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Review

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

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Gatford KL, Kaur G, Falcão-Tebas F, Wadley GD, Wlodek ME, Laker RC, Ebeling PR, McConell GK. Exercise as an intervention to improve metabolic outcomes after intrauterine growth restriction. *Am J Physiol Endocrinol Metab* 306: E999–E1012, 2014. First published March 11, 2014; doi:10.1152/ajpendo.00456.2013.—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 control populations. Such investigations will have implications for customizing the recommended level and timing of exercise to improve metabolic health after IUGR.

IUGR; glucose tolerance; insulin secretion; β-cells; insulin sensitivity; training; physical activity

1. 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 small for gestational age (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 impaired placental function due to poor villus structure of the placenta [placental restriction (PR) (17)]. Placental insufficiency is the leading cause of IUGR in developed countries (47), and is characterized 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 with those who were born appropriate for gestational age (AGA) (28, 31,

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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, among men in their 60s, those who had low birth weight (LBW) and low body weights at one year were more likely to develop poor glucose tolerance and T2D. Many studies have since confirmed that LBW in humans (reviewed in Refs. 82 and 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 hours, whereas 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 one-year lifestyle intervention in obese 10-year-old children improved insulin resistance less in SGA than in 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 β-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). LBW is consistently associated with measures of impaired glucose homeostasis and with the risk of T2D in adulthood (reviewed in Refs. 82 and 150). More recent studies have shown that this adverse association between LBW 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 LBW 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 than in AGA individuals in prepubertal children at 3 and 9 years of age and in young adults, although not in one-year-old infants (55, 73, 139). Together with the increased risk of diabetes in SGA compared with 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 (LBW) 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 in 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 (mus-

cle) 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)γ 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 it 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 in Ref. 155). Maternal exposure to severe undernutrition 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 LBW (reviewed in Refs. 4 and 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 in Refs. 113 and 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 in Ref. 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 a much higher percentage body fat (27 vs. 22%) compared with 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 in Ref. 42). Reduced circulating leptin levels after IUGR have been reported in newborns (53), 48-hour-old infants (7), and prepubertal 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 with 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 focuses 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 (see Supplementary Table S1. The supplementary tables are linked to this article on the Journal website). 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 with regard to translation to humans.

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 Supplementary Table S1). 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 6–25% in various studies (Supplementary Table S1). 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 microstructural pathologies observed in up to 55% of IUGR cases (115, 116, 118). Placental supplies 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 the 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 (Supplementary Table S1 and below). The Wistar-Kyoto strain does not become obese after PR (122), so effects of PR in this strain can be evaluated independently of those induced via obesity, but they also do not develop the insulin resistance characteristic of human IUGR (see section *2.2*). Because effects of PR differ between these two rat strains and laboratories, responses in each strain are described separately in Supplementary Table S1, 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 LBW/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 (Supplementary Table S1). 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 (Supplementary Table S1). 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 (Supplementary Table S1). 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 that seen after moderate restriction (reduced by 25–35% vs. 11–30%), metabolic outcomes for progeny are not markedly different between these models of pregnancy nutrient restriction (Supplementary Table S1). Fasting glucose is normal in animals up to adulthood, and is only mildly elevated in aged males, while glucose tolerance has not been reported (Supplementary Table S1). Studies in this model are hard to evaluate, however, because progeny of severely nutrient-restricted dams were cross-fostered, whereas 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 (Supplementary Table S1). 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 (Supplementary Table S1). 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 (Supplementary Table S1). 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 (Supplementary Table S1). 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 (Supplementary Table S1). 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 the 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 aging and between the sexes in animals when moderate maternal nutrient restriction is continued throughout lactation (Supplementary Table S1). 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 (Supplementary Table S1). 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 life-long 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, while heterozygotes have impaired capacity to increase β-cell mass and insulin secretion in response to developing insulin resistance (13, 60). PR suppresses transcription of *PDX1*, with suppression progressing from ~50% in late-gestation fetuses to ~80% in adults (96, 127). This reflects epigenetic changes at the *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 β-cell mass and function. Together, these findings after experimental IUGR in rats, and in particular after PR, suggest that impaired β-cell function and loss of β-cell mass each contribute to programming of insulin secretion after IUGR and that these are induced at least in part via epigenetic mechanisms.

