Can exercise training rescue the adverse cardiometabolic effects of low birth weight and prematurity?

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Summary

1. Being born pre-term and/or small for gestational age are well-established risk factors for cardiometabolic disease in adulthood.

2. Physical activity has the potential to mitigate against the detrimental cardiometabolic effects of low birth weight from two perspectives: a) maternal exercise prior to and during pregnancy and b) exercise during childhood or adulthood for those born small or prematurely.

3. Evidence from epidemiological birth cohort studies suggests that the effects of moderate intensity physical activity during pregnancy on mean birth weight are small, but reduce the risk of either high or low birth weight infants. In contrast, vigorous/high intensity exercise during pregnancy has been associated with reduced birth weight.

4. In childhood and adolescence, exercise ability is compromised in extremely low birth weight individuals (<1,000g), but only marginally reduced in those of very low to low birth weight (1,000-2,500g).

5. Epidemiological studies show that the association between birth weight and metabolic disease is lost in physically fit individuals and consistently, that the association between low birth weight and metabolic syndrome is accentuated in unfit individuals.

6. Physical activity intervention studies indicate that most cardiometabolic risk factors respond to exercise in a protective manner, independent of birth weight.

7. The mechanisms by which exercise may protect low birth weight individuals include restoration of muscle mass, reduced adiposity, enhanced β-cell mass and function as well as effects on both aerobic and anaerobic muscle metabolism, including substrate utilisation and mitochondrial function. Vascular and cardiac adaptations are also likely important, but are less well studied.

Introduction

Being born pre-term and/or small for gestational age (SGA) are well-established risk factors for metabolic and cardiovascular disease in adulthood.[1-5] Physical activity throughout the life-course contributes to the prevention of metabolic and cardiovascular disease in the general population, and may mitigate against risks associated with low birth weight (LBW) from two perspectives. Firstly, maternal physical activity both prior to and during pregnancy may impact on birth weight, timing of delivery and later disease progression. Secondly, physical activity during childhood or adulthood for those of LBW or born

prematurely may prevent or reduce the detrimental effects of being born small. Both issues represent important clinical and public health questions.

Although mean birth weight in Australia has not changed significantly over the past 30 years, the percentage of babies born small or LBW (defined as <2,500g) increased by 19.6% from 1980 to 2008 and accounted for 6.7% of all births in 2009[6] (Figure 1). These data concur with those from the US, showing a 21% increase in LBW babies in the period from 1980 to 2002.[7] Interestingly, the number of macrosomic babies weighing more than 4,000g accounted for 12.1% of all births in 2008 in Australia, an increase from 11.0% in 1991[6] (Figure 1). The birth weight distribution has thus broadened, putting greater numbers of babies at the extremes and at elevated risk of both perinatal morbidity[8] and later life cardiometabolic disease.[9] The reasons for the increasing prevalence of LBW are likely due to the inter-related factors of increasing maternal age,[10] use of assisted-reproductive technology (ART),[11] as well as advances in neonatal intensive care over the past 40 years, which have reduced the limit of fetal viability to around 24 weeks gestation (term = 40 weeks).[12] On the other hand, the rising prevalence of macrosomic babies relates to high maternal BMI[13] and gestational diabetes associated with maternal insulin resistance and fetal overnutrition.[14,15]
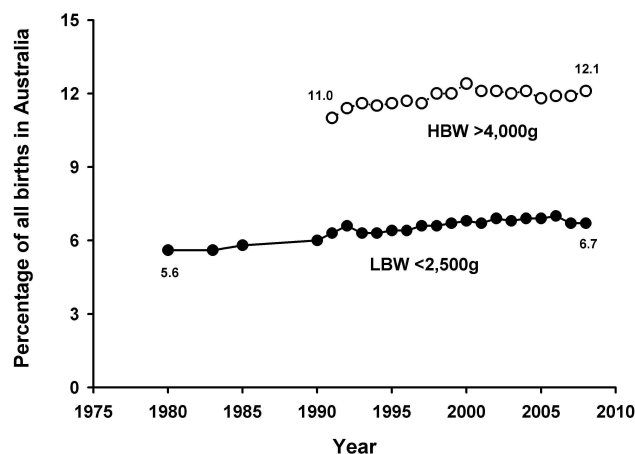

Figure 1. Percentage of babies (all births) born weighing either less than 2,500g (LBW) or more than 4,000g (HBW) in Australia from 1980 to 2009.[6]

Studying the effects of lifestyle factors from birth to disease onset, and ultimately death, presents significant challenges to current epidemiological, clinical and experimental approaches. These challenges have no doubt led to a focus in the literature on the interactions between

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exercise and LBW in relation to metabolic endpoints which manifest earlier in life and generally precede cardiovascular complications. A further limitation is the frequent absence of birth weight information in relation to gestational age, which would allow the effects of pre-term birth to be distinguished from the effects of intrauterine growth restriction. This review will thus focus on metabolic risk in relation to LBW regardless of the cause, including the effects of physical activity during pregnancy and physical activity in LBW individuals throughout life. The latter will include discussion of whether LBW influences propensity to exercise and exercise ability and finally responses to exercise training, their mechanisms and impact on development of cardiometabolic disease.

Exercise and cardiometabolic risk

In the general population there is compelling epidemiological evidence associating self-reported physical activity with a significant reduction in all-cause and cardiovascular mortality.[16] This is a strong dose-response relationship, which becomes steeper with increasing age. Furthermore, walking throughout the day provides additive benefit to purposeful moderate to vigorous exercise.[17] The Aerobics Centre longitudinal study supports such relationships between reported physical activity and mortality with objectively measured aerobic fitness, demonstrating higher maximal oxygen consumption (VO_2max) in association with lower death rates across a wide range of ages from 20 to 82 years.[18]

There has been a recent shift in physical activity research to include reducing and breaking up sedentary time in addition to purposeful physical activity. In the US National Health and Nutrition Examination Survey (NHANES) and Australian Diabetes, Obesity and Lifestyle (AusDiab) cohorts, objectively-measured total sedentary time was detrimentally associated with cardiometabolic risk factors, whereas interruptions or breaks in sedentary time (transition from sedentary to an active state for at least 1 min) were beneficial in relation to cardiometabolic and inflammatory biomarkers.[19,20] Interestingly, these relationships persist after accounting for purposeful moderate to vigorous activity, suggesting that frequent short breaks in sedentary time may impart independent benefits. This has recently been substantiated in an acute intervention trial where interrupting sitting time with short bouts of either light- or moderate-intensity walking lowered postprandial glucose and insulin levels in overweight/obese adults.[21]

The mechanisms contributing to the cardiometabolic risk reduction afforded by physical activity have been extensively studied. Well-controlled exercise intervention and animal studies have supported the epidemiology through elucidation of plausible mechanisms, which include cardiac, vascular, metabolic and neural adaptations. Studies by our team have convincingly demonstrated that aerobic training improves multiple risk factors including blood pressure, plasma lipids and blood glucose.[22-24] Adaptations in large artery biomechanical properties,[25-27] conduit vessel

endothelium dependent vasodilatation[28-32] and autonomic function[25,33-35] are also likely to contribute to improved outcomes.

