Exercise as an intervention to improve metabolic outcomes after intrauterine growth restriction

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ABSTRACT
Individuals born after intrauterine growth restriction (IUGR) are at an increased risk of developing diabetes in their adult life. IUGR impairs β-cell function and reduces β-cell mass thereby diminishing insulin secretion. IUGR also induces insulin resistance, with impaired insulin signaling in muscle in adult humans who were small for gestational age (SGA) and in rodent models of IUGR. There is epidemiological evidence in humans that exercise in adults can reduce the risk of metabolic disease following IUGR. However, it is not clear whether adult IUGR individuals benefit to the same extent from exercise as do normal birth weight individuals, as our rat studies suggest less of a benefit in those born IUGR. Importantly, however, there is some evidence from studies in rats that exercise in early life might be able to reverse or reprogram the long-term metabolic effects of IUGR. Studies are needed to address gaps in current knowledge, including determining the mechanisms involved in the reprogramming effects of early exercise in rats, whether exercise early in life or in adulthood has similar beneficial metabolic effects in larger animal models in which insulin resistance develops after IUGR. Human studies are also needed to determine whether exercise training improves insulin secretion and insulin sensitivity to the same extent in IUGR adults as in as control populations. Such investigations will have implications for customising the recommended level and timing of exercise to improve metabolic health after IUGR.
1) INTRODUCTION

Intrauterine growth restriction (IUGR) can be defined as “a pathological reduction in an expected pattern of fetal growth that leads to attenuation of fetal growth potential due to an insult that has occurred in utero” (28). This often results in a baby who is born SGA, identified as birth weight and/or length at least 2 standard deviations below the mean, or below the 10th centile, for that gestational age (18). SGA is often used as a marker of IUGR in human studies where repeated measures of fetal growth are not available, although some SGA infants are genetically small rather than growth restricted, and exposure to a restricted environment in utero may not reduce size at birth if exposure was in early pregnancy (104). IUGR occurs when the supply of oxygen and nutrients is inadequate to meet the needs of the growing fetus (34). This can be caused by maternal factors including poor nutrition (125, 126), smoking (11) or by impaired placental function due to poor villus structure of the placenta (placental restriction, 17). Placental insufficiency is the leading cause of IUGR in developed countries (47), and is characterised by increased umbilical-vascular resistance and decreased blood flow to the placenta (133) and hence reduced oxygen and nutrient supply to the fetus. Due to effects of gestational age on birth weight, size at birth alone is a poor marker of IUGR. This review will therefore focus on studies of SGA and IUGR, distinct from those of premature birth where possible.

Babies who are born SGA are at an increased risk of developing metabolic disease in adult life, compared to those who were born appropriate for gestational age (AGA) (28, 31, 43, 112). The earliest epidemiological study linking poor fetal growth to subsequent development of type 2 diabetes (T2D) was in 1991 when Hales et al (45) showed that amongst men in their 60’s, those who had low birth weight and low body weights at 1 year were more likely to develop poor glucose tolerance and T2D. Many human studies have since confirmed that low birth weight in humans (reviewed by 82, 150) and experimental restriction of fetal growth in animals (36, 71, 132, 147) increase the risk of metabolic disease in adult life. A more recent study demonstrated that restricted growth before birth and early gestational age at birth (being born preterm) each independently increased the risk of
diabetes and impaired glucose tolerance in adulthood (56). A recent systematic review has further identified that being born preterm impairs insulin sensitivity, particularly in childhood (131). Effects of early delivery per se will not be discussed specifically in the present review, which focuses on effects of restricted growth before birth.

Considering the social and economic burden of chronic metabolic diseases in society, it is important to investigate strategies to either effectively prevent or manage these diseases. Epidemiological studies show that physically active adults are less predisposed to developing T2D (69, 135). Similarly, adults with low levels of physical fitness, and consequently more sedentary lifestyle have increased risks for developing metabolic diseases (10). Aerobic exercise prevents or delays the onset of T2D through numerous mechanisms, including acute enhancements in systemic insulin action lasting up to 72 h, whilst exercise training has beneficial effects on insulin action, blood glucose control, fat oxidation and fat storage in muscle (19).

Whether exercise can prevent or reverse the adverse metabolic effects of IUGR in humans is not yet clear. Epidemiological studies indicate that moderate exercise throughout life protects elderly adults who were born SGA from developing impaired glucose intolerance (29), and protects adolescents from the increase in insulin resistance with decreasing birth weight (87). Few intervention studies have been performed in humans. In the two intervention studies reported to date, a 1-year lifestyle intervention in obese 10-year old children improved insulin resistance less in SGA than AGA children (109), and a 12 week exercise training intervention in young adult men decreased body fat similarly in SGA and AGA groups, with similar effects of training on insulin sensitivity, but with greater impairment of insulin action after bed rest in the SGA group (79, 80). The beneficial effects of adult exercise after IUGR have also been demonstrated in rats, although there is some suggestion that the improvements may be less than in control rats (62). It is possible that intervention early in life when there is more plasticity of organs may provide an opportunity to reprogram the poor prognosis of being SGA. Indeed, the 50% reduction in $\beta$-cell mass in adult IUGR offspring was prevented by only 4 weeks of exercise early in life in rats (62).
These data, although limited, suggest that exercise training may reduce the adverse metabolic effects of restricted fetal growth. This review will describe the current knowledge of metabolic effects of IUGR and responses to postnatal exercise in SGA humans and in animal models used to explore mechanisms and effects of exercise after IUGR. We will identify gaps in current knowledge and will suggest future research directions and approaches to inform translation of exercise recommendations to human IUGR populations.

2) POSTNATAL METABOLIC CONSEQUENCES OF IUGR IN HUMANS

In this section we discuss the metabolic effects of IUGR and the underlying mechanisms in humans. IUGR in humans increases the risk of diabetes due to impaired insulin secretion and insulin resistance. This is an example of developmental programming, where exposures at critical stages of development initiate long-lasting effects on subsequent function, and is hypothesized to reflect a mismatch between fetal adaptations to environmental cues and the subsequent postnatal environment (44). Low birth weight is consistently associated with measures of impaired glucose homeostasis and with the risk of T2D in adulthood (reviewed by 82, 150). More recent studies have shown that this adverse association between low birth weight and diabetes risk persists after correcting for gestational age at birth (56) and current body mass index and socioeconomic status (150). The available evidence from studies of low birth weight and SGA humans suggests that both determinants of insulin action – insulin secretion and insulin sensitivity – are impaired in individuals who were exposed to a restricted environment before birth, as discussed in sections 2.1 and 2.2. Poor insulin sensitivity may be at least partly due to increased risk of obesity after IUGR, although evidence for this is somewhat limited and mixed, as discussed in section 2.3.

2.1 Insulin secretion
Glucose-stimulated insulin secretion and glucose uptake are impaired in the severely IUGR human fetus (83). β-cell mass is reduced in IUGR human fetuses <1.5 kg (137) but not in less severely IUGR human fetuses weighing 1.5-2.5 kg, which might be due to the various IUGR causes and range of gestational ages reported in the latter study (137). The relationship between birth weight and insulin secretion in adulthood has been variable in human studies
(82), probably because insulin secretion is initially elevated to compensate for insulin resistance but later falls due to loss of β-cell function. In the available human studies where glucose-stimulated insulin secretion has been measured relative to insulin sensitivity (insulin disposition), insulin disposition was lower in SGA compared to AGA individuals in pre-pubertal children at 3 and 9 years of age, and in young adults, although not in 1 year-old infants (55, 73, 139). Together with the increased risk of diabetes in SGA compared to AGA humans (56, 82, 150), this suggests that insulin secretion does not increase sufficiently to compensate as insulin resistance develops postnatally after IUGR.

2.2 Insulin sensitivity

In humans, low birth weight and SGA are followed by normal or even enhanced insulin sensitivity in early infancy (139), but this reverses subsequently and insulin resistance develops. Systematic reviews have reported that insulin resistance is a consistent feature in adults born LBW (82). Adult insulin resistance has also been reported in a term-born cohort of men and women assessed by hyperinsulinemic euglycemic clamp, where insulin-stimulated glucose uptake was 16% lower in IUGR than control subjects (51). Over 80% of whole body insulin-stimulated glucose uptake occurs in skeletal muscle (27) and defects in skeletal muscle are likely to play a key role in insulin resistance in IUGR. Consistent with impaired muscle responsiveness to insulin after IUGR, insulin infusion increased forearm (muscle) glucose uptake by 150% in a normal (AGA) birth weight group of 21 year-old men, but only by 34% in men who had been born SGA, with birth weights below the 10th centile (48). Indeed, defects in muscle insulin-signaling have been reported in young adult men born SGA, who had reduced protein expression of insulin signaling proteins including phosphoinositide 3-kinase (PI3K) subunits p85α and p110β and GLUT4 in skeletal muscle, compared with men born AGA (93). Whether IUGR alters insulin-stimulated activation of insulin signaling and GLUT4 translocation in muscle, and these explain muscle insulin resistance after IUGR, has not been addressed in human studies.

Another potential contributor to insulin resistance is through reduced mitochondrial function and hence reduced oxidation of fats and carbohydrates within the cell (58, 76, 78, 100). Skeletal muscle of people with T2D has impaired mitochondrial function, which is mostly due to reduced mitochondrial content (12). Furthermore, key regulatory
components involved in mitochondrial biogenesis, such as peroxisome proliferator-activated receptor (PPAR)-gamma coactivator-1α (PGC-1α) are reduced in the skeletal muscle of people with T2D (76, 100). However it is unlikely that reduced mitochondrial content is causal in the development of T2D, but may be due to reduced physical activity levels in these people, which strongly impacts mitochondrial content (138). At present, despite evidence of altered mitochondrial volume and function in animal models of IUGR, as discussed below, there is little evidence for this in humans, at least in young adults. AGA and SGA young adults have similar skeletal muscle mitochondrial function (14) and normal mitochondrial mRNA and protein expression of oxidative phosphorylation genes including the master regulator PGC-1α (80, 93). Whether mitochondrial function or mitochondrial protein or mRNA expression is reduced after IUGR in older populations has not been investigated in humans to date.

