodent models, which have a much shorter generation timeline, have been used to investigate the effects of maternal environment on offspring metabolic health in adulthood.

Rodent Studies of Maternal Nutrition and Offspring Health.

Similar to human studies [13–15], the detrimental effects of maternal under-nutrition, over-nutrition and obesity on the metabolic health of offspring has been well-established in animal studies [31–36]. Under-nutrition in ICR mice during pregnancy has been shown to increase adiposity [35] and cause severe glucose intolerance [36] in F1 offspring. In studies using Sprague-Dawley rats and C57BL6 mice, maternal over-nutrition increased weight gain and adiposity [31,37], induced hyperlipidaemia, and resulted in impaired glucose tolerance in F1 offspring during adolescence [31], with similar metabolic impairments extending through adulthood [33,34,38]. The mechanisms responsible for altering offspring phenotypes as a result of these nutritional maternal-fetal exposures is not fully understood, but changes in the intrauterine milieu resulting from altered maternal nutrition can have direct effects on fetal tissues, which can alter the metabolic phenotypes seen in offspring at later stages of life. As examples, studies in C57BL/6 mice, Sprague-Dawley rats, and Wistar rats have shown that maternal high-fat feeding resulted in adult offspring with altered pancreatic function [39], increased adiposity [33,40–42] and decreased glucose tolerance [33,34,41].

Mechanisms altering offspring phenotype may also occur through gene-environment interactions leading to epigenetic changes. Epigenetics is defined as heritable changes in gene activity that do not involve changes in the DNA sequence. DNA methylation, histone modification, and non-coding RNAs are typical examples that can regulate gene expression. Various types of exogenous exposures during the prenatal development can influence epigenetic modifications [7,43,44]. Maternal over-nutrition and obesity are well-recognized to influence epigenetic patterns by altering the activity of enzymes or varying epigenetic substrate availability that are involved in the addition or removal of epigenetic marks through the oocyte development or intrauterine environment. Typically, maternal over-nutrition increases the level of DNA methylation at the promoter, resulting in decreased expression of target genes in offspring tissue. For example, maternal high-fat diet during pregnancy increased the level of methylation at the promoter of insulin receptor substrate 2 (Irs2) in C57BL/6 offspring livers, which in turn led to insulin resistance in the adult offspring[45]. Thus, epigenetic modifications are proposed to be an underlying molecular mechanism for developmental programming of metabolic dysfunction of offspring later in life [7]. Therefore, this intergenerational inheritance is likely playing a causal role in the increasing global rates of obesity and diabetes, resulting in a vicious cycle of metabolic disease being propagated across generations.

Maternal Exercise Improves Glucose Homeostasis in Rodent Offspring.

As stated above, the onset of type 2 diabetes and other metabolic diseases typically occur in adulthood, so studies designed to capture the full extent of maternal exercise's effects on offspring health have largely utilized rodent models. As a result of these rodent studies, over

the past decade there has been a significant increase in our understanding of how maternal exercise affects adult offspring metabolic health (Table 2, Figure 3). Treadmill running is one of the two major modes of exercise training that has been used for studies of parental exercise in rodents. Treadmill running has the distinct advantage of controlling the amounts and intensity of exercise but the disadvantage of putting stress on the mothers during the pregnancy. Although it is well-established that treadmill exercise in non-pregnant rodents has many benefits on metabolic health, treadmill exercise can produce high levels of corticosterone and noradrenaline in the kidney and liver, result in modifications of the peripheral clock [46], and cause anxious behaviour [47]. Voluntary wheel running (VWR) is the other mode, which has been used by many groups including all of our maternal exercise studies. With VWR exercise, rodents run voluntarily and at higher levels during their dark active phase, presumably causing little or no stress to the animals. Rodents, including pregnant females will typically perform high levels of exercise daily [33,34,48,49], although running distances will significantly decrease at the later stages of pregnancy. While the intensity and time on the wheel cannot always be controlled or recorded with VWR, there are now systems that can precisely measure these parameters. Braking of the wheels can be used to match volume of exercise, allowing for more control of exercise performed.

Our group and several other laboratories have shown that maternal exercise during pregnancy has profound effects on the metabolic health of F1 male and female offspring (Table 2 and Figure 4) [33,34,37,41,50–52]. Our study of C57BL6 mice reveals that the maximal benefits of maternal exercise on offspring metabolism occur when dams train both preconception and during gestation [33]. Notably, the majority of the effects of maternal exercise on offspring metabolic health are not observed in very young animals, but are present in adult offspring of C57BL6 mice, ICR mice and Sprague-Dawley rats [33,34,50,51]. With respect to glucose homeostasis, the beneficial effects of maternal VWR has included improved glucose tolerance in adult male [33,50] and female [34,50,51] offspring, increased insulin sensitivity in adult male [50] and female [50,51] offspring, and decreased insulin concentrations in male [33,37] and female [34] adult offspring, effects that occurred in both C57BL/6 mice and Sprague-Dawley rats. While these studies have consistently reported improved glucose homeostasis with maternal exercise using VWR, one report using Wistar rats came to a different conclusion (Table 2) [53]. When mothers performed submaximal treadmill exercise for 4 weeks preconception and during the first 18 days of gestation there was improved glucose tolerance and insulin secretory capacity in the F1 offspring at weaning (3–4 wks of age), whereas the reverse was the case in the adult offspring [53]. The reason for the conflicting results is not entirely clear but may be due to species and strain of animals studied, timing of maternal exercise, and/or mode of exercise.

Some studies of maternal exercise suggest that male offspring have a greater improvement in glucose tolerance in response to maternal exercise. For example, we found that while male offspring of exercise trained mothers fed both a chow and high-fat diet had improved glucose tolerance, female offspring only had improved glucose tolerance when the trained mothers where fed a high-fat diet [34]. We speculate that the lack of an exercise effect in the female offspring from chow-fed mothers was because in contrast to male offspring, there was no deterioration in glucose tolerance in female offspring as they aged. In fact, in offspring from sedentary chow-fed mothers, glucose area under the curve was 40% lower in

females compared with male siblings at 52 weeks of age. Thus, females are more glucose tolerant compared with males; therefore, the more minimal effects of maternal exercise on females may be a function of lower glycaemia at baseline.

As discussed above, when sedentary mothers were fed a high-fat diet during pregnancy, both male and female adult offspring had poor metabolic outcomes, most commonly reported as glucose intolerance [32,54–56]. When high-fat diet-fed mothers simultaneously performed VWR or treadmill exercise, their offspring had dramatically improved glucose tolerance compared to offspring from sedentary control mothers, despite the otherwise-detrimental effects of a maternal high-fat feeding [33,34,37,38,41,56]. In addition to improved glucose tolerance, maternal exercise in chow-fed mothers decreased fasting insulin concentrations in adult offspring, an effect that was even greater in the offspring of mothers who had been fed a high-fat diet [33,34,37,56]. In a study that explored the effects of maternal exercise in Sprague-Dawley rats that were mated with high-fat-fed males, maternal treadmill exercise attenuated skeletal muscle insulin resistance and the decrease in pancreatic beta cell mass and insulin secretion observed in the female offspring of obese fathers [57]. Taken together, these studies show that maternal exercise has the ability to improve the metabolic health of adult offspring, and importantly, that maternal exercise can prevent the detrimental effects that parental high-fat diets have on offspring health.