In addition to greater life expectancy[36] and a reduction in cardiovascular mortality, moderately and highly active individuals live more years free of diabetes than their sedentary counterparts.[37-39] With regard to improvement in glycemic control, resistance training provides particular benefit for middle aged to elderly people with type 2 diabetes,[40,41] with mechanisms relating to greater insulin sensitivity secondary to effects on body composition, including an increase in lean body mass and/or a reduction in fat mass.[42,43] With regard to effects on muscle, aerobic and resistance exercise may contribute to elevated glucose disposal *via* different mechanisms. The major effect of resistance training is an increase in muscle mass without an alteration in the intrinsic capacity of the muscle to respond to insulin.[41] In contrast, aerobic training enhances glucose disposal independently of changes in muscle mass or aerobic capacity, suggesting an intrinsic increase in muscle glucose consumption.[42] Furthermore, both aerobic and resistance training likely increase insulin sensitivity through concomitant decreases in visceral and abdominal subcutaneous adipose tissue.[44,45]

In summary, regular moderate intensity aerobic and resistance exercise provide protection against cardiometabolic disease in the general population through well-established mechanisms.

Exercise during pregnancy

The importance of maternal lifestyle and behaviours for fetal health is well recognised. With respect to exercise habits during pregnancy and impact on birth weight, consideration must be given to the type, intensity and timing of the exercise during pregnancy. The differential effects of these exercise variables on birth weight must be gleaned from a variety of scientific approaches ranging from large birth cohort studies to randomised intervention trials. While large cohort studies can provide insight into the effects of physical activity on a population level, intervention trials are necessary to dissect out the effects of exercise modality, dose (intensity, duration and frequency) and timing during pregnancy. Available data permit broad conclusions on the issue of physical activity during pregnancy and birth weight. However, lifestyle intervention studies involving pregnancy are associated with significant challenges and limitations resulting in clear evidence gaps. Animal studies provide useful additional insight, particularly in regard to fetal programming and development of metabolic and cardiovascular disease in offspring of exercise-trained mothers.

Maternal exercise and birth weight

Pre-pregnancy maternal fitness, timing, intensity and frequency of exercise as well as daily leisure time or occupation-related physical activity during pregnancy all have the potential to influence birth weight. Both experimental and observational cohort studies suggest that

regular, low to moderate intensity physical activity generally does not influence mean birth weight of a population (Table 1).[46-48] In particular, there is consistent evidence that light to moderate intensity exercise (55-75% age-predicted maximum heart rate (HR)) during pregnancy is not associated with an increased risk of being born SGA.[49-51] Rather, population studies suggest that regular, low to moderate intensity physical activity reduces the risk of babies born at the extreme ends of the birth weight range. For example, Juhl *et al.*[52] found in their study of 79,692 pregnancies from the Danish National Birth Cohort a small reduction in risk of both SGA and large for gestational age (LGA) offspring of exercising women compared to non-exercisers. In this study, exercise habits were documented at 16 and 31 weeks of pregnancy and modalities included low-impact activities, such as dancing, walking/hiking, yoga and antenatal aerobics through to swimming, cycling, horseback riding and high-impact activities, like jogging, ball games and racquet sports. Another study using National Maternal and Infant Health Survey data from 9,089 women also confirmed a protective effect of regular leisure time physical activity during pregnancy against LBW outcomes.[53]

Consistent with human data, birth weight is unaffected when healthy well-nourished rodents participate in mild to moderate intensity exercise programs during pregnancy.[54] Further, mild training in conjunction with malnourishment during pregnancy indicates that the effect of diet on birth weight predominates over the training effect.[55] Training may, however, attenuate the impact of a low-protein diet on the growth rate of rat offspring.[56] Models of voluntary exercise in the rat may be useful for future studies of the effects of exercise during pregnancy on the developmental origins of health and disease. However, current animal studies are limited and offer little insight into the association between maternal exercise and birth weight in humans.

Exercise intensity and timing during pregnancy have been most comprehensively examined by Clapp and colleagues, particularly in prospective observational cohort studies.[57,58] Continuing vigorous weight-bearing exercise (running, aerobic dance and cross-country skiing) throughout pregnancy led to a reduction in mean birth weight of 509g[58] and 310g[57] compared to sedentary women. In contrast to moderate intensity physical activity, high-intensity or vigorous exercise continuing into the third trimester of human pregnancy in the context of either sport or agricultural work has been associated with reduced mean birth weight, but generally not enough to be classified as SGA.[13,52,59-64] Interactions with ethnicity and environment (*e.g.* nutrition) are also important considerations as high intensity physical activity during pregnancy is associated with LBW in Indian babies,[62,63] but not in urban, low income, black women in the USA.[65] The potential effects of exercise modality (*e.g.* jogging *versus* swimming) have not been explored in these epidemiological investigations. Another potential confounder has been that many of these cohorts of women were self-selected, rather than randomized.

A recent study in a Hispanic cohort found that women in the highest quartile for active living habits, which included walking or cycling to and from work, school and errands in mid-pregnancy and less television viewing had a decreased risk of SGA compared to those in the lowest activity quartile.[66] However, high intensity exercise in mid-pregnancy was associated with an increased SGA risk.[66] This is supported by smaller cohorts in which well-conditioned recreational athletes[57] or healthy women continuing a program of vigorous weight-bearing aerobic exercise in late gestation had lower birth weight babies compared with active age-matched controls. Other studies in previously sedentary women, that began weight-bearing exercise programs during pregnancy found that birth weight either increased,[67] or did not change.[64,68] These differential effects may relate to factors including maternal fitness and physical activity intensity/frequency/duration prior to pregnancy.