2.3 Obesity

Although there is very good evidence for effects of the prenatal environment on total fat and its distribution in humans, studies of effects of birth weight on obesity in humans have generated mixed conclusions. Maternal undernutrition during pregnancy increases the risk of obesity in offspring, and this depends on the timing of exposure (reviewed by 155). Maternal exposure to severe under-nutrition during the Dutch famine increased obesity rates in 19 year-old men and 50 year-old women, but not 50 year-old men, if exposure occurred in the first half of pregnancy (105, 106). Conversely, if maternal exposure occurred during the last trimester of pregnancy and first few months of postnatal life, obesity rates in 19 year-old men were decreased and were unaffected in 50-year old women and men (105, 106).

To date the meta-analyses and systematic reviews in this area have used birth weight or length as a marker of intrauterine growth, and are therefore probably confounded by effects of gestational age on neonatal size. These reviews report increased risk of overweight and obesity, and greater BMI and waist circumference, with large size at birth, rather than low birth weight (reviewed by 4, 156). Nevertheless, rapid infant weight gain, which is characteristically accelerated during catch-up growth after IUGR, predicts a more central pattern of fat distribution and might therefore contribute to poor metabolic health.
after IUGR (reviewed by 113, 148). Consistent with this, three of four studies in adults reported higher measures of abdominal adiposity in subjects born SGA than in AGA subjects (reviewed by 148). There may be disparities between effects of IUGR on fat and BMI, with a study in young adult men and women reporting that although BMI was similar in the IUGR and controls, IUGR individuals had much a higher percentage body fat (27% vs. 22%), compared to controls (51). There may also be interactions between prenatal environment and later amplification of obesity with age. Indeed, a prospective study from Brazil measured 519 individuals at different ages and demonstrated that in overweight children there was a higher risk of developing later obesity if born IUGR (9). Adverse metabolic effects of obesity may also be worse after IUGR, as SGA overweight children exhibited more components of the metabolic syndrome than seen in AGA children (110).

Susceptibility to obesity might reflect altered endocrine regulation of body weight. Leptin is an adipose-secreted hormone, which negatively regulates body weight through central effects on appetite and energy expenditure (reviewed by 42). Reduced circulating leptin levels after IUGR have been reported in newborns (53), 48 hour-old infants (7) and in pre-pubertal children (1). Conversely, IUGR was associated with elevated leptin during the catch-up growth period at 1 year of age, with leptin resistance postulated as contributing to catch-up growth (54). No differences in circulating leptin were found in two studies of SGA compared to control young adult men (14, 52), although the increase in leptin induced in response to 5 days of high-fat diet consumption in AGA men was not seen in SGA subjects, which might decrease negative feedback effects on weight gain when exposed to high-fat diets and suggests altered regulation of appetite after IUGR (14).

3) POSTNATAL METABOLIC CONSEQUENCES OF EXPERIMENTAL IUGR IN ANIMALS

3.1 Models of IUGR in animals

Multiple experimental models of IUGR in animals have been used to investigate effects of fetal environment on postnatal metabolism. This review will focus on those experimental
IUGR models in which effects of exercise have been investigated, including their similarities and differences from human IUGR, and the metabolic consequences of IUGR in each model. To date, studies of exercise interventions after experimental IUGR have been reported in several models in rats, but not in other species. Exercise has been evaluated in rat progeny born after IUGR induced by surgical ligation of uterine vessels to induce placental insufficiency, by maternal nutrient restriction through various periods during gestation and lactation, or by maternal protein restriction during gestation (Table 1). Each of these experimental models reduces fetal nutrient supply, but the severity and timing of restriction and consequences for progeny metabolic health vary between models, and have implications in regards to translation to humans.

Placental restriction (PR) in the pregnant rat at day 18-19 of gestation by surgical ligation of uterine vessels (151) induces an initial severe restriction of nutrient supply with gradual normalization of plasma glucose and amino acid concentrations by day 20-21, although PR fetuses remain hypoxic up to term (86). The severity of the acute reduction in placental delivery of nutrients is reflected in death of up to 36% of the litter (see Fetal outcomes column of Table 1). The most severely affected fetuses are those that are located closest to the ligation sites (151), so that survivors included in postnatal studies may have been subjected to less severe restriction, with average birth weights reduced 6 to 25% in various studies (Table 1). Although the acute nature of this restricted placental delivery of nutrients probably differs from the majority of human IUGR, impaired placental function is a common feature of human IUGR, with placental structural or micro-structural pathologies observed in up to 55% of IUGR cases (115, 116, 118). Placental supply of amino acids and fatty acids are reduced in human IUGR, with hypoxia and acidemia developing with increasing severity of IUGR, indicated by decreasing end diastolic flow in the umbilical artery (16, 94). Metabolic outcomes of PR for progeny are most similar of the rat IUGR models to those seen after human IUGR, and include defects in both insulin secretion and insulin sensitivity (the latter seen only in studies in the Sprague-Dawley strain and in association with obesity), leading to impaired glucose homeostasis (Table 1 and below). The Wistar-Kyoto strain does not become obese after PR (122), so effects of PR in this strain can be evaluated independent of those induced via obesity, but they also do not develop the insulin resistance characteristic of human IUGR (section 2.2). Because effects of PR differ between
these two rat strains and laboratories, responses in each strain are described separately in
Table 1, although effects of exercise after PR have only been evaluated in the Wistar-Kyoto
strain to date. The reasons for differences in progeny responses to uterine vessel ligation at
the same stage of gestation between these two strains are not clear, with similar reductions
in birth weight, but might include differences in postnatal diet or different litter sizes and
nutrition during lactation. In addition, these two rat strains differ in their metabolic
responses to insulin, including insulin-stimulated blood flow and muscle glucose uptake (41),
which might lead to differing effects of changes in these after IUGR. Long-term development
of frank diabetes in all progeny after PR in the Sprague-Dawley rat is more extreme than
effects of human IUGR, where although low birth weight/IUGR increase risk of diabetes this
is not a universal outcome (56). This postnatal phenotype of the Sprague-Dawley PR rat may
reflect the acute and severe nature of the restriction imposed during fetal life.

Effects of moderate (50%) global nutrient restriction of mothers on progeny metabolism has
been evaluated following maternal restriction either only in the second half of gestation,
using cross-fostering to prevent carry-over effects of maternal gestational nutrition on
lactation, or in the second half of pregnancy and throughout lactation (Table 1). Metabolic
consequences of moderate maternal nutrient restriction differ markedly according to the
timing of maternal feed restriction, as well as between progeny ages and sexes (Table 1).
Maternal nutrient restriction to 50% of ad libitum intake in the second half of pregnancy
reduces birth weight by 11-30% with normal litter size (21, 70, 129), consistent with chronic
rather than acute restriction of fetal nutrient supply. Although progeny catch-up in body
weight to that of controls if maternal feed intake is restricted only during the second half of
pregnancy, continuing the restriction throughout lactation causes permanent reductions in
offspring size. Furthermore, restriction during pregnancy but not lactation, mildly impairs
glucose tolerance of progeny at various ages, but if maternal nutrient restriction is
continued throughout lactation glucose tolerance is not impaired in male progeny or in
females except when aged (Table 1). This suggests that early postnatal restriction at least
partially protects against adverse effects of IUGR due to maternal malnutrition in the rat.

Although severe maternal nutrient restriction (30% of ad libitum intake) throughout the
whole of gestation reduces birth weight more than seen after moderate restriction (reduced
by 25-35% cf. 11-30%), metabolic outcomes for progeny are not markedly different between these models of pregnancy nutrient restriction (Table 1). Fasting glucose is normal in animals up to adulthood, and only mildly elevated in aged males, whilst glucose tolerance has not been reported (Table 1). Studies in this model are hard to evaluate however, because progeny of severely nutrient-restricted dams were cross-fostered, whilst progeny of control dams remained with their birth mothers (153, 154), so that postnatal nutrition and stress exposures may also differ between the IUGR and control groups.

Finally, metabolic outcomes have been evaluated after IUGR induced by feeding mothers a diet containing ~50% of the protein content of normal chow through pregnancy and lactation (8% and 17% casein diets)(3). This model may be more reflective of poor quality maternal diets occurring in developing countries, rather than IUGR in developed countries, where placental dysfunction is the major cause of IUGR (47). Exposure to a low protein diet throughout perinatal life appears to induce mild and variable effects on fetal growth, with none or 20% decrease in birth weight reported in various studies, and does not reduce litter size (3, 20, 30, 64, 65). Glucose homeostasis is impaired in progeny, at least in adult males, which have mildly elevated fasting glucose and impaired glucose tolerance (Table 1). It is possible that at least some of the mild metabolic outcomes in the progeny from low protein dams might be due to increased carbohydrate in the gestation diets, as starch content was increased to maintain a similar energy content in the two diets (3).

### 3.2 Insulin secretion

Insulin secretion in vivo and in vitro, and one of their major determinants - β-cell mass, have been evaluated in most, but not all of these models of experimental IUGR (Table 1). PR in the rat impairs glucose-stimulated insulin secretion from early life in the Sprague-Dawley strain (124), with little effect of PR on insulin secretion reported in the Wistar-Kyoto rat (62, 122, 146), but with substantial reductions in β-cell mass in both strains (Table 1). Glucose- and leucine-stimulated insulin secretion are reduced from early life in islets isolated from the male PR Sprague-Dawley rat (123), suggesting that the defect is intrinsic to β-cells, but in vitro β-cell function has not been studied in the Wistar-Kyoto strain. Normal in vivo arginine-stimulated insulin secretion in PR progeny (124) further suggests that the defect is at the
level of glucose uptake or metabolism and that downstream steps in insulin secretion remain intact. Mitochondrial function is decreased in islets of fetal PR rats, and becomes progressively more impaired with ageing postnatally, with consequent reduced ATP supply, increased production of reactive oxygen species and impaired β-cell function (123). In contrast with the persistent effects of PR on β-cell mass, moderate maternal nutrient restriction in the second half of pregnancy appears to only transiently affect β-cell mass around weaning, due to decreased replication and neogenesis of β-cells at this age (Table 1). If nutrient restriction of dams (and hence progeny in early postnatal life) is continued through lactation, β-cell mass relative to body weight is increased, rather than decreased, but this probably reflects the reduction in body size in these animals rather than any improvement in β-cell development. Indeed, replication and neogenesis of β-cells is still decreased in these rat progeny around weaning (Table 1). Absolute insulin secretion is normal in adult offspring after maternal late pregnancy nutrient restriction until aged adulthood (15 months), when effects of IUGR differ between sexes. In aged adult progeny, IUGR increases insulin secretion during an IVGTT by 70% in females but decreases this by 30% in males (36, 37, 39, 129). Absolute insulin secretion fluctuates with ageing and between sexes in animals when moderate maternal nutrient restriction is continued throughout lactation (Table 1). In the more severely restricted model (dams fed 30% of ad libitum throughout pregnancy), insulin secretion has not been evaluated by glucose tolerance test, but fasting insulin is substantially elevated in adult males (Table 1). However, it is not clear whether insulin secretion is impaired or is appropriate for insulin sensitivity in progeny in any of these models of IUGR induced by maternal global nutrient restriction, since insulin disposition has not been reported in these animals. Because insulin secretion adapts for insulin sensitivity in healthy individuals, lower insulin secretion during IVGTT can reflect either decreased demand due to higher insulin sensitivity, or impaired insulin secretion in the face of insulin resistance (8).

