



Exercise epigenetics and the fetal origins of disease

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Exercise epigenetics is a nascent area of research with vast health implications (e.g., from the treatment of obesity-related diseases to beneficially decoupling epigenetic and chronological age). Evidence is accumulating [1] that exercise can acutely modify the epigenome (e.g., via DNA methylation) for short-term regulatory purposes (e.g., mRNA expression). More speculatively perhaps, maternal exercise during the pre- and post-partum period could cause epigenetic changes in offspring. It is generally believed that there are benefits of regular moderate exercise during pregnancy [2]. The phenotypic benefits of maternal exercise notwithstanding, exercise can be viewed as a type of organismal stressor [1]. There is a myriad of ways in which environmental perturbations can affect fetal development. For example, gestational stress could alter the epigenome and subsequent physical development. We suggest that maternal exercise – like most gestational stressors – will have a dose-response relationship on an offspring's epigenome (i.e., negative effects at high doses), akin to the phenomenon of hormesis. Interestingly, there is no research investigating the epigenetic effects of maternal exercise in humans. This editorial is a call for research on the subject.

Effects of maternal exercise on offspring health

Exercise during pregnancy has physiological benefits for the mother and it is commonly accepted that exercise of low to moderate intensity would have no negative effects

on the developing fetus [3]. However, little research has been conducted on the phenotypic effects of higher intensity maternal exercise on the offspring. One notable study tested six pregnant Olympic-level athletes at high levels of oxygen consumption (~90%) on a treadmill at 23–26 weeks. Fetal bradycardia and high umbilical artery pulsatility occurred when women exercised at more than 90% of their maximal heart rate [4].

The current literature indicates that there are advantages and disadvantages of maternal exercise. Bick-Sander *et al.* [5] showed an increase in postnatal hippocampal neurogenesis following voluntary wheel running *ad libitum* in mice samples. Alongside this, May *et al.* [6] demonstrated a decrease in fetal heart rate and increase in stroke volume following data collected at 36 weeks gestational age from regularly exercising pregnant women (>30 min of aerobic exercise, three-times per week). Further to this, May *et al.* [7] showed that the resting fetal heart rate of exercised mothers exhibited a trained response. Carter *et al.* [8] demonstrated an enhancement of insulin sensitivity and improvement of offspring glucose homeostasis in rats with mothers who exercised on a wheel *ad libitum* during pre-conception and mating. This is consistent with Prather *et al.* [9], who note that pre- and perinatal exercise in humans is important for lowering adult disease risk (i.e., diabetes and cardiovascular disease).

Beyond the study of six Olympic-level athletes discussed above (i.e., short-term negative effects on offspring of a single

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bout of maternal exercise), other research has shown negative effects (e.g., growth restriction) of maternal exercise that continued throughout pregnancy. For example, Clapp III *et al.* [10] demonstrated a reduction in fetal size from pregnancies where mothers were well-conditioned recreational runners and dancers who maintained their exercise regimen at 50% or above the preconceptional level throughout pregnancy. It has been shown that exercising beyond preconception levels could limit fetal growth. Specifically, a regular running and/or aerobics program at 50% or above the preconception levels in the last 5 months of pregnancy explained 40% of the variability in birth weight over an 1100 g birth weight range [10]. Hopkins *et al.* [11] demonstrated significantly lower birth weight in offspring born to women undertaking a low intensity home-based stationary cycle intervention programme from week 20 of gestation until the delivery.

Hormesis

We feel that the aforementioned negative and positive phenotypic consequences of maternal exercise on the offspring may be due to epigenetic-based dose-response hormesis. Hormesis theorizes that biological systems respond in a bell-shaped curve when exposed to stresses such as exercise, radiation or toxins [12]. Recent work by Bernal *et al.* [13] provided evidence in the isogenic *A(vy)* mouse model that positive adaptive epigenetic changes result from low-dose ionizing radiation (i.e., radiation hormesis). Why would this be the case? It is important to remember that life emerged under relatively toxic conditions (e.g., acidic and anoxic conditions with higher radiation levels compared with nowadays). Indeed, species still thrive under these seemingly stressful conditions. Likewise, physical activity for the majority of animal evolution was likely a source of organismal stress. Specifically, ancestral physical activities ranged from moderately costly dispersal or daily foraging strategies to extremely costly forms of interspecific and intraspecific competition, both of which had fitness consequences on our ancestors. Modern exercise likely mimics ancient (i.e., predating Animalia) ancestral stress adaptation pathways in a variety of unappreciated subtle ways. For example, the organismal stress induced by exercise may lead to positive biological outcomes through exercise-induced reactive oxygen species [14], in part because our distant ancestors have adapted to anoxic environments for millions of years. Regardless of the exact causes, hormesis models (Figure 1) predict that maternal exercise during gestation could have beneficial effects on the epigenome and subsequent development at low versus high doses.