More intense exercise programs during pregnancy in animals can affect both fetal growth and litter size (reviewed by Gorski, 1985[69]). Strenuous exercise in pregnant animals has been well-documented to reduce fetal weight as shown in mice,[70] rats,[71,72] guinea pigs[73] and goats.[74] Animal studies provide mechanistic insight suggesting that intense exercise may restrict placental blood flow causing fetal nutrient restriction and hypoxia.[72] The greater fetal nutrient demand and placental mass during the latter half of pregnancy and particularly in the third trimester, likely explains the fact that exercise during this period can have a substantial effect on birth weight.[75] In fact, exercise confined to early pregnancy in humans increased the parenchymal component of the placenta, total vascular volume and site-specific capillary volume and surface area. Whereas exercise throughout pregnancy increased these and other histomorphometric parameters associated with the rate of placental perfusion and nutrient transfer function.[59]

A recent study in 84 healthy nulliparous women suggested that regular aerobic exercise (home-based stationary cycling program) from gestational week 20 to delivery, through its effects on improving maternal insulin sensitivity, may influence offspring size by regulating nutrient supply to the developing fetus.[49] Here exercise was associated with reduced umbilical cord concentrations of insulin-like growth factor (IGF)-I and IGF-II compared with offspring of non-exercisers, resulting in lower mean birth weight, but not SGA births, suggesting an influence of exercise on endocrine regulation of fetal growth.[49] Babies of mothers who continued to exercise vigorously into the third trimester were leaner, with no loss of muscle mass, compared to those who continued with a moderate intensity program, or ceased exercise after the second trimester.[76] These data suggest a high volume of moderate-intensity, weight-bearing exercise in mid- and late pregnancy reduces fetoplacental growth overall, but supports development of lean tissue. *Whether such effects on body composition at birth impact on adult cardiometabolic health remains to be tested.*

Table 1. Summary of the effect of maternal exercise on birth weight outcomes in human intervention and cross-sectional observation studies. (In citation order).

First author (Year) Country (ref. no.)	Study design	Total no. of participants (no. exercisers if applicable)	Timing of exercise during pregnancy	Controls	Exercise modality	Effect of exercise on mean birth weight vs control or as stated (P value)	Exercise/PA duration, frequency, intensity
Fleten (2010) Norway[13]	Cross-sectional Observation	43,705	2nd trimester	Sedentary	Brisk walking, running, cycling, weight training, gym, aerobics, dancing, skiing, ball games, swimming	↓2.9g/unit (1×/mo) exercise	1-3×/mo 1×/wk 2×/wk 3+/wk
Hatch (1993) USA[47]	Cross-sectional Observation	462 (277)	Throughout	Sedentary	Strenuous: Aerobics, running; Non-strenuous: Gardening, antenatal exercise class	Low-moderate ↑165g (ns) Heavy ↑325g ($P<0.05$†)	Low-moderate: ≤1,000kcal/wk Heavy: >1,000kcal/wk
Sternfeld (1995) USA[48]	Cross-sectional Observation	361 (119)	Throughout	Sedentary/Low activity=Level IV	Aerobics, cycling, running, swimming	Level I @36wks ↑84g (ns) Level II @36wks ↑121g (ns)	20min/session Level I: 3+/wk - vigorous walking Level II: 3+/wk + vigorous walking Level III: 1-3×/wk Level IV: <1×/wk
Hopkins (2010) NZ[49]	Intervention	84 (47)	2nd & 3rd trimester	Sedentary	Stationary cycle	↓143g (ns§)	≤5×/wk 40min/session 65% VO$_2$max
Juhl (2010) Denmark[52]	Cross-sectional Observation	79,692 (29,763)	1st & 2nd trimester	Sedentary	Swimming, aerobics/gymnastics, dance, walking/hiking, yoga, jogging, ball games, gym, cycling, horse riding	Ex >5h/wk ↓11g (ns) & modest ↓SGA risk (ns)	0-1h/wk 1-2h/wk 2-3h/wk 3-4h/wk 4-5h/wk >5h/wk
Leiferman (2003) USA[53]	Cross-sectional Observation	9,089	Throughout	Active (Con Ex)	Regular leisure physical activity: "Did you exercise or play sports?"	Uncon Nex ↑VLBW risk vs Con Ex ($P<0.05$) Con Nex ↑LBW risk vs Con Ex ($P<0.01$)	Before preg: Conditioned (Con-Exercise 3+/wk) Unconditioned (Uncon-Exercise <3×/wk) During preg: Exerciser (Ex-3+/wk) Non-exerciser (Nex-<3 /wk)
Clapp (1990) USA[57]	Cross-sectional Observation	132 (77)	Throughout	Active	Aerobics, running	↓310g ($P<0.05$)	As for Clapp (1984) below
Clapp (1984) USA[58]	Cross-sectional Observation	228 (76)	Throughout	Sedentary = Group I	Aerobics, running, x-country skiing	Grp III ↓509g vs Grp I ($P<0.01$) Grp II ↑59g vs Grp I (ns)	3×/wk 30min/session 50% age-adjusted max HR; Group II (n=47): Discontinued exercise by 28wks; Group III (n=29): Exercised throughout
Jackson (1995) USA[59]	Cross-sectional Observation	60 (40)	2nd & 3rd trimester	Active	Aerobics, running, x-country skiing	2nd trimester ↓220g (ns) 3rd trimester ↓224g (ns)	3+/wk 30min/session >50% max capacity
Clapp (1998) USA[60]	Cross-sectional Observation	104 (52)	Throughout	Sedentary	Step aerobics, stair stepper, treadmill	↓200g ($P=0.05$) @birth ↓70g (ns) @1 year	3+/wk 20min/session >50% max capacity
Marquez-Sterling (2000) USA[61]	Intervention	15 (9)	2nd & 3rd trimester	Sedentary	Cycling, rowing, running, walking	↓207g (ns)	3×/wk 60min/session 150-156bpm