Studies in the PR rat suggest that epigenetic changes induced during IUGR underlie the lifelong consequences of PR for insulin secretion in this species. PDX1 (pancreatic and duodenal homeobox 1) is a transcription factor critical for β-cell function and development (5). Proliferation and differentiation of pancreatic exocrine and endocrine cell types is blocked in PDX1−/− animals, whilst heterozygotes have impaired capacity to increase β-cell mass and
insulin secretion in response to developing insulin resistance (13, 60). PR suppresses transcription of \textit{PDX1}, with suppression progressing from \textasciitilde50\% in late gestation fetuses to \textasciitilde80\% in adults (96, 127). This reflects epigenetic changes at the \textit{PDX1} promoter induced during PR, which progress from altered histone acetylation and methylation in late fetal and early postnatal life to methylation of CpG islands by adulthood (96, 127). These changes can be reversed in vitro early in postnatal life, but not in adults once DNA methylation has occurred (96), suggesting a window during early life when environmental manipulations might be able to reverse or prevent effects of IUGR on \(\beta\)-cell mass and function. Together, these findings after experimental IUGR in rats, and in particular after PR, suggest that impaired \(\beta\)-cell function and loss of \(\beta\)-cell mass each contribute to programming of insulin secretion after IUGR, and that these are induced at least in part via epigenetic mechanisms.

\textbf{3.3 Insulin sensitivity}

Placental restriction at day 18-19 of gestation in the Sprague-Dawley rat is the only one of these animal models of IUGR in which whole-body insulin resistance is consistently observed, in conjunction with increased obesity. In contrast, evidence for hepatic or skeletal muscle resistance has been reported in several models of IUGR, as discussed below. Reduced insulin sensitivity in the PR Sprague-Dawley rat has been measured by hyperinsulinemic euglycemic clamp, as well as by insulin tolerance test (Table 1 top row). Hepatic insulin resistance, measured directly in the young adult male PR Sprague-Dawley rat via measures of hepatic glucose production, is increased by PR, and insulin-stimulated phosphorylation of proximal insulin signaling molecules is reduced in liver, also consistent with hepatic insulin resistance (145). In the Wistar-Kyoto PR studies, however, whole body insulin sensitivity is normal in (non-obese) adults of both sexes, while there is evidence of reduced mitochondrial function and biogenesis in skeletal muscle at least in adult males (Table 1). Similar to effects of PR, moderate global maternal nutrient restriction in late pregnancy did not alter whole-body insulin sensitivity (21, 37, 129). Effects of moderate global maternal nutrient restriction in late pregnancy on tissue insulin sensitivity differed between tissues, with evidence of hepatic insulin resistance in aged males (36) and skeletal muscle insulin resistance in weanling and young adult females (129), but increased insulin sensitivity of white adipose tissue in young adult females (129). Intriguingly, continuing
moderate global maternal nutrient restriction of dams (and hence suckling progeny) through lactation actually increased whole body insulin sensitivity in adult males, and increased insulin-stimulated glucose uptake in skeletal muscle of aged males (Table 1). This is consistent with those authors’ suggestions that continued nutrient restriction during the neonatal period is protective against at least some adverse metabolic outcomes of IUGR, and that neonatal catch-up growth contributes to adverse metabolic consequences of IUGR (21). Insulin sensitivity appears unaltered after more severe maternal global nutrient restriction throughout gestation (49, 130) and maternal protein restriction throughout gestation and lactation (30), although evidence in these models is currently only available for adult males (Table 1). The Sprague-Dawley PR rat is thus the only one of these animal models in which good evidence has been reported for whole-body insulin resistance, as occurs consistently in humans of low birth weight, including studies correcting for gestational age. Insulin resistance in the Sprague-Dawley develops concurrently with obesity (124), which might therefore contribute to insulin resistance. Nevertheless, development of visceral obesity in particular is not inconsistent with, and may also contribute to, effects of IUGR on insulin resistance in humans (section 2.2). The Sprague-Dawley PR rat may therefore be a useful rodent model in which to investigate effects of exercise on insulin sensitivity and fat deposition after IUGR.

3.4 Obesity

Unlike impaired glucose metabolism, increased abdominal fatness appears to be a common feature of all of these models of IUGR, unless early postnatal growth is also restricted (Table 1). IUGR animals undergo “catch-up” growth and achieve similar weights or greater adult body weights as control animals after PR in Sprague-Dawley (124) and Wistar-Kyoto strains, the latter only in females (63, 85, 122), and after moderate maternal global nutrient restriction in late pregnancy in the Sprague-Dawley rat (21, 37, 70, 129). Measures of abdominal or visceral fat are increased in many of these models (36, 37, 124), although not after PR in Wistar-Kyoto rats (146), unless also cross-fostered (122). Severe maternal global nutrient restriction throughout pregnancy is followed by catch-up growth in some, but not all studies (84, 130, 141, 144), and these progeny also exhibit increased adiposity (130, 141, 144), possibly due to increased appetite (75, 140-142, 144). Maternal dietary protein
restriction throughout gestation and lactation reduces body weight of male progeny into adulthood (3, 20, 25, 26, 30), but there is some evidence of altered hypothalamic control and increased appetite (20), so these animals may become fat if studied into later life. Prevention of neonatal catch-up growth may protect against increased visceral fatness after IUGR, as extending moderate maternal global nutrient restriction from late pregnancy throughout lactation results in progeny that not only remain smaller as adults (21, 70, 129), but are leaner than control animals and resistant to developing obesity when fed a high-fat diet (21, 37, 129). Visceral adiposity thus appears to be a common feature of IUGR in humans and in rat experimental IUGR, but occurs without insulin resistance in several of these animal models, with co-existence of visceral adiposity and insulin resistance only seen after PR in the Sprague-Dawley rat.

4) EFFECTS OF EXERCISE AFTER IUGR IN HUMANS

As yet, few studies have been published reporting effects of exercise or physical activity on metabolic outcomes such as insulin sensitivity in people following IUGR (Table 2). Three observational human studies have been conducted, with two in children and one in elderly people. As described below, although the effects were not large, being more active had beneficial effects in regards to insulin (and leptin) resistance in both SGA and AGA, with some suggestion of greater effects in SGA than AGA individuals (29, 61, 87). There have been only three intervention studies of exercise and physical activity in SGA humans. Of these, one was a one year lifestyle intervention (which included exercise) in obese children (109), whilst two shorter studies have been conducted in young men, investigating metabolic responses to 12 weeks of exercise training or detraining responses after 9 days of bed rest (79, 80). Surprisingly, although insulin sensitivity measured by homeostasis model of insulin resistance (HOMA-IR) remained similar before and after intervention in AGA children, insulin resistance worsened during the lifestyle intervention in the obese SGA children, despite weight loss occurring (109). In young adult men, although exercise training induced a normal increase in insulin action in SGA individuals, they seemed more susceptible to the negative effects of bed rest than AGA men (79, 80).
4.1 Insulin secretion

Lowering of fasting blood glucose levels, as occurs with exercise training (19), may reduce glucotoxicity on pancreatic β-cells allowing for improved β-cell function. As there is significant plasticity of the pancreas during early life (68, 103, 134, 136), this may represent a critical period that responds optimally to exercise intervention in IUGR individuals. We are not aware of any studies in humans that have examined the effect of exercise training on β-cell function/insulin secretion following IUGR. Although it is not possible to measure β-cell mass or morphology in vivo in humans, based on studies in T2D patients, it has been suggested that the ratio of C-peptide to glucose following oral glucose ingestion predicts β-cell mass better than fasting measures (72). Therefore, studies are now required using these techniques to indirectly indicate β-cell mass, together with in vivo insulin secretion tests to determine whether exercise training in IUGR human adults improves β-cell function.

4.2 Insulin sensitivity

Although being physically active is important for metabolic health of all individuals there is some developing evidence that this may especially be the case in people who were born SGA (Table 2). In a study of 500 individuals aged 65-75 years (186 men, 314 women) exercise habits over the previous 12 months were assessed by questionnaires in regards to weekly exercise frequency and intensity and yearly physical leisure time activity (29). In these older adults, those who were more active in terms of exercise frequency (>3/week) and intensity had lower rates of glucose intolerance across all birth weights (Table 2). Importantly, this protective effect was strongest in participants who had low birth weight (<3,000 g), in whom frequent (3 or more sessions/week) moderate exercise reduced the prevalence of developing glucose intolerance by 37% compared with those who did not exercise regularly (29). Although responses to exercise were not corrected for gestational age at birth, and some individuals in the cohort were born prematurely, the majority of the cohort was born at term, based on mean length of gestation (32). Men born thin exercised more than those of higher ponderal index at birth (29), which is good in terms of protecting their health, but at the same time this variation in voluntary exercise might partially confound the relationship between size at birth and efficacy of exercise.
In line with the study in elderly people, an observational study (Table 2) involving 12.5-17.5 year old adolescents from two cohort studies (HELENA and EYHS) that examined physical activity using accelerometers for 4-7 days, found an interaction between birth weight, physical activity and insulin sensitivity measured as HOMA-IR (87). In both cohorts, when physical activity levels were below the median, being born small tended to increase insulin resistance, with $P = 0.06$ for the HELENA cohort and $P = 0.09$ in the Swedish EYHS cohort, whilst this relationship was not present in the more active children (87). Neither cohort was restricted to term-born individuals (77, 149), and gestational age information is not available for the EYHS cohort (149). Importantly, inclusion of gestational age did not modify the relationship of small size at birth with insulin resistance for the HELENA cohort (87), consistent with these results reflecting protective effects of exercise for IUGR rather than prematurely born children. Similarly, in further work using a term-born subset of the HELENA cohort (Table 2), plasma leptin levels were elevated in low birth weight girls (but not boys) who did not meet the physical activity recommendations (60 min/day), but not in those who were sufficiently active (61). These results suggest that being relatively inactive may have greater detrimental effects on insulin and potentially leptin sensitivity in those born SGA than those born of normal weight.