3.3. Insulin sensitivity. PR 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 (Supplementary Table S1, *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 (nonobese) adults of both sexes, while there is evidence of reduced mitochondrial function and biogenesis in skeletal muscle at least in adult males (Supplementary Table S1). 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 (Supplementary Table S1). 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 (Supplementary Table S1). 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 LBW, including studies correcting for gestational age. Insulin resistance in the Sprague-Dawley rat 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 (Supplementary Table S1). 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 coexistence of visceral adiposity and insulin resistance seen only 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 (see Supplementary Table S2). Three observational human studies have been conducted, two in children and one in elderly people. As described below, although the effects were not large, being more active had beneficial effects with regard to insulin (and leptin) resistance in both SGA and AGA, with some suggestion of greater effects in SGA than in 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), while two shorter studies were 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 assessment 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 (Supplementary Table S2). 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 with regard 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 sessions/week) and intensity had lower rates of glucose intolerance across all birth weights (Supplementary Table S2). Importantly, this protective effect was strongest in participants who had had LBW (<3,000 g), in whom frequent (≥3 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 had been born prematurely, the majority of the cohort had been 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 (Supplementary Table S2) involving 12.5- to 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 among 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, whereas 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 (Supplementary Table S2), plasma leptin levels were elevated in LBW 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 9 days tend to support this theory (79) (Supplementary Table S2). 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 susceptibility 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 (Supplementary Table S2). The results of these are limited and mixed in regard to the impact on insulin sensitivity. Effects of a 12-month lifestyle intervention that included exercise, nutrition, and behavioral 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 involved only 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 behavioral components (108). At the commencement of the study, the obese SGA children had higher HOMA-IR than AGA children 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 LBW 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 (Supplementary Table S2). The decrease in BMI *z*-scores during a one-year lifestyle intervention including exercise therapy, nutrition education, and behavior therapy were similar in SGA and AGA children (reduced by 8.9 and 11.3%, respectively) (109). In young adult men, exercise training 4 days a week for 1 hour a day at an intensity corresponding to 65% of their individual $\dot{V}O_{2\ peak}$ 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 (see Supplementary Table S3). 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 regard 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 etiology of these rodent models is often hard to compare to that of humans. In addition, differences 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, need 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 (PR) restored reduced β-cell mass in the IUGR rats and in doing so normalized the diminished first-phase insulin secretion during IPGTT (62). This differs from effects of exercise reported by Garg et al. (38) in 8-week-old rats that had IUGR induced by maternal nutrient restriction. Those IUGR rats had lower IVGTT first-phase insulin secretion than control rats, consistent with effects of PR reported by Laker et al. (62). In contrast with the latter study, however, Garg et al. reported that exercise reduced first-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 et al. (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 et al. (120). In that study, early-life exercise (from 7 to 15 weeks of age) prevented development of diabetes in the insulin-resistant Otsuka-Long-Evans-Tokushima Fatty (OLETF) rat, whereas nonexercised 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 with sedentary controls (120). As discussed earlier, PR 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 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 make up only 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 adult rats with IUGR 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 hyperinulinemic euglycemic clamp than control progeny, at least in old adult (10-month-old) males (Supplementary Table S1). As with the IUGR rats, exercise increased insulin sensitivity by IVITT in these animals 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 aging or with additional postnatal challenges such as high-fat feeding, however, and indeed we have shown that the female progeny have glucose intolerance compared with 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 to 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 with results of an intervention study in obese children, where a lifestyle intervention was less effective in SGA than in AGA children, and HOMA-IR actually worsened in the SGA group (109).

We found that treadmill exercise training from either 5–9 weeks or from 20–24 weeks elicits normal increases in skeletal muscle protein expression of PGC-1α, hydroxyacyl-CoA dehydrogenase β-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/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 with 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 fibers (and more type 2 fibers) in soleus muscle than control rats, with no differences in muscle fiber expression in the extensor digitorum longus muscle (64). Eight weeks of treadmill exercise training tended to normalize fiber types, although not to the proportions observed in exercised control rats (64). Given that

people with T2D have greater proportions of type 2 fibers and less type 1 fibers 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 PR 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 in control until 20 weeks of age (62). In these rats, absolute and dorsal fat was lower in IUGR than in 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 (3–6 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 to 24 weeks, however, resulted in a small but significant 3.5% reduction in body weight of IUGR progeny at 24 weeks (62), while 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 regimen (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 hour/day from 60 to 250 days 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 (nonsignificantly) to diminish the elevated levels of serum leptin in IUGR rats from severely maternally nutrient-restricted pregnancies 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 to 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 with regard to β-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 LBW, 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 LBW 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 monozyotic twins with discordant birth weight might also be useful in evaluating the effects of fetal growth on exercise responses while 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 et al. (29) reported 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. 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 been conducted only 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, whereas adult exercise restored first-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 in Refs. 113 and 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 with 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). PR 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 to rats. In sheep, as in the human, development of the pancreas is mostly prenatal (6, 33, 57, 67, 88, 102, 107, 114), 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 midgestation (6, 33, 57, 67, 102, 107), whereas β-cells are not present in the fetal rat until ~60% of term (107). The pancreas undergoes a wave of apoptosis and developmental remodeling 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 nonrodent animal models of IUGR, is whether early-life exercise can reprogram or reverse the metabolic effects of IUGR.

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AUTHOR CONTRIBUTIONS

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