Developmental origins of health and disease – can exercise improve adult outcomes?

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There is interest in the use of exercise as an intervention to improve long-term progeny health outcomes after adverse pregnancy exposures, with an initial focus on intervening in adult progeny. Individuals born after intrauterine growth restriction (IUGR) or from parents who are consuming a high fat diet and/or obese are at an increased risk of developing cardiometabolic diseases in their adult life. IUGR impairs β-cell function and mass leading to reduced insulin secretion, and also induces insulin resistance, with impaired insulin signalling in muscle in adult humans who were small for gestational age (SGA) and in rodent models of IUGR. There is developing evidence that high fat feeding/obesity in mothers or fathers can have similar detrimental effects. Exercise training improves fitness and cardiometabolic health in humans and in a variety of non-human animal species, where it improves glucose homeostasis, by enhancing both insulin sensitivity and secretion. This has raised interest in using exercise as an intervention to prevent or reverse programming of later cardiometabolic disease (Gatford *et al.* 2014). There is some evidence that adult exercise training programs have similar benefits for control and low birth weight men (Mortensen *et al.*, 2013; Madsen *et al.*, 2015). Intriguingly the deleterious effects of being inactive appear to be worse in low birth weight or SGA adolescents and men than control groups (Ortega *et al.*, 2011, Mortensen *et al.*, 2014).

We have recently completed *in vivo* studies to directly test whether IUGR impairs the metabolic benefits from adult exercise training. In our ovine model of restricted placental and fetal growth, pre-training glucose metabolism in healthy young adult progeny was not impaired by prenatal exposure to placental restriction. In these animals, a month-long exercise training regime profoundly increased fitness in all animals, but improved glucose tolerance and insulin secretion in our control progeny only, and these effects were sex-dependent. In the rat, however, where acute restriction of placental and fetal growth in late pregnancy reduces β-cell mass, adult exercise training increased β-cell mass and first-phase insulin secretion in restricted but not control progeny (Laker *et al.*, 2011). Intriguingly, a short period of exercise training in early life (from 5 to 9 weeks of age) followed by a sedentary period, also protected the restricted progeny from lower adult β-cell mass (Laker *et al.*, 2011).

We hypothesize that interventions to reprogram metabolism and reverse or prevent adverse metabolic effects of IUGR that develop with aging may produce greater benefits if targeted to earlier ages, during periods of greater plasticity.

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