Mechanisms of Maternal Exercise Effects on Offspring Metabolism.

The mechanisms underlying for the beneficial effects of maternal exercise on offspring metabolism are only beginning to be elucidated, but we hypothesize that there are many factors involved. It is important to note that the effects of exercise training in pregnant mothers on the mothers themselves has not been extensively investigated, but studying C57/BL6 mice, we have reported normal training adaptations to the mother as shown by increased GLUT4 and hexokinase protein expression in skeletal muscle, traditional markers of training adaptations [33]. In contrast, there were no changes in maternal glucose tolerance [33] or maternal body weights [33,37,50,52,53,56] in comparing sedentary and exercise trained pregnant mothers in a number of studies, suggesting the maternal glycaemia and body weight are not a mechanism for changes in offspring phenotype. Litter size, which can affect offspring phenotype, has not been shown to be altered by maternal exercise in most studies [33,41,42,50,52,53,58]. In this section, we will discuss other potential mechanisms that may mediate the effects of maternal exercise on offspring metabolism.

Offspring Body Weight and Body Composition.

Body weight is an important factor in regulating glucose tolerance, insulin sensitivity, and overall metabolic health and numerous studies have investigated the effects of maternal exercise on offspring body weight in rodents from the neonatal period to adulthood. In neonates, several studies report that maternal exercise has no effect on litter weight [41,52] or pup body weight [38,50,53]; however, two papers report decreased pup body weight [37,42] and one paper reports increased pup body weight [59]. Given these conflicting findings, it difficult to determine if neonatal body weight is important contributor to the improved metabolic phenotype of offspring in adulthood.

Studies investigating mice and rats during weaning, young adulthood or adulthood have shown that maternal exercise either decreases or does not change offspring body weight (Table 2). Our group found that maternal VWR exercise decreased male offspring body weight, but these effects were not observed until the offspring were 52 weeks of age [33]. These decreases associated with maternal exercise were observed in offspring from both chow- and high-fat-fed mothers, but were more pronounced in the offspring from mothers that were fed a high-fat diet[33]. Among female offspring, maternal exercise decreased offspring body weights only beginning at 52 weeks of age, and only under conditions where the mothers were fed a high-fat diet in combination with exercise [34]. However, 52 week old offspring from exercise-trained mothers that were fed both chow- or high-fat diet-fed had decreased fat mass as measured by DEXA [34]. In adult male offspring, but not in female offspring, maternal VWR exercise in ICR mice increased lean mass and decreased fat mass as measured by NMR [50]. Maternal exercise in Sprague-Dawley rats also resulted in lower fat mass in male, but not female adult offspring [52]. A study in Long-Evans rats investigating only male offspring showed that maternal VWR exercise during pregnancy decreased offspring body weights starting at weaning and persisting during adult life [60]. The effects of maternal exercise on offspring health are also apparent when the offspring themselves are challenged with dietary manipulations, as maternal treadmill running exercise in Wistar rats decreased weight gain and limited fat mass gain in 3-month-old offspring fed a high-fat, high-sucrose diet [42]. Taken together, the majority of studies suggest that maternal exercise training decreases offspring body weights, especially as they age, and that these effects may be more pronounced in male offspring. The reason for a sex-specific effect of maternal exercise is not known but may be due to a greater weight gain in males with ageing. While a reduction in body weight and fat mass may be one of the mechanisms through which maternal exercise improves glucose tolerance in offspring, it should be noted that in our work we found that the improved glucose tolerance in the offspring of trained dams preceded lower body weights, suggesting that at least some metabolic changes in offspring occur independent of changes in body weight [33].

Adaptations to Offspring Tissue.

To understand the mechanisms for the profound effects of maternal exercise on offspring glucose tolerance and metabolic health, numerous metabolic tissues have been investigated, primarily using rodent models. Skeletal muscle is critical for glucose homeostasis, since this tissue is responsible for the majority of glucose disposal in response to a glucose load [61]. We measured glucose uptake in numerous offspring skeletal muscles (tibialis anterior, gastrocnemius, soleus, extensor digitorum longus), but surprisingly found no effect of maternal VWR exercise on glucose uptake in any of these offspring muscles [33]. In contrast, another group investigating Sprague-Dawley rats found that maternal VWR increased glucose uptake in extensor digitorum longus and gastrocnemius muscles in adult offspring [51]. The difference in results between these studies could be due to the animal models; our lab used mice while the other study was based on rats. Another important difference is the way each study handled paternal treatment; our lab locked running wheels during breeding whereas in the other study sires had access to running wheel for 10 days during breeding. This paternal exercise may be affecting the offspring metabolic health, as has been previously reported [49]. Using ICR mice and in vivo measurements, maternal VWR exercise

increased insulin-stimulated glucose uptake in both soleus and adipose tissues in adult female offspring [50]. In C57BL/6 mice, maternal VWR exercise prevented maternal high-fat diet-induced hypermethylation of the PGC-1a promoter in offspring skeletal muscle [38]. This maternal exercise-induced alteration in methylation status was associated with a decrease in Pgc1a expression and some of its target genes (Glut4, Cox4 and Cyt c), which could contribute to the amelioration of age-associated metabolic dysfunction observed in adult offspring [38]. In future studies, it will be important to directly determine how maternal exercise may induce epigenetic alterations in skeletal muscle and how such changes could have downstream implications for offspring physiological functioning.

Because the liver is a major regulator of whole-body glucose homeostasis, we explored the effects of maternal VWR exercise on offspring liver [34]. Maternal exercise reversed the detrimental effects of a maternal high-fat diet on liver function, decreasing glucose production in hepatocytes from offspring and increasing expression of genes involved in mitochondrial biogenesis, Krebs cycle, and fatty acid metabolism in the offspring liver [34]. In addition, other researchers have shown that maternal VWR exercise during pregnancy protects male adult offspring against hepatic steatosis that otherwise develops when the offspring were fed a high-fat diet in Sprague-Dawley rats [52].

Similar to the liver, maternal high-fat diet during pregnancy has been shown to have detrimental effects on the pancreas of F1 offspring including increased beta cell mass, replication and neogenesis in Swiss mice [62]. We found that maternal VWR exercise prevented some of the negative effects that maternal high-fat diet has on the offspring pancreas [49]. Another important metabolic tissue is brown adipose tissue (BAT), and maternal treadmill exercise during pregnancy in C57BL/6 mice was shown to improve brown adipose tissue (BAT) and beige adipose function in offspring, decreasing the development of high-fat diet-induced obesity and metabolic dysfunction [58]. Given that in both rodents and humans BAT contributes to energy expenditure and may function to counteract weight gain [63], this may prove to be another beneficial effect of maternal exercise on offspring metabolic health.

In addition to tissues directly implicated in glucose metabolism, other tissues have been reported to be regulated by maternal exercise. Maternal exercise by treadmill running in C57BL/6 mice prevented cardiac hypertrophy and dysfunction in offspring from obese mothers[64] and maternal VWR exercise resulted in lower incidence of congenital heart defects in the offspring from mothers with pre-gestational diabetes [65]. Maternal VWR was also shown to provide protection from neurodegeneration in adult offspring [66].

Taken together, these studies demonstrate that maternal exercise affects multiple tissues in offspring, and it is likely that additional offspring tissues are directly affected by maternal exercise, an important area for future research. Many of the tissues studied thus far (e.g. muscle, liver, pancreas) are highly metabolically active, and while there are few published mechanisms describing the specifics of these effects, alterations to these offspring tissues caused by maternal exercise during pregnancy are likely contributing to the overall improvements in offspring metabolic health.