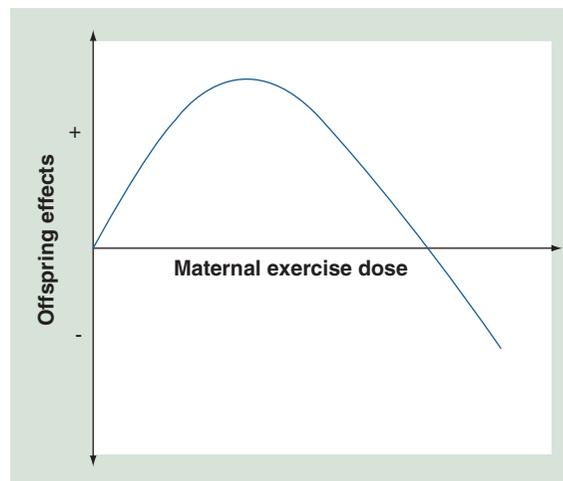


Figure 1. Hypothesized effects of maternal exercise on the fetal epigenome.

Testing the hypothesis: how to develop an exercise epigenetics program

Recent evidence suggests that maternal exercise can alter an offspring's epigenome in mice. Specifically, Laker *et al.* [15] demonstrated in C57BL/6 mice that maternal exercise during gestation reduces high fat diet-induced *Pgc-1a* hypermethylation and ameliorates age-related metabolic dysfunction at 9 months of age. An agouti mouse model could be used to build upon the work conducted by Laker *et al.* [15]. Specifically, previous work by Waterland and Jirtle [16] showed that in variable yellow agouti mice (*A^y/a*), dietary methyl supplementation of *a/a* dams with extra folic acid, vitamin B₁₂, choline and betaine altered the phenotype of their *A^y/a* offspring. The underlying mechanism is increased CpG methylation at the *A^y* locus. Waterland and Jirtle [16] concluded that dietary supplementation, long presumed to be beneficial, may have inadvertent detrimental influences on the establishment of epigenetic gene regulation at high doses. This is consistent with the hormesis model; however, whether exercise at varying doses will exert similar effects as shown in the maternal diet-based agouti system is yet to be investigated.

Pre- and peri-natal nutrition likely effects adult metabolism in humans, potentially via modifications in DNA methylation [17]. Kaati *et al.* [18] found that a paternal grandfathers' food intake during childhood was associated with mortality risk in grandsons. Poor maternal nutrition correlates with low birth weight and adult-onset diseases in epidemiological studies [14]. The underlying mechanisms – epigenetic or otherwise – for these effects remain to be determined. However, using the maternal diet-based agouti system [16] to study exercise epigenetics would be worthwhile since the epigenetic effects are clear and repeatable. Specifically, maternal exercise manipulations could expose offspring's epigenomes to various levels of stress *in utero*. We hypothesize

that maternal exercise will cause hormesis-like epigenetic and phenotypic effects, as seen with maternal nutrition [16]. Specifically, moderate levels of maternal aerobic exercise during gestation would be beneficial at the molecular and phenotypic levels, while higher levels of aerobic exercise during gestation are expected to be detrimental to offspring. To determine the exact dose-response relation of maternal exercise on offspring's epigenome and subsequent health outcomes, carefully controlled experiments using the agouti mouse model are required.

Conclusion

Changes to the fetal epigenome arise during pregnancy through changes in the maternal environment and can have lifelong consequences on an offspring's cardiovascular and metabolic health [19]. Exercise should be added to the candidate list of maternal effects on the offspring's epigenome. Importantly, we hypothesize that the effects of maternal exercise on the fetal epigenome are dose dependent (i.e., beneficial at low to moderate doses and costly at high doses as depicted in **Figure 1**). We also suspect that the same epigenetic patterns will be revealed as for previous work on nutrition and radiation hormesis in agouti mouse studies.

The exercise epigenetics hormesis model in **Figure 1** predicts that low doses of maternal exercise will benefit offspring growth, while higher doses will be detrimental. According to Clapp *et al.* [2,20], the key variables are volume and timing of maternal exercise. The phenotypic evidence could not be clearer when comparing Clapp *et al.* [20] to Clapp *et al.* [2]. Clapp *et al.* [20] showed that moderate maternal exercise during early pregnancy caused enhanced fetal growth, while Clapp *et al.* [2] showed that a high volume of maternal exercise during the later stages of pregnancy was detrimental to fetal growth [20]. We feel that this phenotypic evidence is consistent with the hormesis model presented here.

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The underlying molecular epigenetic mechanisms (if any) for the maternal effects of exercise have yet to be studied using the highly tractable agouti mouse model. Despite an absence of evidence for any effects of exercise at the *A^{VY}* locus, the most studied epigenetic phenomenon – genomic imprinting – is strongly linked to energy homeostasis (including energy expenditure) [21]. Genomic imprinting is the differential expression of genes depending on the parent-of-origin (notably, epigenetic imprints are erased each generation). It is likely that imprinted regions are implicated in agouti mouse hormesis and will figure prominently in the field of exercise epigenetics. Human research is needed to validate any work on the epigenetic effects of maternal exercise using agouti mouse models. It is particularly important to adopt a comparative approach as despite overlap [21], some of the key epigenetic elements (e.g., imprinted genes) responsible for regulating hunger, energy expenditure, adiposity, glucose homeostasis and possibly exercise-induced DNA methylation may well be differentially imprinted (or read differently) in mouse and man.

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