First author (Year) Country (ref. no.)	Study design	Total no. of participants (no. exercisers if applicable)	Timing of exercise during pregnancy	Controls	Exercise modality	Effect of exercise on mean birth weight vs control or as stated (P value)	Exercise/PA duration, frequency, intensity
Rao (2003) India[62]	Cross-sectional Observation	610	2nd & 3rd trimester	Active (low activity)	Agricultural & domestic activities: Cooking, washing, sweeping, fetching water, farm work, resting	High PA @18wks ↓69g (P=0.05) High PA @28wks ↓69g (P=0.02) High PA @18wks ↑LBW risk (P<0.05)	Activity score: Low Medium High See ref. for more detail
Dwarkanath (2007) India[63]	Cross-sectional Observation	546	Throughout	Sedentary activities (>165min/day)	Occupational, exercise, housework, hobbies, sleep	Highest PA tertile in 1st trimester ↑ LBW risk	Relative maternal physical activity level (Tertiles)
Haakstad (2011) Norway[64]	Intervention	105 (52)	2nd trimester	Sedentary	Aerobic dance & strength training; plus 30min self-imposed physical activity	100% exercise adherence ↓232g (ns) NB: n=14 only	2×/wk 60min/session
Orr (2006) USA[65]	Cross-sectional Observation	922	Throughout	Sedentary	Self-reported physical activity	↑LBW risk (ns)	Strenuous vs Non-strenuous exercise
Gollenberg (2011) USA[66]	Cross-sectional Observation	1,040	1st & 2nd trimester	Low activity quartile	Sports/exercise, household, occupational, active living (Categorized in quartiles)	High PA mid-preg ↓SGA risk; High sports/ exercise ↑SGA risk	See ref. for details
Clapp (2000) USA[67]	Intervention	46 (22)	Throughout	Sedentary	Step aerobics, stair stepper, treadmill	↑230g (P<0.05)	3-5×/wk 20min/session 55-60% VO_2 max
Clapp (2002) USA[76]	Intervention	75 (51)	Throughout	Active Mod-Mod (n=24): Moderate intensity throughout	Step aerobics, stair stepper, treadmill	Hi-Lo ↑460g vs Mod-Mod (P<0.001) Lo-Hi ↓100g vs Mod-Mod (ns)	5×/wk Low=20min/session Mod=40min/session High=60min/session 55-60% VO_2max; Lo-Hi (n=26): Low int. 8-20wks; High int. 24-40wks; Hi-Lo (n=25): High int. 8-20wks; Low int. 24-40wks
Erkkola (1976) Finland[140]	Intervention	44 (23)	Throughout	Sedentary	Cycling, running, stair climbing, swimming, walking	↑88g (ns)	3×/wk 60min/session HR >140bpm
Collings (1983) USA[141]	Intervention	20 (12)	2nd & 3rd trimester	Sedentary	Cycling	↑243g (ns)	3×/wk for 7-19wks 50min/session 65-70% VO_2max
Zeanah (1993) USA[142]	Cross-sectional Observation	173 (87)	3rd trimester	Active	Unknown	High intensity ↑255g vs Low intensity (ns); Long duration ↑17g vs short duration; ↑99g vs moderate duration (ns)	Duration: Long=40min/session Moderate=20-39min Short=≤19min Intensity: High=HR >150bpm Moderate=HR 130-149bpm Low=HR ≤129bpm
Bell (1995) AUS[143]	Cross-sectional Observation	99 (58)	2nd trimester	Sedentary	Aerobics, swimming, running.	5+/wk ↓315g (P<0.02) 3×/wk ↑318g (P<0.05)	3+/wk 30min/session 50% age-adj.max HR
Bell (2000) AUS[144]	Intervention	43 (23)	2nd & 3rd trimester	Active=Grp 2	Vigorous exercise	Grp 1 ↑75g (ns)	30min/session 50% age-adj.max HR Grp 1 continued: 5+/wk Grp 2 reduced: 1-3×/wk
Campbell (2001) USA[145]	Intervention	529 (164)	3rd trimester	Active (3-4×/wk)	Recreational exercise & occupational activity	↑LBW risk (Adjusted OR 4.61 vs NBW, P<0.05)	Structured exercise 3-4×/wk vs 5+/wk

In summary, moderate intensity exercise during pregnancy may reduce the risk of babies born at the extreme ends of the birth weight range. High-intensity or vigorous exercise, particularly during the third trimester generally leads to a reduction in mean birth weight. Finally, exercise during pregnancy may influence endocrine regulation of fetal growth and promote an increase in the ratio of muscle to adipose tissue mass.

Maternal exercise and pre-term birth

In the US, the prevalence of pre-term birth (defined as delivery before 37 weeks of gestation) has risen to approximately 12.5% over the last twenty years[77] and is the leading cause of neonatal and infant morbidity and mortality.[78] The latest data from Australia reported that in 2009, 8.2% of babies were born pre-term.[6] Length of gestation is obviously a potential mechanism whereby maternal exercise might indirectly influence birth weight. It is possible that both the beneficial effects of moderate intensity exercise in protecting against birth weight extremes and the detrimental association between vigorous exercise in late pregnancy and LBW may be underpinned by the effects of exercise on the length of gestation.

A protective effect against pre-term birth was found with both leisure time physical activity throughout pregnancy in two well-powered Brazilian studies[79,80] as well as with first trimester vigorous activity.[81] A more recent review included studies from 1987 to 2007 and found that although the associations between physical activity and pre-term birth were not strong, recreational or leisure-time activities performed regularly provides some protection against prematurity.[82] It was also pointed out that the evidence is confounded by many methodological flaws.

It has been suggested that vigorous exercise during the second and third trimesters of pregnancy may increase the risk of pre-term delivery. Whilst a systematic meta-analysis reported an increased risk of pre-term birth in the exercise group, there was no overall effect on mean gestational age and the increased risk may have been biased by post-randomisation exclusion of women with pre-term labor.[83] Duncombe and colleagues examined the effects of intense exercise on birth weight and gestational age in 148 recreational exercisers. Only four women in the study gave birth prematurely, with two of these exercising into the second trimester. Therefore, it was concluded that exercise was not a contributing factor, however it was noted that other risk factors such as maternal age, socioeconomic status, diet and obstetric complications were not accounted for.[84] Another group studied 5,749 healthy pregnant women who competed in sport *versus* those who did not. Women who engaged in moderate to heavy leisure time physical activity *versus* sedentary women showed a significantly reduced risk of pre-term delivery. The authors therefore concluded that there was a strong association between sedentary lifestyle and pre-term delivery.[85] The most recent randomized controlled study was in 105 sedentary, nulliparous pregnant women, which examined the effect of a supervised exercise-program on birth weight and

gestational age at delivery. The exercise program consisted of supervised aerobic dance and strength training for 60 minutes, twice per week from 24-36wks of gestation. No difference in length of gestation was reported in this study.[64] Other studies have also shown no relationship between physical activity exercise and gestational age[48,86-89] again highlighting the challenges of interpreting these studies given the many inconsistencies in methodologies.

In summary, regular moderate intensity exercise throughout pregnancy may protect against pre-term delivery.

Longer term effects of maternal exercise on the next generation

There is a large body of evidence demonstrating the influence of the *in utero* environment on postnatal growth. The link between size at birth and adult disease has been confirmed by many research groups across different ethnicities; in general the association between small size at birth and adult disease is secondary to the development of obesity in adolescence and adulthood due to rapid "catch-up" growth in infancy (reviewed by Barker, 1999[90]). Therefore, the effects of maternal exercise on cardiometabolic risk of the offspring may not be solely attributable to effects on birth weight, but also to effects on postnatal growth, an independent risk factor for later disease. A recently published review found that regular aerobic exercise during pregnancy elicits maternal and fetal adaptations that have the potential for both positive and negative health outcomes for offspring, although it appears that the effect of exercise on offspring size at birth may occur primarily at the upper end of the birth weight range.[91] Thus, regular exercise may be particularly important for overweight and obese mothers, who are more at risk of having macrosomic babies with increased risk for developing later obesity and cardiometabolic complications.[14,15]

Whilst physical activity during pregnancy may benefit both mother and fetus; mode, intensity, frequency, duration and timing of exercise are important determinants of its direct or indirect effects. Fetal effects may include decreased growth of adipose depots, improved stress tolerance, and advanced neurobehavioral maturation (reviewed by Clapp, 2000[92]). Clapp *et al.* found that although continuing vigorous exercise into the third trimester resulted in a reduction in mean birth weight (200g), this difference was lost by 1 year of age.[60] Furthermore, offspring of exercised mothers are leaner and have a better neurodevelopmental outcome at 5 years of age.[93] *Long-term follow-up of the health consequences for the offspring of women who perform vigorous exercise during pregnancy is required.*

It is plausible that exercise during pregnancy could program later health outcomes *via* fetal DNA adaptations such as histone modifications[94] or *via* increased global DNA methylation.[95] Physical activity has been shown to influence such epigenetic mechanisms to control gene expression.[94,95] However, post-pubertal, adult and

intergenerational effects of maternal exercise on offspring remain to be studied. In the absence of medical contraindications, women should be encouraged to establish regular moderate physical activity patterns as per current guidelines[96-99] prior to pregnancy and to maintain these during pregnancy in consultation with their physician/obstetrician.