Placental Responses to Maternal Exercise.

Metabolic phenotypes of offspring are modified by maternal environmental factors including nutritional state, oxygen availability, stress, and endocrinological adaptations [67]. The placenta is the central organ connecting the developing fetus to the maternal environment and thus is responsible for conferring the effects of external stimuli and the maternal condition to offspring. The anatomical components of the placenta are the basis for its physiological roles in embryonic offspring maintenance. For instance, its size and vascular nature are necessary for the effective removal of fetal waste and the transmission of hormones, nutrients and oxygen to developing offspring [67]. Collection of the post-partum placenta has allowed for the study of placental responses to maternal exercise in human subjects [68]. In a study of weight bearing aerobic exercise, mid-trimester placental growth rate was faster and morphometric indexes of placental function were greater in exercise trained pregnant women, indicating that maternal exercise is associated with a balanced increase in fetoplacental growth, decreasing risk of having low-birth-weight outcomes [69]. Exercise during pregnancy not only effects placental architecture but also placental gene expression that is essential for adequate nutrient delivery to the fetus and optimal fetoplacental growth. Studies of aerobic exercise during pregnancy [70] and women that were highly active during pregnancy [71,72] revealed that exercise alters the expression of numerous genes including endothelial nitric oxide synthase (eNOS) [70], sodium-coupled neutral amino acid transporter 2 (SNAT2) [71], and fatty acid transport protein 4 (FATP4) [71,72]. Although there are experimental limitations, these results suggest that placenta is an organ that can respond to exercise and physical activity during pregnancy, and that exercise interventions can be utilized as means to reduce the risk of developmental disturbances.

Rodent studies have provided important insight into the multiple roles of the placenta with maternal exercise under both normal and high-fat diet conditions. Maternal high-fat diet can disturb the physiological characteristics of the placenta, including placental size, thickness and cell population makeup [73,74] whereas a recent study reported that maternal exercise may provide a moderating environmental factor which protects against the harmful effects of maternal high-fat diet on placental morphology [75]. Placental efficiency, as determined by fetal weight divided by the weight of placenta, was decreased by maternal high-fat diet, but this effect was reversed by treadmill exercise training in C57BL/6 mice. Anatomically, maternal high-fat diet decreased labyrinth thickness and increased decidua and junctional zone thickness, effects that were normalized by maternal exercise [75]. The expression of placental growth-related genes including insulin growth factor 1 (IGF-1) [76], IGF1 receptor [76], fibroblast growth factor2 (FGF2) [75], FGF2 receptor [75], neurotrophin-4 (NT-4) [77], and placental growth factor (PGF) [78] were increased in the placenta of treadmill exercised trained C57BL/6 mice [75], treadmill trained Wistar rats [76,78] and VWR exercised Wistar rats [77]. The expression of placental vascularization-related genes, including Apelin, vascular endothelial factor (VEGF), VEGF receptor 1 and hypoxia inducible factor 1-α (HIF1-α), decreased as a result of maternal high-fat diet, but were recovered by maternal exercise [75,78]. Collectively, the data demonstrates that maternal exercise may stabilize morphometrical changes in the placenta that result from a maternal high-fat diet, preventing disturbances to placental function.

Nutritionally regulated genes, including amino acid transporters and genes involved in fatty acid metabolism, are important for developmental processes in offspring [79,80]. Maternal high-fat diet decreased the expression of solute carrier family 38 member 1 (Slc38a1), which uptakes glutamine, and Slc38a2, which transports neutral amino acid, effects that were reversed by exercise training [75]. Conversely, the expression of lipoprotein lipase (Lpl), Cd36 (fatty acid transporter), glucose transporter 3 (Glut3) and leptin receptor B (Leprb) were increased by maternal high-fat diet, but were normalized by maternal treadmill exercise in C57BL/6 mice, Wistar rats, and Sprague-Dawley rats [75,81,82]. In accordance with this expression pattern, maternal treadmill exercise prevented excess placental lipid deposition and hypoxia in C57BL/6 mice [56]. Maternal high-fat diet pathogenically increased the placental expression of inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukine-1β (IL-1β), whereas maternal exercise reduced their levels. On the other hand, the level of IL-6 increased in the placenta from trained dams [75], suggesting that maternal exercise not only down-regulates the negative effects of maternal high-fat diet on placental homeostasis, but also up-regulates placental secretion of cytokines, reinforcing its role in the endocrine system.

Several rodent studies reported that maternal exercise affects several signalling pathways in placenta that are known to regulate growth and metabolic processes. Exercise during pregnancy reversed the high-fat diet-induced down-regulation of 5’ adenosine monophosphate-activated protein kinase (AMPK), Akt, extracellular signal-regulated kinase (ERK), and insulin receptor substrate 1 (IRS1) [75], which may be related to the protective effect of maternal exercise on maternal high-fat diet-induced placental dysfunction. Moreover, exercise during pregnancy induced the phosphorylation of numerous proteins involved in transcriptional regulation including 4E-binding protein 1 (4E-BP1), ribosomal protein S6 (rpS6), and mammalian target of rapamycin (mTOR), and the dephosphorylation of signal transducer and activator of transcription 3 (STAT3) [75,81,82]. These reports suggest that exercise could play a broad role in placental function through direct regulation of placental signalling mechanisms. Exercise-induced circulating factors, including hormones, cytokines and metabolites, might act as the exercise-mediated molecules involved in placental signal transduction that ultimately contribute to the alterations in placental morphology and function that are observed with exercise.

Collectively, the results of these studies suggest that the placenta is an exercise-sensitive organ that changes its physiological functioning in response to alterations in the maternal environment. These physiological and morphological changes are the basis for the dynamic and communicatory role of the placenta and enable the placenta to transmit maternal information to offspring. These studies also demonstrate that maternal exercise counteracts the harmful effects of maternal high-fat diet on offspring metabolic health by normalizing the alterations to placental morphology, gene expression and signal transduction that are otherwise seen in maternal high-fat diet conditions. Further study is needed to determine the mechanism(s) behind the regulatory role of maternal exercise in placental function and offspring phenotypes.

Other Putative Mediators of Offspring Metabolic Health.

Recently, other factors that may explain the mechanisms of transmission through which maternal exercise affects offspring health have been proposed. Oligosaccharide 3'-sialyllactose (3'-SL) in mothers' milk has been reported to be an important mediator of health in C57BL/6 mouse offspring and we have investigated the role of 3'-SL in responses to maternal exercise [83]. Maternal exercise in global 3'-SL knockout mice (3'-SL−/−) failed to improve glucose metabolic health and cardiac function of offspring, whereas cross-fostering of offspring from trained 3'-SL−/− to trained wild type dams partially restored the benefits of maternal exercise. The supplementation of 3'-SL during the nursing period also improved hepatic and cardiac gene expression in offspring. Although the mechanisms by which maternal exercise changes the composition of milk and how 3'-SL improves offspring metabolism are not known, the effects of maternal exercise on lactation is a potentially consequential topic that should be expanded upon and may ultimately be translated to humans. Another group recently reported that maternal treadmill exercise enhanced brown adipogenesis in C57BL/6 mouse offspring through Apelin, an exercise-induced adipo-myokine [58]. Maternal exercise was proposed to increase the level of maternal circulating Apelin, inducing placental hypoxia, which then activated the placental secretion of Apelin. DNA demethylation at the promoter of PR domain containing 16 (Prdm16), a central regulator of browning, was induced by placental Apelin and enhanced brown adipogenesis in offspring. This study of the apelinergic system further highlights the involvement of the placenta as a potential transmitter of the effects of maternal exercise to offspring during prenatal development.