Indeed, a study in young men born SGA using bed rest for nine days tend to support this theory (79) (Table 2). Surprisingly, insulin sensitivity determined using hyperinsulinemic euglycemic clamp was not different between the 20 SGA and 20 AGA men prior to commencement of the study and bed rest reduced insulin sensitivity to a similar extent in the two groups (79). Although effects of physical inactivity on whole-body insulin sensitivity did not differ between the groups, SGA individuals did have evidence of impaired insulin signaling in skeletal muscle, with lower insulin-stimulated AS160 phosphorylation before and after bed rest (79). Muscle-specific proximal insulin signaling (measured as insulin-stimulation of Akt phosphorylation) was similar in SGA and AGA men before bed rest, but after bed rest insulin-stimulated Akt phosphorylation was significantly lessened in the SGA men (79). AS160 phosphorylation appears to represent a convergence of signaling controlling GLUT4 translocation in response to both insulin and non insulin-independent pathways such as exercise (66, 79, 80, 146). Given that insulin-stimulated AS160 phosphorylation is reduced in skeletal muscle of T2D patients (59), as in men born SGA (79),
and this defect can be rescued by exercise training in T2D patients (59), the defective responses to inactivity of skeletal muscle Akt- and AS160 phosphorylation in men born SGA may play a role in their increased susceptible to developing T2D later in life.

In terms of intervention studies using exercise training in humans there have been only one study in children and one in young adults (Table 2). The results of these are limited and mixed in regards to the impact on insulin sensitivity. Effects of a 12 month lifestyle intervention which included exercise, nutrition and behavioural aspects have been reported in obese 10 year-old boys and girls, including 26 SGA and 315 AGA children (109). The structured exercise component of this intervention only involved weekly sessions. Therefore it is likely that effects of exercise explain a relatively minor proportion of the intervention responses, compared with effects of nutrition and behavioural components (108). At the commencement of the study, the obese SGA children had higher HOMA-IR than AGA due to greater fasting plasma insulin concentrations. The 12-month intervention was successful in that 79% of children lost weight (109). However, the intervention surprisingly had little effects on HOMA-IR in the AGA children and HOMA-IR actually increased in the SGA children, due to increases in plasma insulin concentration (109). These results are difficult to interpret and are inconsistent with greater effects of physical activity on metabolic health in low birth weight individuals in observational studies (29, 61, 87), as described above. The only intervention study to examine the effects of exercise training in adult humans born SGA found that fasting glucose, insulin and C-peptide were similar prior to exercise in SGA and AGA individuals (80). Twelve weeks of exercise training decreased plasma glucose similarly in both groups with no effect on plasma insulin or C-peptide (80).

As mentioned in Section 2.2 above, there may be some relationship between insulin sensitivity and mitochondrial function / volume. However, there are no differences in skeletal muscle oxidative phosphorylation gene expression (including PGC-1α) between young AGA and SGA men and mitochondrial function in response to contraction, as determined by calculated aerobic ATP turnover rate (15). In addition, recovery kinetics of phosphocreatine and inorganic phosphate after contraction are not different between the two groups (15). Given that mitochondrial function and volume are strongly influenced by the level of physical activity, these results may simply indicate that SGA and AGA are equally
active. Indeed, other studies by this group have demonstrated no difference in aerobic capacity between SGA and AGA young adult men, with similar whole-body insulin sensitivity in these two groups (79, 80). Studies that examine all of these factors in the same individuals are required to assess the potential role of mitochondrial function and volume in metabolic outcomes after IUGR, and their role in responses to exercise.

4.3 Obesity

It is not presently clear whether IUGR affects body composition responses to exercise, with only limited evidence currently available (Table 2). The decrease in BMI z-scores during a one year lifestyle intervention including exercise therapy, nutrition education and behaviour therapy, were similar in SGA and AGA (reduced by 8.9% and 11.3% respectively) children (109). In young adult men, exercise training 4 days/week for 1 hour/day at an intensity corresponding to 65% of their individual VO2 peak for 12 weeks similarly decreased total body fat percentage in both SGA (by 5%) and normal birth weight participants (by 8%) with no significant difference between groups (80). As mentioned above, birth weight has been negatively associated with leptin levels (an obesity biomarker) in girls aged 12-17 years not meeting the physical activity recommendations, whereas no significant association was observed in those meeting the physical activity recommendations (61). To our knowledge, however, there are no exercise training studies in adults investigating the effects of exercise on leptin (or adiponectin) levels in SGA vs. AGA humans. Effects of early life exercise on body composition after IUGR have also not been investigated to date, although in the broader population, children who spent more time undertaking moderate to vigorous activity at 5 years of age had lower fat mass at 8 and 11 years of age than those who exercised less (50).

In summary, although there is some evidence that physical activity/exercise is not only beneficial but may be more beneficial in those born SGA, few studies have been conducted and results are mixed. Studies examining the effects of exercise training on insulin sensitivity using hyperinsulinemic euglycemic clamps and on insulin signaling in SGA humans are required.
5) EFFECTS OF EXERCISE AFTER EXPERIMENTAL IUGR IN ANIMALS

More exercise studies have been conducted in rodents born following IUGR than in SGA humans (Table 3). The rodent studies generally provide more consistent evidence of beneficial effects of exercise and naturally provide more mechanistic insight than the human studies, especially in regards to effects on the pancreas. However, as mentioned earlier, it should be noted that the PR animal models of IUGR are more extreme than likely to occur commonly in humans and the aetiology of these rodent models often hard to compare to that of humans. In addition, difference in developmental rates in rodents and humans mean that some of the results from exercise studies in rodents, and in particular the age equivalence of comparisons to humans, needs to be interpreted with caution.

Indeed, exercise studies in species closer to humans than rodents are required.

5.1 Insulin secretion

Only two studies have examined the effect of exercise training on insulin secretion (measured during IPGTT or IVGTT) after IUGR in animals, with both being rat studies. Four weeks of exercise from 20-24 weeks of age in adult Wistar-Kyoto IUGR rats induced by bilateral uterine vessel ligation at 18 days gestation (placental restriction, PR) restored reduced β-cell mass in the IUGR rats and in doing so normalized the diminished 1st phase insulin secretion during IPGTT (62). This differs from effects of exercise reported by Garg and co-authors in 8 week-old rats that had IUGR induced by maternal nutrient restriction (38). These IUGR rats had lower IVGTT first phase insulin secretion than control rats, consistent with effects of PR reported by Laker and co-authors (62). In contrast with the latter study, however, Garg and co-authors reported that exercise reduced 1st phase insulin secretion in both control and IUGR rats (38), rather than increasing it (62).

Interestingly, exercise in early life appears to at least partially reverse long-term adverse effects of PR in rats. If exercise training of PR rats was undertaken early in life (from 5-9 weeks of age) there was a small but significant increase in their β-cell mass at 9 weeks, although this was still only ~60% of control levels (62). Critically, when PR rats that were
exercised in early life were examined at 24 weeks, with no further exercise between 9 and 24 weeks of age, β-cell mass was fully restored in adulthood (6 months), reversing the ~65% deficit in IUGR offspring at that age (62). Although this study by Laker and colleagues (62) is the only study of persistent effects of early life exercise after IUGR, this is consistent with protective effects of early life exercise in insulin-resistant rats reported by Shima and co-authors (120). In that study, early life exercise (from 7-15 weeks of age) prevented development of diabetes in the insulin-resistant Otsuka-Long-Evans-Tokushima Fatty (OLETF) rat, whereas non-exercised animals all developed diabetes by 28 weeks of age (120). At 28 weeks of age, 13 weeks after the completion of the early life exercise regimen, OLETF rats that had exercised early in life still had improved glucose tolerance compared to sedentary controls (120). As discussed earlier, placental restriction in rats induces epigenetic changes at the PDX1 promoter that silences PDX1 gene expression by adult life, and this is at least in part due to increased activity of the histone deacetylases in β-cells (95, 96). It is therefore possible that the effects of early exercise in improving the β-cell mass later in life are via increased PDX1 expression, thereby improving the β-cell development and function (97). We found no effect of exercise early in life on gene expression of PDX1, GLUT2, IRS2 and IGF1R in whole pancreas of IUGR rats (62). Because the β-cell containing islets only make up 2-4% of the pancreas, however, studies that measure gene expression and epigenetic responses in isolated islets are needed to more definitively determine whether altered gene expression and/or epigenetic mechanisms are responsible for the remarkable effects of early exercise in adult β-cell mass. Similar exercise intervention and mechanistic studies in a larger mammal model of IUGR are also needed to confirm whether such mechanisms are common across species.

5.2 Insulin sensitivity

In IUGR adult rats, induced by moderate maternal nutrient restriction, moderate exercise (treadmill, 5 days/week, 15 min/day, at a speed of 11 m/min) from 21 to 60 days reduces fasting HOMA-IR, improves the insulin area under the curve in response to an IVGTT and suppresses hepatic glucose production to a similar extent in control and IUGR rats (38). However, given that exercise training improved insulin sensitivity as assessed by an insulin tolerance test only in IUGR rats, and not in control rats (38), it could be argued that exercise
training had a greater effect after IUGR. An additional group of pups in this study had
maternal nutrient restriction continued throughout lactation after IUGR, and without
exercise these rats had better insulin sensitivity by hyperinsulinemic euglycemic clamp than
control progeny, at least in old adult (10 month-old) males (Table 1). Like the IUGR rats,
exercise increased insulin sensitivity by IVITT in these animal restricted during gestation and
lactation, suggesting that continuing restriction into early postnatal life does not alter
responses to exercise after IUGR (38).