In summary, exercise during pregnancy could program later physiological and pathological outcomes in offspring and subsequent generations, with definitive mechanisms yet to be elucidated.

Exercise throughout life in individuals born small or pre-term

The long term consequences of being born small and the ability of exercise to mitigate such effects are clearly related to the severity of prematurity or growth restriction. The preventive and therapeutic potential of physical activity in LBW individuals will also depend on inter-related factors including propensity to exercise, exercise ability and the physiological responses to exercise bouts, particularly effects on cardiometabolic risk factors.

Effects of LBW on the amount of exercise performed in later life

Prior to and during early adolescence (≤15 years of age) the amount of physical activity in which children engage does not appear to be linked to being born small in general,[100,101] or being born extremely pre-term[102] (Table 2). In a cohort of extremely premature (<25 weeks) 11 year-olds, in spite of impaired lung function and reduced aerobic exercise capacity, the same amount of physical activity was recorded as full-term children.[102] This finding is congruent with four separate, large and varied cohorts compiled by Ridgway *et al.*,[101] in which a small number of participants were excluded from each cohort due to being born less than 1,500g. In one of these cohorts, the Pelotas cohort from Brazil, no exclusion of VLBW children resulted in the same findings.[100] They also suggested that low activity levels in adolescence were not related to birth weight, but were related to female gender, high socioeconomic status and levels of activity in early childhood (1-4 years of age). In this Brazilian cohort low socioeconomic status was related to increased activity due to increased levels of non-leisure time activity; this is often contrary to previous studies in other populations in which there is little demand for manual labour in lower socioeconomic status communities.[103] Regardless, it is apparent that factors related to early habit formation are the most important predictor of later childhood activity level, and birth weight is not a significant contributor.

From mid-adolescence onward, in contrast to younger children, participation in physical activity is reduced in ELBW[104] and VLBW[105] individuals compared with normal birth weight (NBW) (Table 2). Furthermore, data obtained *via* surveys of current participation in organized sports, ELBW 16-19 year olds reported less participation.[104] VLBW young adults (~20-22 years of age)

also exercised less than their NBW counterparts in a cohort of normal weight (BMI ~22 kg/m^2) LBW participants. After accounting for socioeconomic factors, body composition and presence of impaired lung function total leisure time activity as well as frequency, duration and intensity of exercise were lower.[105] No studies have definitively explained why participation rates fall after childhood. However, smaller body size and late maturation are known to delay development of motor skills and reduce sporting prowess.[106] Such factors may play a role in perpetuating a vicious cycle to explain the reduced participation in physical activity of LBW individuals after childhood.

Based on evidence available in younger adult VLBW cohorts and clear evidence of reduced exercise capacity throughout life (detailed subsequently) it seems reasonable to speculate that activity levels from young adulthood through to old age remain reduced in LBW compared with NBW individuals. Thus far, however, the only human study to examine this has been a cross-sectional analysis of 65-75 year olds, which indicated that individuals with a birth weight of less than 3,000g exercised *more* frequently than those with a birth weight of more than 3,000g.[107] This analysis was based on an interaction between exercise frequency and birth weight in cohorts segregated for those with and without type 2 diabetes. LBW subjects in this study also appeared to benefit from exercise to a greater extent, prompting the authors to suggest a 'survival of the fittest' phenomenon whereby fitter LBW individuals exercised more, with a consequent longevity effect. From available evidence it is thus difficult to determine the effects of LBW on exercise habits in the elderly. A study in animals, however, supports the finding of higher activity in association with LBW, showing from early adulthood (80-100 days) to middle-old age (~1 year) growth restricted (LBW) rats are more habitually active than control rats.[108] Given the psychosocial factors associated with physical activity in human LBW cohorts, rodent models may not be ideal for understanding long term trends in human activity levels throughout life. While not a primary outcome measure of the study, the Hertfordshire Physical Activity Trial may elucidate the relationships between physical activity levels and birth weight in older individuals.[109]

In summary, prior to adolescence, the amount of physical activity in which children engage is not linked to birth weight, whereas in adolescence participation in physical activity is reduced in LBW individuals. There are insufficient data to determine whether LBW influences physical activity patterns in mid and later life.

Effects of LBW on physical work capacity

In LBW individuals, differences in habitual physical activity levels compared to NBW cohorts only appear from early teenage years onwards, whereas ELBW individuals have reduced ability to perform various exercise tasks, whether primarily aerobic/endurance or power/strength based, from early childhood (Table 2). This reduction in exercise capacity is apparent at all ages that have been

Table 2. Summary of effect of low birth weight on human physical activity levels, exercise capacity and physiological function. (In citation order).

First author (year) (ref. no.)	Study design	Cohort age (yrs)	Cohort birth weight category	Habitual activity level compared to NBW	Exercise capacity compared to NBW	Physiological effects compared to NBW
Hallal (2006)[100]	Observational	10-12	LBW	↔		
Ridgway (2011)[101]	Observational	12-15	Various LBW cohorts, VLBW, ELBW excluded	↔		
Welsh (2010)[102]	Cross-sectional	11	ELBW	↔	↓ VO₂max	
Rogers (2005)[104]	Cross-sectional	16-20	ELBW	→	↓ aerobic fitness, muscular strength, power, endurance and flexibility	
Kajantie (2010)[105]	Cross-sectional	19-27	VLBW	→		
Eriksson (2004)[107]	Observational	65-75	LBW	←		
Baraldi (1991)[110]	Cross-sectional	7-12	VLBW-AGA		↔ VO₂max, max HR, aerobic endurance	↔ mechanical efficiency (running), lung function
		7-12	VLBW-SGA		↔ VO₂max, max HR, aerobic endurance	↓ mechanical efficiency (running), ↔ lung function
Keller (1998, 2000)[112,115]	Cross-sectional	5-7	ELBW		↓ neuromuscular coordination, reaction time, anaerobic power	↓ lean mass, ↑ fat mass
	Cross-sectional	5-7	VLBW			↓ lean mass, ↑ fat mass
Kilbride (2003)[116]	Cross-sectional	9-15	ELBW	→	↓ VO₂max, aerobic endurance	↓ lung function
Vrijlandt (2006)[117]	Observational, Cross-sectional	19	VLBW		↔ VO₂max, ↓ aerobic endurance	↓ lung function
Kriemler (2005)[111]	Cross-sectional	5-7	ELBW to VLBW	→	↔ VO₂max	↓ mechanical efficiency (cycling), ↓ lung function
Sipola-Leppänen (2011)[122]	Cross-sectional	22	VLBW	→		↓ lean mass, ↑ fat mass
Ozanne (2005)[128]	Cross-sectional	19	LBW			↔ lean, fat mass; ↓ insulin signalling proteins

examined to date.