Epigenetic Changes.

Epigenetic alterations such as DNA methylation, histone modifications, and microRNAs regulations during embryological development have been proposed to impact offspring metabolic health [84]. Maternal obesity is widely recognized as a detrimental factor that disturbs the normal epigenetic landscape in offspring [7]. Since maternal exercise commonly counteracts the unfavourable effects of maternal obesity on offspring health, the benefits of maternal exercise may be attributed to the stabilization of offspring epigenetic status during development. Maternal VWR exercise prevented maternal high-fat diet-induced hypermethylation at the promoter of Pgc-1α in skeletal muscle of C57BL/6 mouse offspring [38]. In another study, exercise-induced placental Apelin activated the enzymatic activity of ten-eleven translocation (Tet) to convert 5-methylcytosine to 5-hydroxymethylcytosine of Prdm16 [58]. Maternal obesity-induced changes in DNA methylation levels are related to histone posttranslational modifications in Wistar rats [85], suggesting that the normalizing effects of maternal exercise on offspring epigenetics are likely to be even broader. Recent advances in the application of omics technology for the systematic characterization of gene expression and histone modifications have great potential for elucidation of a comprehensive mechanism describing the benefits of maternal exercise on offspring metabolism.

C. Paternal Nutrition and Exercise Effects on Offspring Health

While most research has focused on the role of the mother on offspring health, there is now strong evidence that fathers play an important role in the metabolic programming of

offspring and that the paternal lineage is responsible for more than just its genetically encoded information [86–90] (Figure 2). In adult men, obesity can impair sperm number and motility [91–93] and decrease live birth rates [91,94]. Since offspring development *in utero* occurs without the physical presence of the father, the effects of paternal diet are likely transmitted to offspring through the sperm [95–97]. Thus, paternal lineage can transmit disease risk to the offspring, and strategies to interrupt this intergenerational disease transmission, such as physical activity, my help to stop this harmful cycle [98].

In some rodent models, altered-metabolic phenotypes resulting from paternal diet have been observed in offspring generated via *in vitro* fertilization, confirming that the relevant dietary information is present in sperm [99–101]. Impaired paternal nutrition, either by a high-fat diet or a low protein diet, has similar effects of sperm health parameters [94] and negatively affected embryo metabolism [102,103], fetal growth [102], and the cardiovascular [104] and metabolic health of offspring [87,88]. Compared to maternal exercise, there have been relatively few studies investigating the effects of paternal exercise training on offspring metabolic health in rodents (Table 2 and Figure 4). In C57BL/6 mice fed a high-fat diet, 9 weeks of paternal exercise by swim training improved glucose metabolism in 16 week-old male [105] and female [106] offspring. Male offspring were further investigated and showed that paternal exercise in high-fat-fed males resulted in offspring with reduced total adiposity, decreased plasma free fatty acids, increased muscle mass and improved pancreatic function [105]. Our group found that high-fat feeding of C57BL/6 for 3 weeks prior to breeding impaired glucose tolerance and increased body fat mass in both male and female adult offspring. We found that paternal VWR exercise attenuated these detrimental effects of paternal high-fat diet on offspring metabolism by improving glucose tolerance, decreasing body fat and increasing glucose uptake in skeletal muscles of adult male and female offspring [49,107]. Counter to this, a study focusing on longer duration paternal VWR exercise training had detrimental effects on energy expenditure and whole-body and skeletal muscle glucose metabolism in offspring [108]. The reason for the difference between this study and the others [49,105–107] is not known, but could be due to higher volume of paternal exercise performed [108]. Nevertheless, though the literature is still sparse and occasionally conflicting, there is a growing body of evidence showing that paternal diet and exercise play a concerted role in defining offspring metabolic phenotypes.

Potential Mechanisms for Paternal Exercise Impacts on Offspring Health.

Both paternal diet and exercise have been identified as factors that affect morphological, physiological, and epigenetic aspects of semen and subsequently offspring metabolic health, but the mechanisms that underlie this intergenerational inheritance are currently ambiguous, as are the specific effects of these factors on offspring outcomes. Published literature points to sperm physiology, epigenetically active molecules contained in sperm, and/or the sperm epigenome as the basis for the mechanism by which the paternal exercise influences offspring health.

Sperm Physiology.—Specific aspects of sperm morphology are necessary for its unique role as a mobile reproductive cell. Human studies have shown that abnormalities in semen morphological parameters, such as sperm concentration, vitality, and motility have been

linked to paternal factors such as age, BMI, and diet [93,98,109–111]. Some human studies have demonstrated negative correlations between BMI and male reproductive potential [112–114] and paternal obesity has been shown to reduce sperm motility [107] and mitochondrial activity [115], and increase intra-sperm reactive oxygen species and sperm DNA damage [91,116].

Rodent models have been extensively used to investigate mechanisms for modifications of sperm in response to diet-induced obesity and exercise. In mice, paternal high-fat diet decreased sperm functionality during fertilization [91], reduced blastocyst development and implantation [117], and smaller litter sizes [107]. While these findings are not shared by all studies investigating paternal high-fat diet [118], paternal diet has consistently been shown to affect sperm physiology, with concomitant alterations to offspring metabolic health [86,100,119] that can be seen in multiple offspring generations [120,121]. These alterations to sperm as a result of paternal high-fat diet and their associated consequences on offspring metabolic health are not immutable, as paternal exercise interventions have been shown to reduce or reverse many of the alterations to sperm and offspring that otherwise result from paternal high-fat diet. In sires fed a high-fat diet, 8 weeks of swim training increased sperm motility, improved sperm tail morphology, improved markers of oxidative stress, reduced sperm DNA damage, and increased sperm capacitation [122]. In our study where paternal VWR exercise training fully counteracted the deleterious effects of paternal high-fat diet on offspring metabolism [107], paternal VWR exercise did not affect total sperm number or reverse the effects of high-fat diet on litter size. However, similar to the study of paternal swim exercise described above, we found that VWR reversed the high-fat diet-induced reduction of sperm motility [107].

Micro RNAs (miRNAs).—Multiple classes of sperm small non-coding RNAs (sncRNAs) can be altered by the paternal environment and subsequently impact offspring metabolic health [123–126]. Microinjection studies have confirmed that these sncRNAs present in sperm are indeed capable of transferring aspects of paternally acquired phenotypes to the next generation [94,100,124,125]. Micro RNAs (miRNAs) are one class of endogenous sncRNAs that play a role in post-transcriptional gene expression by interacting with specific mRNAs through complementary base pairing [127]. miRNAs in sperm function as vectors for the epigenetic programming of offspring by directly modifying sperm before fertilization or by acting as modifiers of the postfertilization processes [128]. Studies investigating the combined impact of paternal diet and exercise have shown some level of overlap in the species of miRNA that are altered by both types of paternal exposures, positing them as a potential mechanism through which paternal metabolic phenotypes can be transmitted to offspring. Paternal diet and exercise interventions have been shown to restore some classes of miRNAs altered by paternal high-fat diet, but which specific RNAs were normalized depended on the paternal intervention modality [106,108]. Our group has also shown that the paternal environment can alter the RNA payload of sperm, evident in changes to a large number of small RNAs [107]. However, between these studies, the effects of paternal diet or exercise on the miRNA profiles in sperm did not completely overlap, potentially as a result of the differences in study protocols. Only changes in miR-465a3p and miR-21 were found to be congruent between studies, suggesting they may be robust regulators that can bridge the interaction of diet and exercise in sperm. Further assessment of the predicted mRNA targets

of the sperm miRNAs that are changed by paternal diet and exercise is needed to explain the involvement of paternal miRNAs in offspring developmental programs and metabolic function.