As mentioned earlier the phenotype of adult Wistar-Kyoto rats exposed to PR in utero is
quite mild in terms of glucose tolerance and insulin sensitivity despite profound effects on
β-cell mass (62). The phenotype of these rats might worsen with ageing or with additional
post-natal challenges such as high-fat feeding, however, and indeed we have shown that the
female progeny have impaired glucose intolerance compared to control females when
pregnant (35). In addition, we did not find large effects of exercise training on HOMA or
glucose tolerance in the Wistar-Kyoto PR rat. Interestingly, however, we found some
evidence that when exercise was undertaken later in life (from 20-24 weeks) there appeared
to be less of an improvement in adult insulin sensitivity at 24 weeks of age, based on
glucose and insulin profiles during IPGTT, in IUGR rats than in controls (62). This contrasts
with the results of an observational study in elderly humans, where physical activity was
protective against glucose intolerance, especially in LBW individuals (29), but is consistent
results of an intervention study in obese children, where a lifestyle intervention was less
effective in SGA than AGA children, and HOMA-IR actually worsened in the SGA group (109).

We found that either treadmill exercise training from 5-9 weeks or from 20-24 weeks elicits
normal increases in skeletal muscle protein expression of PGC-1α, hydroxyacyl-CoA
dehydrogenase beta subunit (β-HAD) and citrate synthase enzyme activity in control and
IUGR rats when measured within days of the last exercise bout (63). In contrast, Huber et al
(49) found no increase in the diminished skeletal muscle PGC-1α following 190 days of
voluntary wheel running (from 60 days of age) in rats with IUGR caused by maternal
nutrient restriction (mothers fed 30% of ad libitum intake during pregnancy). It should be
noted though that this study had rats only exercising a surprisingly small amount with the
voluntary wheel running for an hour per day and clamped at 56 m per day, so it is unlikely
that this was sufficient for substantial training effects (49). Despite this, however, exercise normalized the diminished protein expression of PKCζ, an enzyme in the pathway for insulin-stimulated GLUT4 translocation (146), and almost normalized the diminished protein expression of GLUT4 in IUGR compared to control progeny (49). Retinol binding protein 4 (RBP-4) has been linked in some studies to insulin resistance and interestingly exercise (again only 56 m/day) after IUGR induced by severe maternal nutrient restriction reduces the elevated circulating RBP-4 plasma concentrations in IUGR rats back to control levels (74). Adult (120 days) IUGR rats, where the IUGR was caused by protein restriction in the mother, have reduced type 1 muscle fibres (and more type 2 fibres) in soleus muscle compared with control rats, with no differences in muscle fibre expression in the extensor digitorum longus muscle (64). Eight weeks of treadmill exercise training tended to normalize fibre types, although not to proportions observed in exercised control rats (64). Given that people with T2D have greater proportions of type 2 fibres and less type 1 fibres in skeletal muscle than individuals with normal glucose tolerance (128), this may be beneficial for insulin sensitivity.

In contrast to the remarkable normalization of β-cell mass at 24 weeks of age after early life exercise (5-9 weeks of age) in IUGR rats (62), early life exercise did not have a sustained or reprogramming effect on skeletal muscle mitochondrial markers at 24 weeks of age (63). This greater beneficial effect of early life exercise after IUGR in a distal organ such as pancreas rather than in the muscles contracted during exercise is somewhat surprising.

5.3 Obesity

In general, exercise in rats born following IUGR reduces body weight as well as circulating leptin. In Wistar-Kyoto rats born IUGR after placental restriction at day 18 of pregnancy, treadmill exercise training from 5-9 weeks of age had no effect on postnatal growth trajectories and body weight remained lower in IUGR than control until 20 weeks of age (62). In these rats, absolute and dorsal fat was lower in IUGR than control at 9 weeks of age and exercise training from 5-9 weeks of age reduced absolute and dorsal fat at 9 weeks similarly in the two groups (63). By 24 weeks of age, there was no difference in absolute and dorsal fat between IUGR and control groups after early life exercise (63). This contrasts with
the protective effect of early life exercise in rats selectively bred for susceptibility to diet-induced obesity (DIO) and fed a high energy diet (98, 99). In these DIO-susceptible rats, early life exercise (3 to 6 weeks of voluntary wheel running starting at 5 weeks of age), was protective against the development of obesity and leptin resistance, and this protective effect persisted for 4-10 weeks after exercise (98, 99). Adult exercise from 20-24 weeks, however, resulted in a small but significant 3.5% reduction in body weight of IUGR progeny at 24 weeks (62), whilst treadmill exercise training from 20-24 weeks of age reduced absolute and dorsal fat similarly in control and IUGR groups (63).

Consistent with beneficial effects of adult exercise for obesity after IUGR in the PR rat, adult exercise improved body composition and tissue leptin in IUGR rats induced by maternal low protein diet in gestation and lactation. In these relatively young rats, a moderate exercise training regime (8 weeks, 5 day/week, 60 min/day, up to 18.3 m/min) from 60 to 120 days of age normalized the accelerated postnatal growth and reduced lean mass in IUGR rats, and normalized the elevated leptin content of adipose tissue in IUGR rats at 120 days of age, compared with sedentary IUGR animals (26). Adult exercise was also beneficial in IUGR rats induced by severe maternal nutrient restriction in gestation, where voluntary exercise (1 h/d from 60 d to 250 d of age, 56 m/day) reduced body fat percentage at 100, 150 and 250 days and body weight at 250 days compared with IUGR sedentary controls (74). Consistent with the lower adipose leptin expression after exercise training reported in the low protein-induced IUGR rat (26), 190 days of voluntary wheel running tended (non-significant) to diminish the elevated levels of serum leptin in IUGR rats from severely maternally nutrient-restricted pregnancies, when compared with their IUGR sedentary controls (74). In that study of severe maternal global nutrient restriction, exercise also significantly reduced the plasma concentrations of free fatty acids, glycerol and triglycerides in control and IUGR progeny, although only plasma triglycerides were elevated in IUGR without exercise (74). Surprising, 6 weeks of treadmill running in young rats (exercise training from 21-60 days of age) had no effect on body weight in either IUGR (moderate maternal nutrient restriction in late pregnancy) or control progeny and actually increased white adipose tissue in both groups (38).
Taken together, these results in general indicate that exercise or increased physical activity in rats after IUGR reduces body and fat mass, increases insulin sensitivity, increases muscle mitochondrial biogenesis and tends to reduce leptin content. In general these responses are similar in control and IUGR rats. Although more studies need to be conducted, there is some evidence that exercise early in life after IUGR can cause benefits later in life that are greater than the immediate effects of exercise training (at least in regards to $\beta$-cell mass). Further studies are required to determine the mechanisms involved.

6) CONCLUSIONS AND FUTURE DIRECTIONS

6.1 Current knowledge and future directions for studies in humans

It is clear that IUGR/SGA increases the risk of impaired metabolic health in adult humans, particularly diabetes and impaired insulin-regulated glucose homeostasis (section 2). Effective interventions are needed to improve adult metabolic health in this population. Although exercise is beneficial, current evidence has not resolved whether exercise is as effective in the SGA population as in those whose growth was normal during gestation (section 4) and little is known about underlying changes in insulin secretion or insulin sensitive tissues. Although observational studies provide evidence of a protective effect of physical activity against adolescent insulin resistance in individuals born with low birth weight, including in cohorts born at term (61, 87), these would be improved by use of $z$-scores (birth weight expressed as a standard deviation from the mean at that gestational age), rather than absolute birth weight. The single observational study in elderly adults also does not separate effects of gestational age from those of restricted growth in utero (29), and both probably contribute to insulin resistance in low birth weight humans (56). Ideally, future studies will ensure clear separation of effects of restricted growth in utero from those of prematurity, by correcting for gestational age. Studies in monozygotic twins with discordant birth weight might also be useful in evaluating the effects of fetal growth on exercise responses whilst minimizing variation due to genetics and postnatal environment.

In addition, tests of whether metabolic responses to exercise differ with size at birth might be confounded if individuals with small size at birth spontaneously do more or less exercise
than those of normal birth size. Contradictory relationships between size at birth and spontaneous activity have been reported in two studies in the Helsinki cohort (29, 117). In their study of metabolic responses to exercise, Eriksson and co-authors report that adult exercise frequency, intensity and yearly physical activity evaluated by questionnaire correlated inversely with birth weight and/or ponderal index, indicating that small size at birth resulted in adults who were more active (29). In contrast, Salonen et al reported that leisure time physical activity was positively correlated with weight and length at birth (117). Although the inclination to be active is extremely important for metabolic health, it is also important to know if the benefits of exercise are normal after IUGR. Interventional studies of exercise in humans have only been conducted in obese children (109) and in young adult males to date (80), although the former involved a lifestyle intervention and did not study responses to exercise per se. Plasma glucose, body fat and aerobic capacity responses to a 12-week exercise training program were similar in adult SGA and AGA men (80), but effects of exercise on insulin sensitivity have not been reported in this cohort to date. Additionally, there is evidence that SGA worsens metabolic responses to physical inactivity in young adult men (79) and to a lifestyle intervention in obese children (109). Accurate measures of baseline fitness and activity, and preferably matching of these between SGA and AGA individuals would assist in characterizing responses to exercise interventions. Studies in older adults, in whom insulin resistance has emerged after IUGR, and of women born SGA, are also needed to fully assess effects of exercise on insulin action after IUGR in humans.