With regard to aerobic capacity, two studies have reported no differences in maximal oxygen uptake (whether expressed relative to body weight or in absolute terms) in LBW children and adolescents, whether SGA or VLBW.[110,111] Further, these two studies both reported reductions in gross mechanical efficiency during submaximal exercise, and most other studies indicate some degree of impairment in aerobic capacity. In ELBW and VLBW children aged 5-7 years, reaction time and neuromuscular coordination are also reduced.[112] Interestingly, this may explain the drop off in exercise participation soon after this age due to the fact that poor ability in comparison to peers in sporting pursuits is a barrier to participation.[113,114] ELBW children in this age group also have reduced anaerobic exercise capacity (Wingate testing) compared to NBW children.[115]

Impairments in exercise capacity in ELBW and

VLBW children and adolescents include reduced aerobic capacity, whether expressed in absolute or relative terms[116] or indirectly estimated *via* an incremental exercise test[104] (Table 2). Multiple indices of muscular power and endurance are also reduced[104,117] (Table 2). The common theme in these latter studies compared with an earlier study by Baraldi *et al.*[110] is the presence, or not, of chronic bronchopulmonary disease in some participants, a common affliction, particularly in the lowest birth weight categories.[118] Based on evidence available it is not possible to determine for certain whether, in the absence of impaired lung function, VLBW individuals retain normal exercise capacity compared to NBW subjects. This is especially relevant since a lung disease-free SGA (but not VLBW) cohort had reduced running economy (oxygen cost relative to body mass for a given submaximal steady state running speed), indicative of a functional, but not clinically relevant impairment in the skeletal muscle and/or cardiovascular systems.[110] Studies of VLBW children support this reduction in mechanical efficiency while cycling, but only in those diagnosed with chronic lung disease.[111]

In summary, exercise capacity is impaired to some degree in LBW, VLBW and ELBW individuals.

Mechanisms for altered exercise capacity in LBW, VLBW and ELBW individuals

Human and relevant animal studies consistently report reduced muscle mass and a corresponding increase in relative fat mass in VLBW individuals.[115,119-122] In adult LBW rats both red and white muscle fibres are smaller (cross-sectional area) than in control animals.[123] Corticosteroids used to treat chronic lung disease in LBW individuals[124] may also induce muscle atrophy.[125] While lower relative muscle mass may provide a simple explanation for the observation of reduced VO_2max in ELBW individuals, maximal oxygen consumption is maintained in VLBW individuals (in the absence of chronic bronchopulmonary lung disease) despite reduced muscle mass.

This apparent disparity between muscle mass and maximal oxygen consumption in LBW individuals may relate to effects on muscle fibre type composition. In humans fast/Type II (white, glycolytic) muscle fibres develop later in gestation (>30 weeks) than slow/Type I (red, oxidative) fibres.[126] As a result LBW is often associated with a greater proportion of oxidative fibres. This has been demonstrated in newborn growth restricted piglet hind-limb flexor[120] and adult rat soleus[123] muscles which contain a greater proportion of slow/Type I fibres than in controls. A relative increase in the proportion of oxidative fibres would be expected to contribute to an increase in intrinsic oxidative capacity of LBW skeletal muscle. This is consistent with the observation by Baraldi *et al.*[110] of a greater oxygen consumption per kg of body weight at a given submaximal workload in SGA children (reduced running economy). It may also explain why LBW individuals can achieve a normal VO_2max despite reduced muscle mass. Thus the effect of LBW on fibre type ratio

and specifically a reduction in the relative proportion of glycolytic fibres may also explain observed reductions in isometric force development in the hind-limb flexors of newborn LBW piglets.[120] This is supported by reductions in phosphocreatine concentration, phosphocreatine:ATP ratio and the ATP:ADP ratio in VLBW infant muscle.[127]

LBW also influences metabolic signalling cascades affecting substrate utilisation. For example, the glucose transporter GLUT4 is reduced in skeletal muscle of LBW individuals.[128] While a small reduction in total GLUT4 is probably not implicated in reduced maximal capacity for glycolysis in skeletal muscle, it certainly raises the possibility that other proteins essential for regulation of energy metabolism during exercise are affected. Of particular relevance, one study in growth restricted adult rats[129] and another in newborn mice following maternal protein restriction[130] showed reduced expression of proteins and genes responsible for mitochondrial biogenesis and function. The latter, however, reported that citrate synthase activity in the muscle of these newborn mice exposed to protein restriction *in utero* was not different to control mice.[130] A separate study in young adult LBW men found no difference compared to age-matched NBW subjects in either mitochondrial flux or oxidative gene expression.[131] Results from sheep studies are conflicting regarding the effect of LBW on gene and protein expression of insulin signaling and glucose transport related markers in skeletal muscle after birth. On one hand, insulin receptor protein was higher in the muscle of 3 week old LBW lambs in conjunction with an up-regulation of PI3Kinase, AKT2/protein kinase B and GLUT4.[132] Whereas four to six weeks after birth, De Blasio *et al.* showed a reduction in whole body insulin sensitivity with a concomitant decrease in skeletal muscle insulin receptor, insulin receptor substrate 1 (IRS1), AKT2 and GLUT4 mRNA expression.[133] Consequently, it is difficult to determine the role of substrate transport and maximal mitochondrial volume or capacity in the impairment of exercise capacity in LBW individuals.

The disparity highlighted earlier between animal and human studies regarding habitual activity levels may be partly explained by the increased muscle oxidative capacity associated with LBW. In LBW animals with no pulmonary impairment or sociological influences, increased oxidative capacity may promote increased quantity of lower intensity activity. In humans, however, impaired lung function associated with LBW may restrict physical activity.[118] Thus, despite increased muscle oxidative capacity, aerobic performance may be lower in VLBW and ELBW humans due to reduced physical activity secondary to pulmonary impairment and reduced exercise capacity.[102,105] This is, however, not supported by a study in 9-15 year old ELBW individuals who had significantly ($\approx$20%) reduced absolute (L/min) and relative (ml/kg body mass/min) maximal oxygen uptake compared with NBW controls, independent of chronic lung disease status.[116]

In summary, potential mechanisms for altered exercise capacity in LBW individuals include, but are not restricted to: reduced muscle mass, increased intrinsic

oxidative capacity and impaired lung function.