Transfer RNA-Derived Small RNAs (tsRNAs).—tsRNAs are largely made up of two classes of tRNA fragments: tRNA halves (tiRNAs) and tRNA-derived fragments (tRFs). These molecules are derived from mature tRNAs or precursor tRNAs and are regulatory non-coding RNAs involved in gene expression and post-transcriptional regulation[129]. Paternal dietary manipulations have been shown to cause rapid change in tsRNA populations in human sperm [130], and paternal high-fat diet [86] and paternal exercise [131] have been shown to alter a number of tsRNAs in rodent sperm. We found that paternal high-fat diet increased the abundance of several tsRNAs in sperm, while paternal VWR exercise suppressed the increased tsRNAs that was observed in sedentary high-fat diet-fed sires, leaving the tRF profile similar to that of the sedentary chow-fed fathers [107]. Relatedly, we found that exercise training in the chow-fed fathers significantly reduced multiple classes of tsRNAs compared to sedentary controls. The highly abundant fragments tRF-Gly-GCC, tRF-Gly-CCC, and tRF-His-GTG were prominent examples of diet-induced RNAs that were suppressed to baseline levels by exercise training. One interesting tRF is tRF-Gly-GCC, which was upregulated in the sperm of F1 mice generated from Avy/a obese prediabetic sires and was associated with a latent phenotype of metabolic dysfunction in F2 mice [120]. However, another group reported that tRF-GCC and tRF-Gly-CCC was significantly increased in sperm by paternal exercise using wheel cage [131]. At present, current studies provide a persuasive, though sparse, description of the role that tsRNAs play in paternal-mediated intergenerational inheritance.

DNA Methylation.

Though most genomic DNA is demethylated during gametogenesis and embryo preimplantation, some regions escape this process, suggesting differential methylation resulting from paternal environmental exposures can occur in the regulatory regions of paternally imprinted [132,133] and nonimprinted [134] genes, potentially impacting metabolic phenotypes of offspring. Additionally, miRNAs present in sperm can also target enzymes involved in the DNA methylation/ demethylation cycle, leading to *de novo* DNA methylation that may alter embryonic development [121,135,136]. Although studies are limited, paternal exercise has been shown to alter the global methylome in human [137] and animal sperm [106,108]. DNA methylation at the promoter region, which directly represses mRNA expression, was changed in a variety of metabolic genes associated with insulin signalling pathway and the insulin sensitivity of muscle and adipose tissues, as well as in an imprinted gene involved in body weight regulation [108]. While these data are far from conclusive, they do support the hypothesis that the paternal environmental exposures, such as physical exercise, can influence the sperm methylome and ultimately influence offspring phenotypes.

Perspective of Paternal Epigenetic Mechanisms.

While the precise mechanism of action remains unclear and the conclusions made by different groups lack consensus, recent studies indicate that miRNAs, tsRNAs and DNA methylation in sperm respond to paternal exercise and have the potential to define the

trajectory of offspring metabolic health. Additionally, other epigenetically active aspects of semen, including long non-coding RNAs (lncRNAs), RNA methylation (m^6A), and alterations to the protein or exosome profile of seminal plasma have been shown to change as a result of the paternal environment. While there are currently no studies relating these changes in semen to paternal exercise, to varying degrees they have been shown to contribute to offspring programming as a result of other types of paternal exposures [94]. Similarly, the positive and/or negative impacts of paternal exercise on offspring metabolic phenotypes remains unclear, as do the effects of paternal exercise on non-metabolic offspring processes. Continued investigations into the role of each mechanism, as well as the broader contribution of paternal exercise to holistic offspring health will be needed before we can define a comprehensive paradigm through which paternal exercise influences future generations.

D. Future Directions and Clinical Translation

Current research, primarily based on studies rodent models, clearly demonstrate that maternal and paternal exercise have important effects on the metabolic health of offspring (Figure 5). There are many critical areas for future investigation using animal-based models. Given emerging data demonstrating that maternal environment effects F2 offspring, it will be of great value to determine the effects of maternal exercise on this generation. Further studies are also needed before we can comprehensively describe the central mechanisms that regulate the beneficial effects of parental exercise on offspring health. For example, it is essential that future research take a holistic approach to analysing epigenetic states like DNA methylation, histone modification, and non-coding RNAs that influence gametes and zygotes from trained parents. The placental-fetal system is another hot spot for offspring developmental programming as it plays an enormous role during the critical windows of prenatal offspring development. Identifying the mediating factors and signalling pathways that connect exercise stimuli to these phenotypic and developmental outcomes is essential for human translation; and given the ever-expanding issues of global obesity, these issues will only become more relevant in the future.

Moving forward, one of the largest hurdles in research on the effects of parental exercise will be the application of knowledge gained from rodent studies to human interventions. As is evident by this review, the role of parental exercise on offspring and grand-offspring health is multi-faceted and complex. However, with the goal of eventually addressing the worldwide obesity and type 2 diabetes epidemics in mind, considerations for the relationship between rodent models and human applications need to be built into the research. The differences intrinsic to rodent and human physiology present another set of obstacles in analogizing human and animal research; however, common serum proteins or metabolites that have been identified in both pregnant rodents and humans could be utilized as predictive factors to evaluate the effects of exercise. The gestational period provides a unique opportunity to promote positive health behaviours that can have both short- and long-term benefits for the mother and child. Based on current research findings and future studies, the employment of parental physical activity may become a primary means for combating the ever-growing issues of obesity and type 2 diabetes that currently threaten the health of our future generations.

