Exercise Epigenetics and the Foetal Origins of Disease

Thomas E.W. Chalk and William M. Brown[1]

Health, Epigenetics and Ageing Laboratory (HEAL), Muscle Cellular and Molecular
Physiology Research Group, Institute for Sport and Physical Activity Research (ISPAR),
Department of Sport Science and Physical Activity, University of Bedfordshire,
Bedford, MK41 9EA, United Kingdom

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[1] Author for correspondence

Tel: +44 (0) 1234 793264

Email: epigenomics@icloud.com

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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 are a myriad of ways in which environmental perturbations can affect foetal 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

There are physiological benefits to exercise during pregnancy for the mother and it is commonly accepted that low to moderate intensity exercise would have no negative effects on the developing foetus [3]. However, little research has been conducted on the phenotypic effects of offspring at higher intensities maternal exercise. One notable study tested six pregnant Olympic-level athletes at high levels of (~90 percent) of oxygen consumption on a treadmill at 23-26 weeks. Fetal bradycardia and high umbilical artery pulsatility occurred when women exercised more than 90% of maximal heart rate [4].

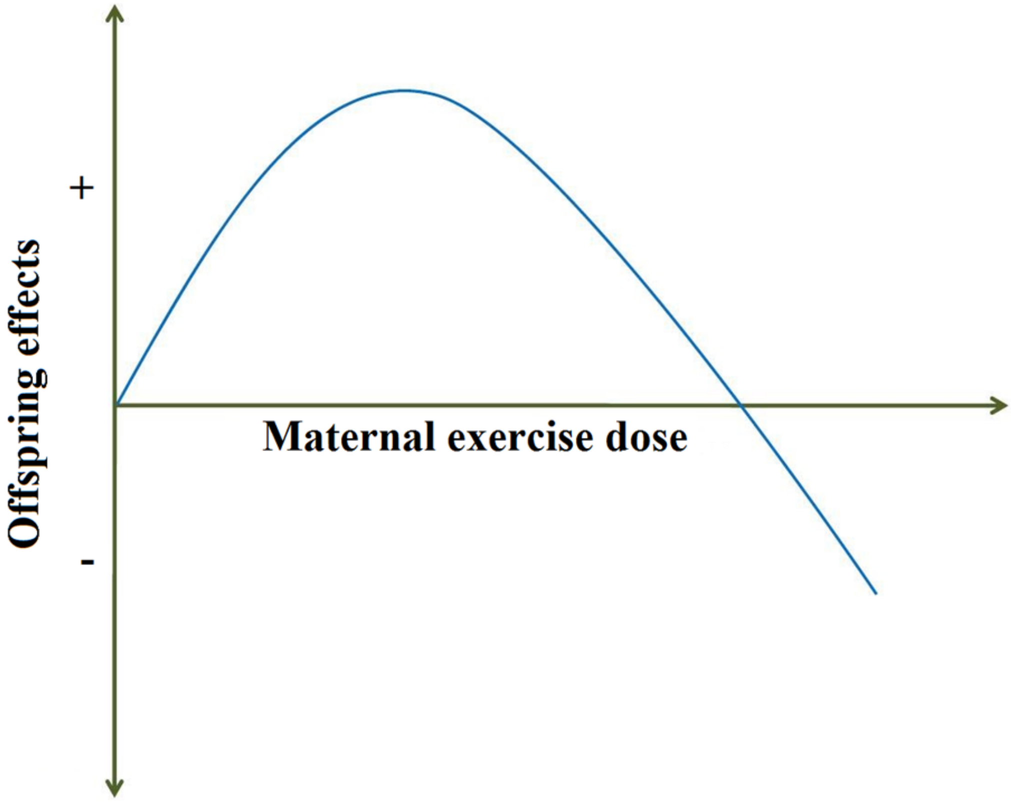
The current literature indicates that there are costs and benefits of maternal exercise. Bick-Sander *et al.*, [5] showed an increase in postnatal hippocampal neurogenesis following voluntary wheel running *ad libitum* in mice samples. Alongside this, May *et al.*, [6] demonstrated a decrease in foetal 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, 3× per week). Further to this, May *et al.*, [7] showed that resting foetal heart rate of exercised mothers exhibited a trained response. Carter *et al.*, [8] demonstrate an enhancement of insulin sensitivity and improvement of offspring glucose homeostasis in rats with mothers who exercised on a wheel *ad libitum* during preconception 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 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] demonstrate a reduction in foetal size from pregnancies where mothers who were well-conditioned recreational runner and dancers who maintained their exercise regimen at 50% or above the preconceptional level throughout pregnancy. It has been shown that exercising beyond pre-conception levels could limit foetal growth. Specifically, a regular running and/or aerobics program at or above 50% of preconception levels in the last 5 months of pregnancy explained 40% of the variability in birth weight over an 1100g 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 till the delivery.

Hormesis

We feel that the aforementioned negative and positive phenotypic consequences on offspring of maternal exercise may be due to epigenetic based dose-response hormesis. Hormesis theorises 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, anoxic and higher radiation than today). 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 been adapted to anoxic environments for millions of years. Regardless of the exact causes, hormesis models (Fig. 1) predict that maternal exercise during gestation could have beneficial effects on the epigenome and subsequent development at low versus high doses.

Figure 1 | Hypothesised foetal epigenetic effects of maternal exercise.



Testing the hypothesis: How to develop an exercise epigenetics programme

Recent evidence suggests that in mice, maternal exercise can alter an offspring's epigenome. Specifically, Laker *et al*, [15] have shown 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. Building upon Laker *et al* [15] would be to use an agouti mouse model. Specifically previous work by Waterland & Jirtle [16] show that in variable yellow agouti mice (A^{vy}/a), dietary methyl supplementation of *a/a* dams with extra folic acid, vitamin B_{12}, choline, and betaine alter the phenotype of their A^{vy}/a offspring. The underlying mechanism is increased CpG methylation at the A^{vy} locus. Waterland & Jirtle [16] conclude 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 but no work has investigated whether exercise at varying doses will exert similar effects as shown maternal diet-based agouti system.

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 as the epigenetic effects are clear and repeatable. Specifically maternal exercise manipulations could expose offspring's epigenomes to various levels of stress, *in utero*. We hypothesise that hormesis epigenetic and phenotypic effects will occur due to exercise as they have with maternal nutrition [16].

Concluding remarks

Changes to the foetal epigenome arise during pregnancy through changes in maternal environment. *Exercise* should be added to the candidate list of maternal effects on offspring's epigenome. Importantly we hypothesise that the effects of maternal exercise on the foetal epigenome are dose-dependent (i.e., beneficial at low to moderate doses and costly at high doses as depicted in Fig 1). We also suspect that the same epigenetic patterns will be revealed as the previous work on nutrition and radiation hormesis in agouti mouse studies.

Recall in Figure 1 the exercise epigenetics hormesis model predicts that low doses of maternal exercise will benefit offspring growth, while higher doses will be detrimental. According to Clapp *et al.*, [20; 2] 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]. Specifically, Clapp *et al.*, [20] show that moderate maternal exercise during *early* pregnancy causes enhanced foetal growth; however Clapp *et al.*, [2] show that high volume of maternal exercise during *later* stages of pregnancy is detrimental to foetal growth [20]. We feel that this phenotypic evidence is consistent with the hormesis model presented here.

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 parent-of-origin (note: 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. A comparative approach is particularly important to adopt 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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