6.2 Current knowledge and future directions for studies in animal models of IUGR

Studies of responses to exercise in various rat models of IUGR have provided proof of concept that exercise is beneficial for metabolic health after IUGR (section 5), although the effects of exercise vary between models, possibly reflecting the different types and timings of perturbations during pregnancy, and depend on age and sex of progeny, and not all outcomes have been evaluated across all models. Even fairly limited amounts of exercise improved insulin sensitivity in rats that were IUGR due to a 50% restriction of maternal feed intake in the second half of pregnancy, although the exercise-induced improvement in glucose tolerance observed in controls was absent in the IUGR group (38). Intriguingly, early life exercise normalizes the greatly reduced adult β-cell mass in PR Wistar-Kyoto rats, whilst
adult exercise restored 1st phase insulin secretion in the adult PR rat (62). The PR Wistar-Kyoto model has thus been pivotal in demonstrating benefits of exercise after IUGR for insulin secretion, as well as providing the first proof of early life reprogramming by exercise. Nevertheless, translation of these findings to humans is difficult because none of the animal models of IUGR in which exercise has been tested to date induced insulin resistance or diabetes (section 3). Ideally, efficacy of exercise as an intervention after IUGR also needs to be evaluated in a model where IUGR induces diabetes and impairments in both insulin sensitivity and secretion, such as occurs in IUGR progeny induced by PR in the Sprague-Dawley strain (123, 124, 127, 145). To some extent the insulin resistance seen after PR in the Sprague-Dawley rat might reflect development of obesity (124), which is not induced by PR in the Wistar-Kyoto rat strain (63, 85, 122). Effects of IUGR on insulin resistance secondary to central obesity may also apply in human populations where increased visceral fat in SGA individuals and after neonatal catch-up growth have been reported in several studies (reviewed by 113, 148). Such rodent studies permit adult outcomes to be measured within months to a few years due to the shorter life spans of rats compared to humans and other large mammal species.

Additionally, because the degree and timing of restriction are critical for metabolic outcomes, effects of adult and early life exercise also need to be tested in an animal model in which exposure to a restricted environment is chronic during gestation, mimicking the placental dysfunction that is a major cause of human IUGR in developed countries (47). Placental restriction in sheep, by removal of the majority of placental attachment sites prior to pregnancy (2, 111), provides an animal model where placental function, and hence oxygen and nutrient delivery (46, 89-91, 111), are chronically impaired throughout pregnancy. This model reduces average birth weight by ~25%, although with some variation in effect size due to variable numbers of placental attachment sites remaining after surgery, compensatory increases in growth of individual placentomes, and twinning in some ovine pregnancies (2, 23, 24, 40, 46, 92, 111). Both insulin sensitivity and insulin secretion are impaired from early postnatal life in the PR sheep (23, 24, 40, 92), consistent with effects of IUGR in humans (sections 2.1 and 2.2). These growth-restricted lambs also undergo catch-up growth with increased visceral fat deposition and evidence of leptin resistance in early postnatal life (22, 24), for which there is also evidence in humans (section 2.3). This ovine
model of IUGR also has the advantage, particularly for studies of insulin secretion responses
to interventions, that the timing of pancreas development is more similar to humans than
rats. In sheep, as in the human, development of the pancreas is mostly prenatal (6, 33, 57,
67, 88, 102, 107, 114), and hence subject to effects of IUGR, whereas development of the
rat pancreas commences later in pregnancy and continues after birth (81, 101, 107, 119). In
fetal sheep and humans, β-cells can be detected by ~25% of term, with islets and insulin
secretory function evident by mid-gestation (6, 33, 57, 67, 102, 107), whereas β-cells are not
present in the fetal rat until around 60% of term (107). The pancreas undergoes a wave of
apoptosis and developmental remodelling to a glucose-responsive phenotype, which occurs
before birth in sheep and humans (57, 67, 88, 114), but during days 10-17 after birth in rats
(81, 101, 119). We have recently shown (unpublished data) that whole-body insulin
sensitivity is elevated on the day after acute exercise in sheep, consistent with effects of
exercise in humans. Studies of responses to differing exercise regimens and the underlying
mechanisms in the PR sheep are therefore more likely to be directly translatable to
recommendations for human IUGR.

6.3 Conclusions

IUGR impairs adult insulin sensitivity in most adult human populations and in animals, with
good evidence for increased visceral adiposity after IUGR in animals, although the limited
evidence for IUGR-induced obesity is more variable in adult humans. Recent evidence in
humans and animals suggests that adult exercise may be effective as an intervention to
improve metabolic health after IUGR. This is an emerging area of research, particularly in
human studies, and only limited conclusions can be drawn from those studies published to
date. Although exercise improves metabolic outcomes in most studies, it is not currently
clear whether the metabolic responses to adult exercise are normal or blunted in SGA
individuals compared with those born AGA. A further exciting question, based on studies in
the PR rat, but not yet tested in SGA humans or in non-rodent animal models of IUGR, is
whether early life exercise can reprogram or reverse the metabolic effects of IUGR.

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References


Table 1: Effects of IUGR on metabolic outcomes in animal models

<table>
<thead>
<tr>
<th>Species (strain) and restriction model</th>
<th>Restriction induced by</th>
<th>Timing of restriction</th>
<th>Fetal outcomes</th>
<th>Metabolic outcomes of the offspring</th>
</tr>
</thead>
</table>
| Rat (Sprague-Dawley), Placental restriction at day 18-19 of gestation | Surgical bilateral ligation of uterine arteries (151) | From day 18 or day 19 of gestation until term (22 days) | • Birth weight ↓15-25% (123, 124) • Litter size/fetal death not reported | Glucose tolerance/diabetes:  
- Mild ↑ fasting plasma glucose from 7 weeks (progeny sex not stated) (124) or from 15 weeks in males (123), diabetic by adulthood (124)  
- Impaired glucose tolerance in IPGTT from 1 week, worsens with age (progeny sex not stated) (124, 127)  

Insulin secretion:  
- β-cell mass normal (=) at 1 week, = or ↓50% (males) at 7 weeks, ↓50% at 15 weeks, ↓70% at 6 months (123, 124, 127)  
- β-cell proliferation ↓~30% at 2 weeks (127)  
- in vivo glucose-stimulated insulin secretion: 1st phase ↓50% at 1 week insulin response to glucose lost by adulthood (6 months) (124)  
- = arginine-stimulated in vivo insulin secretion (124)  
- Glucose-stimulated insulin secretion from isolated islets in vitro ↓~50% at 1 and 7 weeks, ↓75% in adults. In vitro leucine-stimulated insulin secretion ↓~40-50% at 1 and 7 weeks, ↓27% in adults. Only males studied (123)  

Insulin sensitivity:  
- ↓ whole-body insulin sensitivity (IPITT) from 1 week of age, worsens with age with minimal glucose response to IPITT in adults (124)  
- ↓ whole-body insulin sensitivity by HEC in young adult (2 months) males (females not studied) (145) |
| Rat (Wistar-Kyoto), Placental restriction at day 18 of gestation | Surgical bilateral ligation of uterine arteries (151) | From day 18 of gestation until term (22 days) | • Fetal weight ↓~15% at day 20 of gestation (85, 152) | • Fetal weight ↓~15% at day 20 of gestation (85, 152) | • Birth weight (day 1) ↓6-16% (63, 122) | • Litter size ↓21-25% at day 20 of gestation and ↓32-36% at birth (63, 85, 152) | • ↑basal HGP and hepatic resistance to insulin, ↓insulin-stimulated phosphorylation of proximal insulin signaling (IRS2 and Akt) in liver in young adult males (females not studied) (145) | Obesity: | • ↑body weight from 2 months onwards (124) | • Absolute fat depot weights (epididymal, perirenal, mesenteric) ↑20+% in young adults and ↑73+% in adults (124) | Glucose tolerance/diabetes: | • = fasting plasma glucose in adults of both sexes (62, 122) | • Glucose tolerance varied: impaired in adult males but not females (122), = in adult males and females (146), or = in young adult and adult males (62) | Insulin secretion: | • Relative β-cell mass ↓68% in young adult, ↓45-65% in adult males (females not studied) (62, 121) | • ↓1st phase insulin secretion in adult males but not females in one study (122), = in adult males and females (146), or = in young adult and adult males (62) | Insulin sensitivity: | • = insulin sensitivity by IPITT in adults (6 months) of both sexes (122) | • = PGC-1α protein in skeletal muscle of young adult males, ↓20-40% PGC-1α protein and mRNA in adult males, = in adult females. 30-60% ↓expression of other markers of mitochondrial biogenesis (mtTFA, COX III and COX IV) in adult males but not females (63, 146) | Obesity: | • Females undergo catch-up growth, = body weights at weaning (21 d) and in young adults, males lighter throughout life (63, 85, 122) | • In cross-fostered progeny, post-weaning food intake ↓ in both sexes at 5 weeks, = in }
female patients at 5 – 12 weeks, ↑ in males at 6 and 10 weeks (122)

- In cross-fostered progeny, = perirenal fat % in adult males and females, retroperitoneal fat ↑50% in adult males, = in females (122).
- When not cross-fostered, = body fat % in adult males and females (146)

Glucose tolerance/diabetes:
- Glucose tolerance by IPGTT impaired (↑50% AUC glucose) in neonates (2 d), glucose tolerance by IVGTT = in young adult (2 months) females, 25% poorer in adult (6-8 months) females, = in old adult (10 month) males, 11% better in aged females (15 months) and 15% poorer in aged males (36, 37, 39, 129)

Insulin secretion:
- = relative β-cell mass at birth (male and female), ↓50% in males and = in females at weaning, = in aged males (females not studied) (36, 70)
- = β-cell apoptosis and replication rates in neonates; = apoptosis, ↓35% replication, ↓80% neogenesis of β-cells at 21 d (mixed sexes, 70)
- Absolute insulin secretion (IVGTT) = in young adult females, = in adult males, ↑70% in aged females, ↓~30% in aged males (36, 37, 39, 129)

Insulin sensitivity:
- = insulin sensitivity by IVITT in young adult females, = insulin sensitivity by HEC in old and aged (17 months) adult males (21, 37, 129)
- Evidence of hepatic insulin resistance in aged (15 months) males (36)
- = insulin-stimulated glucose uptake in skeletal muscle, liver, WAT in aged (17 months) males (21)
- Skeletal muscle GLUT4 ↓50+% in neonates, = in young adult females (129)
- ↑~200% basal plasma membrane GLUT4 and complete loss of insulin-stimulated GLUT4 translocation in skeletal muscle of neonates and young adult females (129)
- = white adipose GLUT4, ↑~25% insulin-stimulated GLUT4 translocation in young