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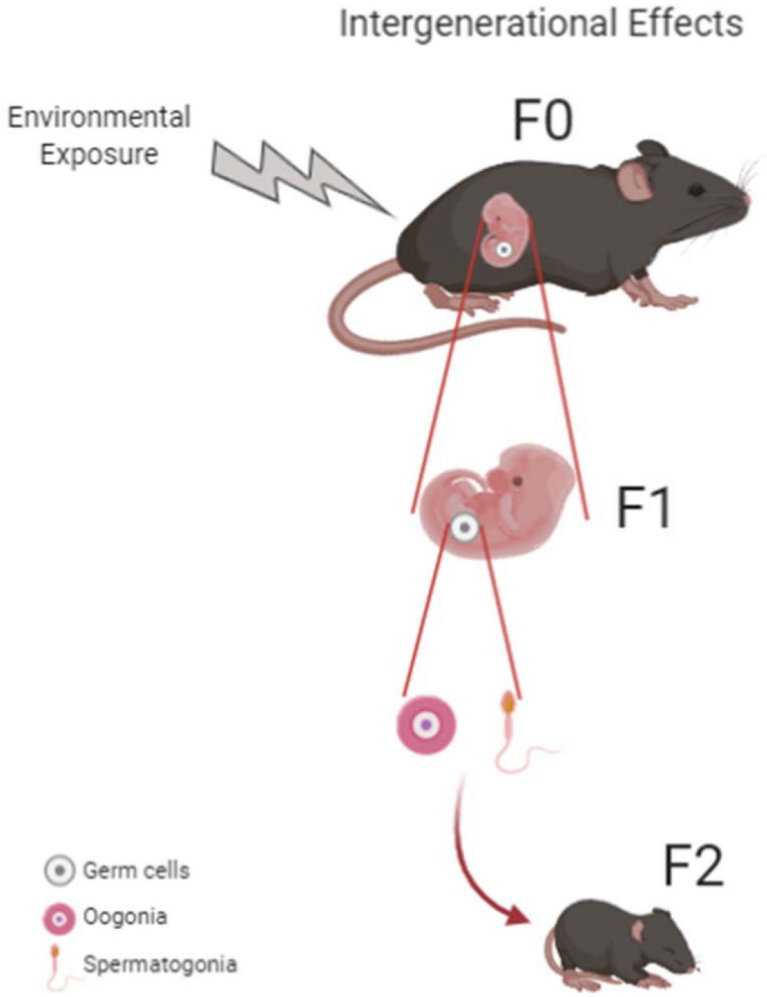

Fig 1: Intergenerational Effects of Environmental Exposure.

In females, intergenerational transmission occurs when a dam receives an environmental exposure during pregnancy, affecting not only F0, but also the F1 and F2 generations. Exposures during pregnancy can directly affect the embryo and its progenitor germs cells. During F1 maturation, these germ cells will become the adult gametes that create the F2 generation.

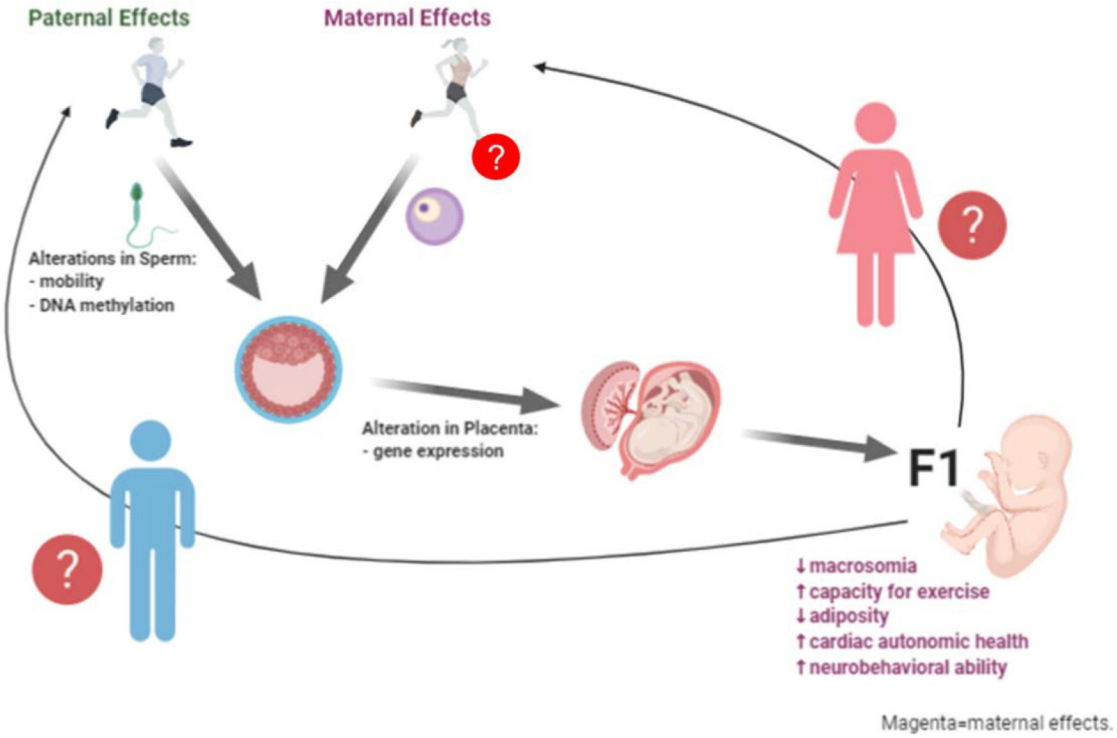

Fig 2: Parental Exercise Training Affects Parents and Offspring.

When women exercise before pregnancy, their oocytes may be affected and exercise during pregnancy affects placenta. These alterations result in numerous effects in the F1 newborn, adaptations that may continue into adulthood. When men are exposed to exercise before breeding, their sperm physiology is changed which may lead to changes in F1 as newborns. Whether these changes affect health of the offspring as they age to adulthood is not known. More studies are needed to understand the effects of maternal and paternal exercise on offspring health in adulthood and to determine mechanisms for these effects.

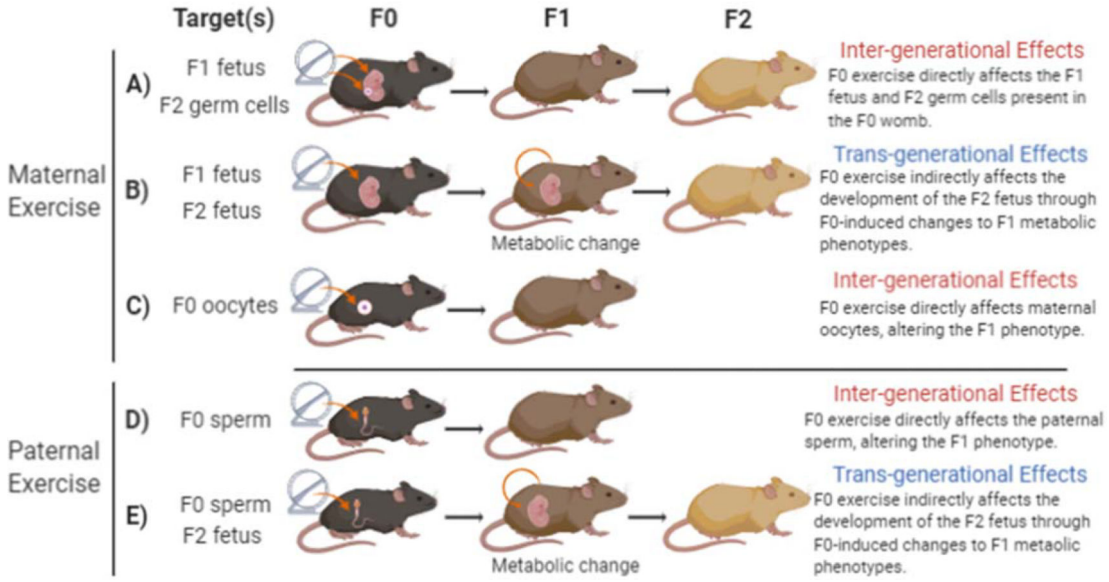

Fig. 3: Targets and Timing of Parental Exercise Differently Affect Offspring Through Inter- or Trans-generational Modes of Inheritance.