Effects of exercise training on adult cardiometabolic risk factors in LBW individuals

As discussed above, regular exercise training is well known to protect from cardiometabolic disease, and most studies suggest this holds true for LBW individuals. In general, factors known to be dysregulated as a result of being born small are responsive to exercise training. Physiological mechanisms that may be implicated include restoration of muscle mass, pancreatic β-cell mass and function, vascular and cardiac muscle adaptations as well as effects on both aerobic and anaerobic muscle metabolism, including substrate utilisation and mitochondrial function. Although there is limited available information, some conclusions can be drawn from the small number of studies published.

Epidemiological studies indicate that older men (~50-65 years) born small have elevated fasting insulin and glucose, but that this association is lost in members of the cohort that are physically fit and exercise often.[107,134] In two separate study cohorts, when adolescents were segregated into low and high levels of physical activity, a significant inverse relationship was observed between the HOMA-IR index and birth weight in the low activity groups, which was lost in the high activity groups.[135] These observations are refuted by a recent study of 9-15 year olds, where there was no evidence for a loss of the association between birth weight and indices of the metabolic syndrome when adjusted for physical fitness in 1,254 individuals.[136] These data imply that LBW is a major contributor to the phenomenon of "non-responders"; individuals who do not improve health as a result of exercise training.[18,137] *Given this lack of congruence, the small number of studies conducted and absence of interventional studies in humans, more work is required.*

Studies using animal models are, like those in humans, low in number, but favour the concept that physical activity can improve metabolic health in LBW individuals, and provide some causal mechanistic insight. In growth restricted rats, exercise only during weaning to early adulthood (5-9 weeks of age) resulted in both short (immediately after cessation of the training program) and long term (15 weeks after cessation of training) improvement in pancreatic β-cell mass, which was otherwise depleted in growth restricted animals.[138] Likewise, a similar training program reduced fasting insulin to control levels in growth restricted rats, along with decreased hepatic glucose production during a glucose tolerance test, and decreased area under the curve in an insulin tolerance test compared with control rats.[139] *Future studies in animal models of LBW would provide valuable insight into the potential for training-induced improvement in cardiometabolic health, and researchers should focus on gold-standard measures of whole body and tissue-specific insulin sensitivity and cardiovascular function.*

In summary, there is evidence to suggest that exercise in LBW individuals can improve insulin sensitivity and pancreatic β-cell mass, but further studies are required in relation to potential cardiovascular benefits.

Conclusion

Studying the interactions between physical activity, LBW and adult disease poses significant challenges. Despite these challenges and the resulting evidence gaps in the literature, it is still possible to gain insights into the role physical activity may play in mitigating against both LBW babies and the risk of such infants for cardiometabolic disease in later life.

During pregnancy, regular moderate intensity exercise has no significant effect on mean birth weight, nor is it associated with intrauterine growth restriction or pre-term birth. In fact, moderate intensity exercise appears to promote birth weight within the normal range by reducing the risk of both SGA and LGA births. This is an important observation given the current birth weight trends in Australia which have seen increases in the proportion of both small and large babies over the past 20 years. Lifestyle programs encouraging prospective mothers to achieve optimal physical activity patterns and BMI prior to pregnancy as well as maintaining a moderate level physical activity program during pregnancy may help to reverse current birth weight trends and the associated elevation in the cardiometabolic risk of offspring. Exercise-induced increases in placental volume may be a key factor in optimising fetal nutrition and birth weight.

Exercise capacity in LBW individuals appears to be largely preserved, except in ELBW individuals who have clear deficits in exercise capacity. Despite this, physical activity has been shown to have benefit across a broad range of birth weights and may help to overcome developmental delays. While exercise ability is a strong psychosocial determinant of lifelong exercise participation, it is not possible to draw firm conclusions as to whether birth weight impacts on adult physical activity patterns. The available data indicate that early habit formation during childhood is probably more important than birth weight in terms of lifelong exercise habits.

For those born small who participate in regular physical activity, the epidemiology generally suggests that this ameliorates the elevated cardiometabolic risk of LBW. Restoration of muscle mass together with reduction in adiposity are important mechanisms accounting for improved peripheral insulin sensitivity. Together with restoration of pancreatic β-cell mass, these effects of exercise likely protect against insulin resistance, β-cell failure and development of type 2 diabetes. Both aerobic and resistance training are well documented to reduce multiple cardiovascular risk factors in the general population. Such actions likely also have relevance in LBW individuals, but as yet the interactions between LBW, physical activity and future cardiovascular risk remain to be explored. *The application of devices such as accelerometers and inclinometers to assess habitual activity in LBW cohorts at regular intervals over the life course, together with carefully controlled intervention trials are*

needed to further unlock the interactions between physical activity and birth weight. In the meantime, initiatives directed to increasing physical activity could have particular health benefit for those of LBW and also for the offspring of physically active mothers.