<table>
<thead>
<tr>
<th>Rat (Sprague-Dawley), Moderate global maternal nutrient restriction in late pregnancy only</th>
<th>Maternal feed intake restricted to 50% of ad libitum (129)</th>
<th>Second half of gestation only (day 11 to 21), pups cross-fostered and reared by control mother</th>
<th>Birth weight (day 1) ↓11-30% (21, 70, 129) = litter size (70, 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose tolerance/diabetes:</td>
<td>Glucose tolerance by IPGTT impaired (↑50% AUC glucose) in neonates (2 d), glucose tolerance by IVGTT = in young adult (2 months) females, 25% poorer in adult (6-8 months) females, = in old adult (10 month) males, 11% better in aged females (15 months) and 15% poorer in aged males (36, 37, 39, 129)</td>
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</tr>
<tr>
<td>Insulin secretion:</td>
<td>= relative β-cell mass at birth (male and female), ↓50% in males and = in females at weaning, = in aged males (females not studied) (36, 70)</td>
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<tr>
<td>= β-cell apoptosis and replication rates in neonates; = apoptosis, ↓35% replication, ↓80% neogenesis of β-cells at 21 d (mixed sexes, 70)</td>
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<tr>
<td>Absolute insulin secretion (IVGTT) = in young adult females, = in adult males, ↑70% in aged females, ↓~30% in aged males (36, 37, 39, 129)</td>
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<tr>
<td>Insulin sensitivity:</td>
<td>= insulin sensitivity by IVITT in young adult females, = insulin sensitivity by HEC in old and aged (17 months) adult males (21, 37, 129)</td>
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<tr>
<td>Evidence of hepatic insulin resistance in aged (15 months) males (36)</td>
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<tr>
<td>= insulin-stimulated glucose uptake in skeletal muscle, liver, WAT in aged (17 months) males (21)</td>
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<tr>
<td>Skeletal muscle GLUT4 ↓50+% in neonates, = in young adult females (129)</td>
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<tr>
<td>↑~200% basal plasma membrane GLUT4 and complete loss of insulin-stimulated GLUT4 translocation in skeletal muscle of neonates and young adult females (129)</td>
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<tr>
<td>= white adipose GLUT4, ↑~25% insulin-stimulated GLUT4 translocation in young</td>
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<tr>
<td>Rat (Sprague-Dawley), Moderate global maternal nutrient restriction in late pregnancy and lactation</td>
<td>Maternal feed intake restricted to 50% of ad libitum (129)</td>
<td>Second half of gestation (day 11 to 21) and through lactation: pups cross-fostered and reared by mother fed 50% during lactation</td>
<td>adult females (males not studied) (129)</td>
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<tr>
<td><strong>Obesity:</strong></td>
<td></td>
<td></td>
<td><strong>Glucose tolerance/diabetes:</strong></td>
</tr>
<tr>
<td>• Body weight catches up by 21 d in females and by 3-4 months in males, weight ↑ in adults from 90 d in females and from 4-10 months in males, normal at 17 months in males (21, 37, 70, 129)</td>
<td></td>
<td>• Fasting glucose ↓ 47% in young adult females (2 months) (129)</td>
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<tr>
<td>• In females, absolute weights of WAT and BAT normal in young adults and adults (129)</td>
<td></td>
<td>• Glucose tolerance by IVGTT = in young adult females (2 months), adult and old adult males (10 and 15 months), 25% poorer in old (6-8 months) adult females (36, 37, 129)</td>
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<tr>
<td>• In males, ↑ 100% in subcutaneous and ↑ ~50% in visceral fat cross-sectional areas in abdominal region as old adults, = relative WAT content as aged adults (36, 37)</td>
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<td><strong>Insulin secretion:</strong></td>
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<tr>
<td></td>
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<td>• Relative β-cell mass ↑ 50% in weanling (21 d) males, = in weanling females, ↑ 3-fold in aged males (36, 129)</td>
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<td></td>
<td></td>
<td>• = apoptosis, ↓ 50% replication and ↓ 60% neogenesis of β-cells at 21 d (70)</td>
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<td></td>
<td>• Absolute insulin secretion during IVGTT ↓ 60% at 2 months in young adult females, ↑ 20% in old adult males, = in aged adult males (36, 37, 129)</td>
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<td><strong>Insulin sensitivity:</strong></td>
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<tr>
<td></td>
<td></td>
<td>• Insulin sensitivity by IVITT = in young adult females, insulin sensitivity by HEC ↑ 100% in old adult males (10 months), normal in aged males (17 months) (21, 37, 129)</td>
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<tr>
<td></td>
<td></td>
<td>• Insulin-stimulated glucose uptake ↑ ~50% in skeletal muscle, normal in liver, WAT in aged (17 months) males (21)</td>
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<tr>
<td></td>
<td></td>
<td>• Total GLUT4 content ↓ 38%, ~two-fold increase in basal plasma membrane GLUT4 and complete loss of insulin-stimulated GLUT4 translocation in skeletal muscle in</td>
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</tbody>
</table>
| Rat (Wistar), Severe global maternal nutrient restriction in pregnancy only | Maternal feed intake restricted to 30% of ad libitum | Throughout gestation only: nutrition restricted day 1 after mating until delivery (d 23 of gestation), IUGR pups cross-fostered and reared by control mother, CON pups not cross-fostered (153, 154) | young adult females (males not studied) (129)  
• Normal total GLUT4 content and insulin-stimulated translocation of GLUT4 to plasma membrane in WAT in young adult females (males not studied) (129)  
**Obesity:**  
• Body weight lower throughout life in females and males (21, 70, 129)  
• In females, absolute weights of WAT ↓72% in young adults and ↓60% in adults (129)  
  = subcutaneous and visceral fat in abdominal region in old adult males, relative WAT ↓25% in aged males (at 17 months), resistant to developing obesity when fed a high-fat diet (21, 37)  
**Glucose tolerance/diabetes:**  
• Fasting glucose normal in neonates and at 1 months of age (mixed sex, and in adult males (4 months), ↑12% in aged adult (8 months) males (84, 130, 143)  
**Insulin secretion:**  
• Fasting insulin normal in mixed-sex weanlings, ↑76% in adult (4 months) and ↑>3-fold in old adult (8 months) males (84, 130, 143)  
**Insulin sensitivity:**  
• Normal insulin sensitivity by HEC in old adult (8 months) males (49, 130)  
• Normal or ↓40% GLUT4 in muscle from old adult (8 months) males (130)  
• ↓muscle fibre size in skeletal muscle (soleus & gastrocnemius) and ↑type 1 and ↓type 2 muscle fibres in skeletal muscle (soleus) of old adult males (8 months) (49)  
**Obesity:**  
• Males remain smaller to adulthood (4 months), body weight catches up by old adulthood in some but not all cohorts (8 months), normal (additive) weight responses to high fat diet from weaning to 4 months (84, 130, 141, 144)  
• ↑22% BMI in old adult (8 months) males, greater total body fat by DXA in adult |
Maternal dietary protein restriction in pregnancy and lactation

- Mothers fed 8% casein diet (17% casein in controls), diets kept isocaloric by adding starch (3)
- Throughout gestation and lactation: mothers fed low protein diet from day after mating to weaning (3)
- Birth weight normal in two studies, ↓20-23% in others (3, 20, 26, 30, 64, 65)
- = litter size (64, 65)

<table>
<thead>
<tr>
<th>Exercise in those born after IUGR</th>
<th>males (100-250 d old) (74, 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↑29% relative retroperitoneal fat weight as adults (4 months), ↑28% relative perirenal fat weight as old adults (8 months) in males (130, 141, 144)</td>
<td></td>
</tr>
<tr>
<td>• Appetite normal in some studies, but increased in others, ↑ in male progeny from weaning to adults (4 months), ↑40% in females at 5 months (75, 140-142, 144)</td>
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<tr>
<td>• Voluntary activity ↓20-30% in weanling (35 d old) and aged adult (14 month old) males and females (142)</td>
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<tr>
<td>• Shift in behavioural preference from lever-pressing (food reward) to voluntary running in adults (2-12 months) (75)</td>
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</table>

Glucose tolerance/diabetes:
- ↑15% fasting glucose, ~10% poorer glucose tolerance in adult (5 months) males (30)

Insulin secretion:
- Not reported

Insulin sensitivity:
- Normal insulin sensitivity by IPITT in adult (5 months) males (30)
- ↓5% type 1 and ↑25% type 2 muscle fibres numbers in skeletal muscle (soleus) of adult males (4 months) (64)

Obesity:
- Body weights ↓5-18% from 10 d to weaning (mixed sex) and in males from weaning until 6 months (3, 20, 25, 26, 30)
- Postnatal growth rates ↓50% from birth to weaning (mixed sex), ↓32-39% in week after weaning, then ↓14-18% to 2 months, ↑15-30% from 2 to 4 months in males (3, 64)
- ↓BMI from weaning to 5 months, but ↑5% abdominal circumference in adult
m&masculines;ales (26, 30)

- Leptin protein ↑ 2-fold+ in visceral fat, = in subcutaneous fat of adult (4 months)
  males (26)

- ↑ task motivation from a food reward at 2-3 months old and ↑ food-activation of hypothalamic regions involved in hedonistic control of intake at 6 months in females (males not studied) (20)

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1 For reasons of space and focus, this table describes effects of IUGR only in those animal models of IUGR in which postnatal exercise has been evaluated.

Effects of IUGR are indicated as follows: = unchanged or normal, ↓ decreased, ↑ increased.