A. Inter-generational effects of maternal exercise during pregnancy on F1 and F2 offspring. F0 exercise directly affects the F1 fetus and F2 germ progenitor cells present in the F0 womb. **B.** Trans-generational effects of maternal exercise during pregnancy on F2 offspring. F0 exercise indirectly affects the development of the F2 fetus through F0-induced changes to F1 metabolic phenotypes, which subsequently influence the F2 generation. **C.** Inter-generational effects of maternal exercise while non-pregnant on F1 offspring. F0 exercise directly affects maternal oocytes, altering the F1 phenotype. **D.** Inter-generational effects of paternal exercise on F1 offspring. F0 exercise directly affects the paternal sperm, altering the F1 phenotype. **E.** Trans-generational effects of paternal exercise on F2 offspring. F0 exercise indirectly affects the development of the F2 fetus through F0-induced metabolic changes to F1 males (F1 phenotype affecting spermatogenesis) or females (F1 phenotype affecting oogenesis or the intrauterine environment).

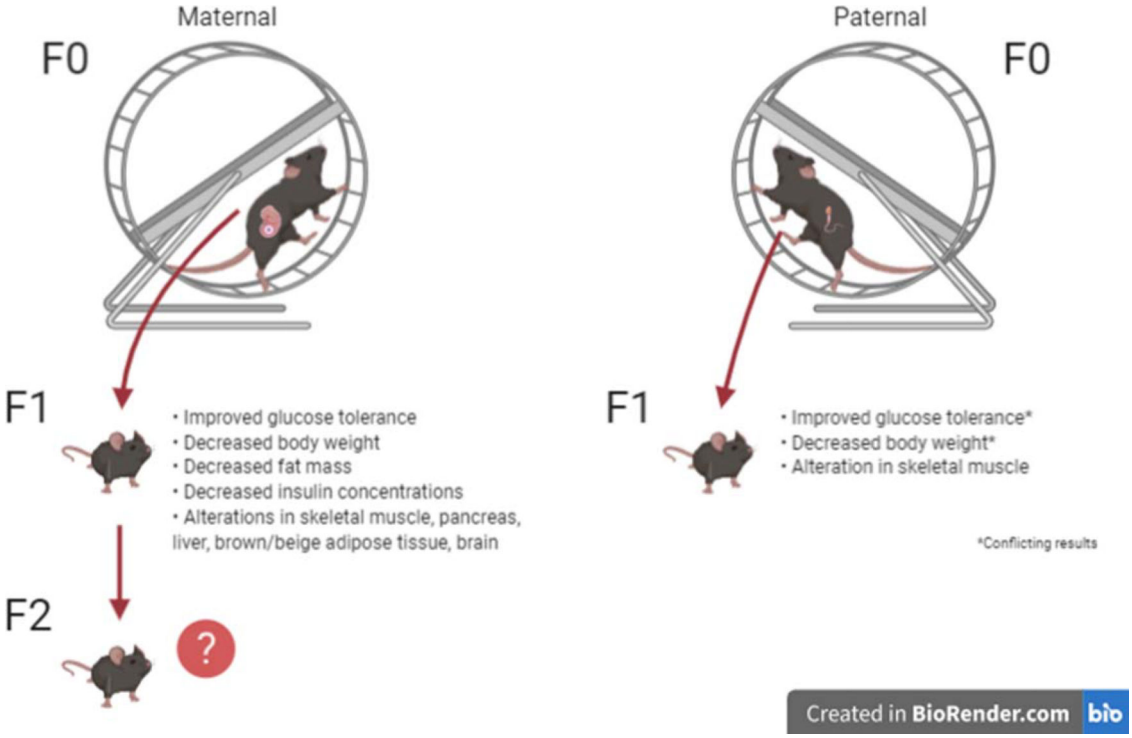

Fig 4: Effects of Maternal and Paternal Exercise Training on F1 Offspring Metabolism.

Maternal exercise improves numerous aspects of offspring metabolism. Whether maternal exercise effects F2 offspring is not known. Most studies show that when sires are exposed to exercise before breeding, F1 offspring have improved metabolism.

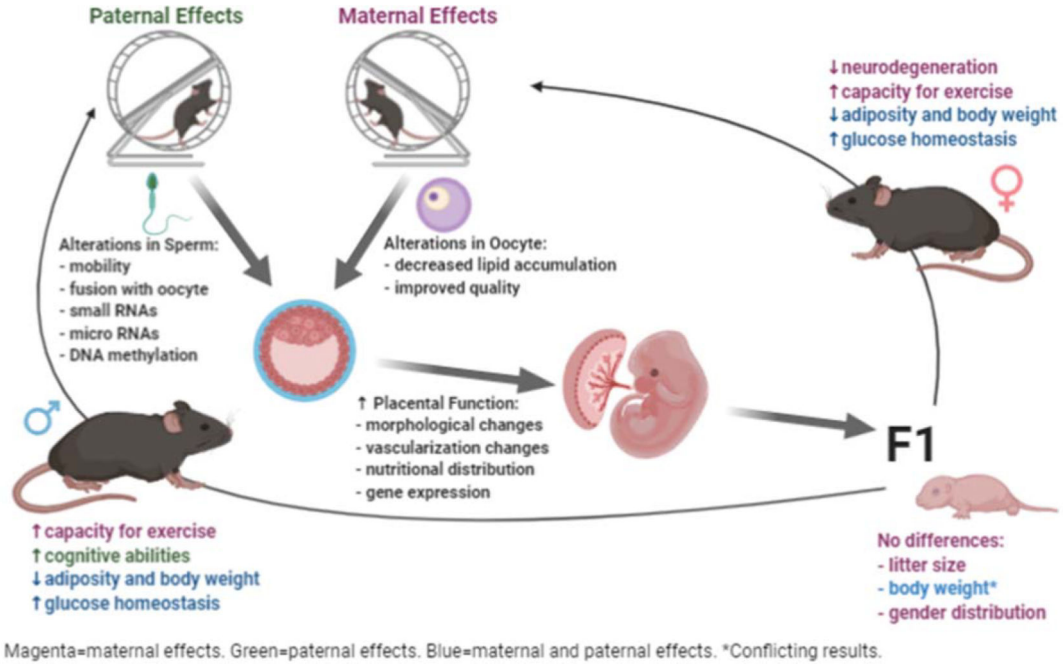

Fig 5: Effects of Exercise Training in Rodents on F0 Gametes and Placenta, and on F1 Newborn and Adults.

When dams are exposed to exercise before and during pregnancy, their oocytes and placenta are affected. While litter size and pup weight are generally not affected by maternal exercise, there are numerous beneficial metabolic changes in offspring, most prevalent in adulthood. Sires that are exposed to exercise have numerous alterations in sperm and these changes likely mediate the beneficial metabolic changes in F1 offspring. There are some sex-specific adaptations in the offspring in response to both maternal and paternal exercise. The beneficial effects of parental exercise offspring may be propagated across subsequent generations, ensuring healthier life cycles for further progeny.

Table 1:

Effects of exercise in women during pregnancy in systematic review and meta-analysis studies.