Abbreviations: AUC, area under the curve; BAT, brown adipose tissue; GLUT4, glucose transporter 4; COX, cytochrome c oxidase; HEC, hyperinsulinemic euglycemic clamp; HGP, hepatic glucose production; IRS2, insulin receptor substrate-2; IUGR, intrauterine growth restriction; IAGTT, intra-arterial glucose tolerance test; IPGTT, intra-peritoneal glucose tolerance test; IVGTT, intra-venous glucose tolerance test; IPITT, intra-peritoneal insulin tolerance test; IVITT, intra-venous insulin tolerance test; mtTFA, mitochondrial transcription factor A; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PR, placentally-restricted; WAT, white adipose tissue
### Table 2: Effects of exercise training/ physical activity on metabolic outcomes after IUGR in SGA/LBW humans

<table>
<thead>
<tr>
<th>Study population</th>
<th>Exercise Timing/ Age</th>
<th>Physical activity measurement or Exercise protocol</th>
<th>Metabolic outcome results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adolescents from HELENA study and Swedish part of EYHS study (gestational age only available for HELENA cohort) HELENA study: n=520 (247 boys, 325 girls) EYHS study: n=269 (127 boys, 147 girls)</td>
<td>HELENA study: 12.5-17.5 years old; EYHS study: 14.5-16.5 years old;</td>
<td>Physical activity measured for 4 or 7 d using accelerometers, water-based activities not included HELENA study: for 7 days EYHS study: for 4 days</td>
<td>• Insulin resistance (HOMA-IR) tended to increase with decreasing birth weight in children with physical activity $&lt;$ median, HOMA-IR did not correlate with birth weight in children with physical activity $&gt;$ median (87)</td>
</tr>
<tr>
<td>Adolescents from HELENA cohort (inclusion required birth at term: ≥37 weeks of gestation) n=520 (223 boys, 315 girls)</td>
<td>12.5-17.5 years old;</td>
<td>Physical activity measured using accelerometers for 7 days</td>
<td>• In boys and girls who met physical activity recommendations (60 min/day), low birth weight did not predict plasma leptin concentrations (61)</td>
</tr>
<tr>
<td>Adults including LBW adults (identified by birth weight and birth length, gestational age not specified) n=500 (186 men, 314 women)</td>
<td>65-75 years old;</td>
<td>Exercise habits over the previous 12 months assessed by questions on weekly exercise frequency and intensity and yearly physical leisure time activity.</td>
<td>• Frequent and intense exercise ($&gt;$3/week) both associated with lower rates of glucose intolerance (OGTT) or diabetes (combined) across all birth weights • Protective effect of exercise interacted with size at birth, and was strongest in subjects who were small at birth, either as low birth weight (&lt;3,000 g) or low ponderal index (&lt;26kg/m$^3$) (29)</td>
</tr>
</tbody>
</table>

**Intervention studies**
| Obese SGA children (birth weight or length below 10\textsuperscript{th} percentile for gestational age) | 5-16 years old (10.5 ± 0.1yr) | • 1 year intervention of weekly exercise sessions plus nutrition education and behaviour therapy (108)  
• Weekly exercise therapy (ballgames, jogging, trampoline jumping)  
• Instructions were given in physical exercise and time spent watching television was reduced | • Baseline: SGA children had greater insulin resistance (HOMA-IR), higher insulin concentrations, blood pressure, and triglycerides (109)  
• After intervention: 79% lost weight overall, similar decreases in BMI z-score and blood pressure in SGA and AGA. Fasting plasma insulin concentration and insulin resistance (HOMA-IR) increased in SGA while largely unchanged in AGA (109) |
| SGA adult males (birth weight below 10\textsuperscript{th} percentile, born at term) and control adults | 22 years old | • Acute: 1 h of cycle exercise at 65% of VO\textsubscript{2} peak  
• Training: 1 h, 4 times/week at 65% of their individual VO\textsubscript{2} peak for 12 weeks | • Baseline: Plasma glucose, insulin and C-peptide and aerobic capacity, blood pressure, fat mass and fat distribution similar in SGA and AGA. (80)  
• Exercise training decreased plasma glucose and total body fat % and increased aerobic capacity similarly in both groups. No effect on plasma insulin or C-peptide. (80) |
| SGA adult males (birth weight below 10\textsuperscript{th} percentile, born at term) and control adults | 25-26 years old | • Physical inactivity rather than activity.  
• Outcomes measured before and after 9 days bed rest | • Baseline: Insulin sensitivity by HEC similar in both groups (79)  
• Bed rest decreased insulin sensitivity similarly in both groups but decreased insulin-stimulated Akt phosphorylation only in SGA (79)  
• Insulin-stimulated AS160 phosphorylation was lower in SGA subjects before and after bed rest (79) |

Abbreviations: AGA, appropriate size at birth for gestational age; BMI: body mass index; EYHS: European Youth Heart Study; HEC: hyperinsulinemic euglycemic clamp; HELENA: Healthy Lifestyle in Europe by Nutrition in Adolescence study; HOMA: Homeostasis model assessment; LBW: Low birth weight; SGA: small size at birth for gestational age; OGTT, oral glucose tolerance test;
Table 3: Effects of exercise training/physical activity on metabolic outcomes in animal models of IUGR.

<table>
<thead>
<tr>
<th>Species (strain) and restriction model</th>
<th>Exercise Timing</th>
<th>Exercise protocol</th>
<th>Age at evaluation of outcomes</th>
<th>Metabolic outcomes</th>
</tr>
</thead>
</table>
| Rat (Wistar-Kyoto), Placental restriction at day 18 of gestation | 5 to 9 weeks of age | • Treadmill running 5 days/week for 4 weeks.  
• Running duration increased from 20 up to 60 min, with the treadmill speed set at 15 m/min for the first week and 20 m/min thereafter | 9 weeks | • Fasting insulin not different between groups and unaffected by exercise. No differences between groups in glucose tolerance or insulin secretion by IPGTT and no effect of exercise (62)  
• Exercise increased relative islet surface area in IUGR and controls and partially restored 60–68% deficit in β-cell mass in IUGR rats (62)  
• Exercise increased muscle protein expression of PGC-1α and β-HAD and CS enzyme activity in both groups (normal in IUGR pre-exercise) (63) |
| | 5 to 9 weeks of age | • As above | 24 weeks | • Plasma glucose and insulin higher in IUGR with no effect of exercise (however, HOMA-IR tended to reduce) (62)  
• Early life exercise reversed the 60-68% β-cell mass deficit in IUGR offspring, despite no exercise training after 9 weeks of age; Sedentary IUGR littermates retained a 45% deficit (62)  
• Early life exercise did not restore PGC-1α to control levels (63) |
| | 20 to 24 weeks of age | • As above | 24 weeks | • Plasma insulin higher in IUGR and no effect of exercise.  
• Adult exercise restored the diminished 1st phase insulin secretion in IUGR rats (62)  
• Adult exercise restored β-cell mass to values comparable to |
| Rat (Sprague-Dawley), Moderate global maternal nutrient restriction in late pregnancy only | 21 days to 60 days of age | Treadmill running at a speed of 11 m/min for 15 min/day, 5 days/week for 6 weeks | 8 weeks | Exercise had no effect on body weight or fasting glucose concentration, decreased fasting insulin and HOMA-IR similarly in control and IUGR groups (38)  
Exercise improved glucose tolerance ~15% in controls but not IUGR, and decreased insulin secretion during IVGTT by ~50% in both groups (38)  
Exercise increased insulin sensitivity (by IVITT) ~20% in IUGR but not in controls (38)  
Exercise suppressed HGP similarly in IUGR and control rats (38)  
Exercise doubled WAT weights in control and IUGR (38) |
|---|---|---|---|
| Rat (Sprague-Dawley), Moderate global maternal nutrient restriction in late pregnancy and lactation | 21 days to 60 days of age | Treadmill running at a speed of 11 m/min for 15 min/day, 5 days/week for 6 weeks | 8 weeks | Exercise had no effect on body weight or fasting glucose concentration, decreased fasting insulin similarly in control and IUGR+PNGR groups (38)  
Exercise improved glucose tolerance ~15% in controls but not in IUGR+PNGR, and halved insulin secretion during IVGTT by ~50% in controls with no change in IUGR+PNGR (38)  
Exercise increased insulin sensitivity (by IVITT) ~20% in IUGR+PNGR but not in controls (38)  
Exercise suppressed HGP in control rats, but increased HGP |
| Rat (Wistar), global maternal nutrient restriction (30% of ad libitum throughout pregnancy). IUGR pups cross-fostered and reared by control mother, CON pups not cross-fostered | 60 - 250 days of age | 250 days | in IUGR+PNGR rats (38)  
- Exercise doubled WAT weights in control and IUGR+PNGR groups (38)  
- Exercise training tended to normalize the reduced protein expression of GLUT4 in IUGR rats.  
- Lower PGC1α protein content in IUGR rats was not increased with exercise training (49)  
- Exercise training increased muscle PKCζ protein expression in control rats by 20% (compared to non-exercised controls) and by 40% in IUGR rats (49)  
- Exercise reduced body weight in both IUGR and controls and prevented the onset of obesity in IUGR rats (74)  
- Exercise had no effect on the elevated plasma leptin levels in IUGR rats (74)  
- Exercise normalized the elevated plasma RBP-4 in IUGR rats (74)  
- Elevated hepatic PKCζ in IUGR was not affected by exercise training (74) |
|---|---|---|---|
| Rat (Wistar), Maternal dietary protein restriction (8% vs 17% during gestation and lactation) | 60 days -115 days of age | 120 days | in IUGR+PNGR rats (38)  
- Exercise doubled WAT weights in control and IUGR+PNGR groups (38)  
- Exercise training tended to normalize the reduced protein expression of GLUT4 in IUGR rats.  
- Lower PGC1α protein content in IUGR rats was not increased with exercise training (49)  
- Exercise training increased muscle PKCζ protein expression in control rats by 20% (compared to non-exercised controls) and by 40% in IUGR rats (49)  
- Exercise reduced body weight in both IUGR and controls and prevented the onset of obesity in IUGR rats (74)  
- Exercise had no effect on the elevated plasma leptin levels in IUGR rats (74)  
- Exercise normalized the elevated plasma RBP-4 in IUGR rats (74)  
- Elevated hepatic PKCζ in IUGR was not affected by exercise training (74) |

- Voluntary running wheel activity, 1 h/d during the light phase.  
- Amount of activity controlled in all rats (56 m/d)  
- 8 weeks of treadmill running, 5 days/week, 60 min/day, at 70% of VO₂max,
Exercise increased the proportion of type I fibres and reduced type 2 fibre percentage in the soleus skeletal muscle of IUGR rats, to similar levels as control rats (64).