Study (PMID)	Population	Gestational Age for Enrolment	Training Cessation	Protocol	Mode of Exercise	Major Findings
Davenport et al, 2018 (30337463)	106 studies met the criteria: N=273,182. 65 RCTs, 9 non-RCTs, 13 cohorts, 11 cross-sectional and 8 case-control studies. Studies dates: up to 6 January 2017. 27 countries and five continents.	Anytime during pregnancy	To the end of the 3rd trimester	Majority of the studies identified the exercise as moderate intensity. Frequency of exercise ranged from 1–7 days/week, duration ranged from 10–90min/session.	Walking, swimming, cycling, water gymnastics, resistance training, stretching, yoga or pelvic floor muscle training.	Reduced risk of developing GDM, GH and PE. Pregnant women need to accumulate at least 600 MET-min/week of moderate-intensity exercise (for example: 140 min of brisk walking, water aerobics, stationary cycling or resistance training).
Ming et al, 2018 (30419848)	8 RCTs studies met the criteria: N=3256. Studies dates: 2011–2014. European countries.	6 – 20 weeks	To the end of 3rd trimester	Light-moderate intensity exercise performed 3 times/week (only one study performed exercise once/ week), duration of 35–60min each time.	Aerobic and/or resistance training/ muscle strength.	Reduced risk for gestational diabetes & decreased gestational weight gain
Beetham et al, 2019 (31391016)	13 studies met the criteria: 5 RCTs studies N=623, 8 cohorts studies N=7225. Studies dates: 1983–2018. RCTs: Canada, Brazil, New Zealand, China. Cohorts: Australia, USA, Denmark, United Kingdom.	10 – 20 wks (2 studies were retrospectives; 1 not reported)	During the 3rd trimester	Vigorous/high-intensity exercise. RCTs: performed a minimum of 3 times/week duration of 25–60min each time. Cohorts: performed 1–3 times/ week (1 study was unable to evaluate), duration of more than 3min to 180min each time.	Walking, running, swimming, circuit training, interval training, weight lifting, or plyometrics.	Increased gestational age & reduced risk of prematurity
Wang et al, 2019 (31277127)	23 RCTs studies met the criteria: N=4462. Studies dates: 1999–2017. Europe, USA, Asia, South America.	1st trimester	To the end of the 3rd trimester	Light-moderate intensity ranged from 1–2 to 4–5 times per week.	Aerobic exercises, strength training, walking, cycling, or weight training.	Reduced risk for gestational weight gain, especially with exercise 3 times/week, duration of 30–45min/session

RCT = Randomized controlled trials. GDM = gestational diabetes mellitus. GH = gestational hypertension. PE = pre-eclampsia. MET=metabolic equivalent task.

Nat Metab. Author manuscript; available in PMC 2021 March 14.

Table 2:

Characteristics of F1 offspring in response to maternal, paternal and maternal + paternal exercise.

Author/year (PMID)	Offspring Gender	Species (strain)	Maternal Exercise	Paternal Exercise	Offspring Age	Offspring BW	Offspring Glucose Metabolism	Tissue (response)
Carter et al, 2012 (22932781)	Male and Female	Mouse (ICR)	VWR: 7 days before & pregnancy & 14 days during lactation *	-	Adult	No change	Improved	Females: Soleus (↑ glucose uptake) Adipose tissue (↑ glucose uptake)
Carter et al, 2013 (23247711)	Female	Rat (Sprague Dawley)	VWR: 7–10 days before & during pregnancy & 12 days during lactation *	-	Adult	Decreased	Improved	Skeletal Muscle (↑ glucose uptake) Heart (↓ glucose uptake) Liver (↓ glucose production)
Laker et al, 2014 (24430439)	Female	Mouse (C57BL/6)	VWR: 6 wks before & during pregnancy	-	Adult	No change	Improved	Skeletal Muscle (↓ Pgc1α promoter methylation)
Stanford et al, 2015 (25204976)	Male	Mouse (C57BL/6)	VWR: 2 wks before & during pregnancy	-	Adult	Decreased	Improved	Skeletal Muscle (↔ glucose uptake)
Quiclet et al, 2016 (27382034)	Male	Rat (Wistar)	Treadmill: 4wks before & first 18 days of pregnancy (submaximal exercise, 5 days/wk)	-	Adult	No change	Worsened	Skeletal Muscle (↓ PKB signaling) Pancreas (↓ secretory capacity)
Eclarinal et al, 2016 (27033262)	Male and Female	Mouse (C57BL/6)	VWR: 1 wk before & during pregnancy and 10 days postnatal #	-	Adult	No change	-	↑ Physical Activity
Stanford et al, 2017 (28572303)	Female	Mouse (C57BL/6)	VWR: 2 wks before & during pregnancy	-	Adult	No change	Improved	Liver (↓ glucose production)
Quiclet et al, 2017 (28971475)	Male	Rat (Wistar)	Treadmill: 4 wks before & first 18 days of pregnancy (55% VO_2 max, 5 days/wk)	-	Young adult	Decreased	Improved	Skeletal Muscle (↓ PKB signaling)
Son et al, 2020 (32494609)	Male and Female	Mouse (C57BL/6)	Treadmill: 1 wk before (10min at 10m/min, 3×/wk) & E1.5 to E20.5 of pregnancy (10–14m/min for 40 min daily)	-	Young	Decreased in females. No change in males.	Improved	BAT (↑ BAT function by ↓ Prdm16 promoter methylation)
Falcao-Tebas et al, 2020 (32539156)	Female	Rat (Sprague Dawley)	Treadmill: 4 wks before and until day 19 of pregnancy (60–76% VO_2 max before pregnancy and 50–65% VO_2 max during pregnancy, frequency not stated)	-	Adult	No change	No change	Skeletal Muscle (↑ insulin-stimulated glucose uptake) Pancreas (↑ beta cell mass and number of islets, and ↑ insulin secretion)
Zheng et al, 2020 (32111717)	Male	Mouse (C57BL/6)	VWR: 2 wks before & during pregnancy	-	Adult	No change	Improved	Pancreas (↓ beta cell size)

Author/year (PMID)	Offspring Gender	Species (strain)	Maternal Exercise	Paternal Exercise	Offspring Age	Offspring BW	Offspring Glucose Metabolism	Tissue (response)
Zheng et al, 2020 (32111717)	Male	Mouse (C57BL/6)	VWR: 2 wks before & during pregnancy	VWR: 3wks before mating	Adult	Decreased	Greater improvement	Pancreas (↓ beta cell size and mass, and islet size)
Zheng et al, 2020 (32111717)	Male	Mouse (C57BL/6)	-	VWR: 3wks before mating	Adult	No change	Improved	Pancreas (↓ beta cell size)
Stanford et al, 2018 (30344184)	Male and Female	Mouse (C57BL/6)	-	VWR: 3wks before mating	Adult	No change	Improved	Skeletal Muscle (↑ glucose uptake)
McPherson et al, 2017 (28208792)	Male	Mouse (C57BL/ 6NHsd)	-	Swimming: 9 wks before mating (3 × 30 min session/wk)	Adult	No change	Improved	Pancreas (↑ islet cell number and alters pancreatic microRNAs)
Murashov et al, 2016 (26506979)	Male and Female	Mouse (C57BL/6)	-	VWR: 12wks before mating	Young adult	Increased	Worsened	Skeletal Muscle (altered metabolic gene expression)
McPherson et al, 2015 (25690453)	Female	Mouse (C57BL/6)	-	Swimming: 9 wks before mating (3 × 30 min session/wk)	Adult	No change	Improved	-

VWR: voluntary wheel running. Pgc1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha. PKB: protein kinase B. BAT: Brown Adipose Tissue. Prdm16: PR-domain containing 16.

*Males performed exercise during bleeding period (10 days).

#Males performed exercise during breeding period (1–4 days).

Pink shading indicates maternal exercise; Blue shading paternal exercise; Purple shading maternal and paternal exercise.