References

1. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993; **36**:62-7.
2. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991; **303**:1019-22.
3. Langley-Evans SC, McMullen S. Developmental origins of adult disease. *Med. Princ. Pract.* 2010; **19**:87-98.
4. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol. Rev.* 2005; **85**:571-633.
5. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989; **298**:564-7.
6. Li Z, McNally L, Hilder L, Sullivan EA: Australia's mothers and babies 2009. 25 ed. Unit ANPEaS, Ed. Sydney, Australian Institute of Health and Welfare, 2011
7. Atrash HK, Johnson K, Adams M, Cordero JF, Howse J. Preconception care for improving perinatal outcomes: the time to act. *Matern. Child Health J.* 2006; **10**:S3-11.
8. Cramer JC. Social factors and infant mortality: identifying high-risk groups and proximate causes. *Demography* 1987; **24**:299-322.
9. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989; **2**:577-80.
10. Reichman NE, Pagnini DL. Maternal age and birth outcomes: data from New Jersey. *Fam. Plan. Perspect.* 1997; **29**:268-72, 95.
11. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *N. Engl. J. Med.* 2002; **346**:731-7.
12. Wilson-Costello D. Is there evidence that long-term outcomes have improved with intensive care? *Semin. Fetal Neonatal Med.* 2007; **12**:344-54.
13. Fleten C, Stigum H, Magnus P, Nystad W. Exercise during pregnancy, maternal prepregnancy body mass index, and birth weight. *Obstet. Gynecol.* 2010; **115**:331-7.
14. Catalano PM, Thomas AJ, Huston LP, Fung CM. Effect of maternal metabolism on fetal growth and body composition. *Diabetes Care* 1998; **21 Suppl 2**:B85-90.
15. Vambergue A, Fajardy I. Consequences of gestational and pregestational diabetes on placental function and birth weight. *World J. Diabetes* 2011; **2**:196-203.
16. Paffenbarger RS, Jr., Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N. Engl. J. Med.* 1986; **314**:605-13.
17. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N. Engl. J. Med.* 2002; **347**:716-25.
18. Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA* 1995; **273**:1093-8.
19. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, Owen N. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes Care* 2008; **31**:661-6.
20. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *Eur. Heart J.* 2011; **32**:590-7.
21. Dunstan DW, Kingwell BA, Larsen R, Healy GN, Cerin E, Hamilton MT, Shaw JE, Bertovic DA, Zimmet PZ, Salmon J, Owen N. Breaking up prolonged sitting reduces postprandial glucose and insulin responses. *Diabetes Care* 2012; **35**:976-83.
22. Jennings G, Nelson L, Nestel P, Esler M, Korner P, Burton D, Bazelmans J. The effects of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in man: a controlled study of four levels of activity. *Circulation* 1986; **73**:30-40.
23. Nelson L, Jennings GL, Esler MD, Korner PI. Effect of changing levels of physical activity on blood-pressure and haemodynamics in essential hypertension. *Lancet* 1986; **2**:473-6.
24. Kingwell BA, Jennings GL. Effects of walking and other exercise programs upon blood pressure in normal subjects. *Med. J. Aust.* 1993; **158**:234-8.
25. Kingwell BA, Cameron JD, Gillies KJ, Jennings GL, Dart AM. Arterial compliance may influence baroreflex function in athletes and hypertensives. *Am. J. Physiol. Heart Circ. Physiol.* 1995; **268**:H411-8.
26. Kingwell BA, Berry KL, Cameron JD, Jennings GL, Dart AM. Arterial compliance increases after moderate-intensity cycling. *Am. J. Physiol. Heart Circ. Physiol.* 1997; **273**:H2186-91.
27. Kingwell BA, Arnold PJ, Jennings GL, Dart AM. Spontaneous running increases aortic compliance in Wistar-Kyoto rats. *Cardiovasc. Res.* 1997; **35**:132-7.
28. Kingwell BA, Tran B, Cameron JD, Jennings GL, Dart AM. Enhanced vasodilation to acetylcholine in athletes is associated with lower plasma cholesterol. *Am. J. Physiol. Heart Circ. Physiol.* 1996;

270:H2008-13.

29. Lewis TV, Dart AM, Chin-Dusting JP, Kingwell BA. Exercise training increases basal nitric oxide production from the forearm in hypercholesterolemic patients. *Arterioscler. Thromb. Vasc. Biol.* 1999; **19**:2782-7.

30. Maiorana AJ, Naylor LH, Exterkate A, Swart A, Thijssen DH, Lam K, O'Driscoll G, Green DJ. The impact of exercise training on conduit artery wall thickness and remodeling in chronic heart failure patients. *Hypertension* 2011; **57**:56-62.

31. Green DJ, Walsh JH, Maiorana A, Burke V, Taylor RR, O'Driscoll JG. Comparison of resistance and conduit vessel nitric oxide-mediated vascular function in vivo: effects of exercise training. *J. Appl. Physiol.* 2004; **97**:749-55; discussion 8.

32. Newcomer SC, Thijssen DH, Green DJ. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: role of exercise-induced hemodynamics. *J. Appl. Physiol.* 2011; **111**:311-20.

33. Kingwell BA, Dart AM, Jennings GL, Korner PI. Exercise training reduces the sympathetic component of the blood pressure-heart rate baroreflex in man. *Clin. Sci. (Lond).* 1992; **82**:357-62.

34. Meredith IT, Jennings GL, Esler MD, Dewar EM, Bruce AM, Fazio VA, Korner PI. Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. *J. Hypertens.* 1990; **8**:859-66.

35. Meredith IT, Eisenhofer G, Lambert GW, Jennings GL, Thompson J, Esler MD. Plasma norepinephrine responses to head-up tilt are misleading in autonomic failure. *Hypertension* 1992; **19**:628-33.

36. Sanchis-Gomar F, Olaso-Gonzalez G, Corella D, Gomez-Cabrera MC, Vina J. Increased average longevity among the "Tour de France" cyclists. *Int. J. Sports Med.* 2011; **32**:644-7.

37. Jonker JT, De Laet C, Franco OH, Peeters A, Mackenbach J, Nusselder WJ. Physical activity and life expectancy with and without diabetes: life table analysis of the Framingham Heart Study. *Diabetes Care* 2006; **29**:38-43.

38. Goodpaster BH, Katsiaras A, Kelley DE. Enhanced fat oxidation through physical activity is associated with improvements in insulin sensitivity in obesity. *Diabetes* 2003; **52**:2191-7.

39. Irwin ML, Mayer-Davis EJ, Addy CL, *et al.* Moderate-intensity physical activity and fasting insulin levels in women: the Cross-Cultural Activity Participation Study. *Diabetes Care* 2000; **23**:449-54.

40. Wing RR, Epstein LH, Paternostro-Bayles M, Kriska A, Nowalk MP, Gooding W. Exercise in a behavioural weight control programme for obese patients with Type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1988; **31**:902-9.

41. Dunstan DW, Daly RM, Owen N, Jolley D, De Courten M, Shaw J, Zimmet P. High-intensity resistance training improves glycemic control in older patients

with type 2 diabetes. *Diabetes Care* 2002; **25**:1729-36.

42. Poehlman ET, Dvorak RV, DeNino WF, Brochu M, Ades PA. Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: a controlled randomized trial. *J. Clin. Endocrinol. Metab.* 2000; **85**:2463-8.

43. Ryan AS, Pratley RE, Goldberg AP, Elahi D. Resistive training increases insulin action in postmenopausal women. *J. Gerontol. A Biol. Sci. Med. Sci.* 1996; **51**:M199-205.

44. Davis JT, Limpisvasti O, Fluhme D, Mohr KJ, Yocum LA, Elattrache NS, Jobe FW. The effect of pitching biomechanics on the upper extremity in youth and adolescent baseball pitchers. *Am. J. Sports Med.* 2009; **37**:1484-91.

45. Santa-Clara H, Fernhall B, Baptista F, Mendes M, Bettencourt Sardinha L. Effect of a one-year combined exercise training program on body composition in men with coronary artery disease. *Metabolism* 2003; **52**:1413-7.

46. Barakat R, Lucia A, Ruiz JR. Resistance exercise training during pregnancy and newborn's birth size: a randomised controlled trial. *Int. J. Obes. (Lond.)* 2009; **33**:1048-57.

47. Hatch MC, Shu XO, McLean DE, Levin B, Begg M, Reuss L, Susser M. Maternal exercise during pregnancy, physical fitness, and fetal growth. *Am. J. Epidemiol.* 1993; **137**:1105-14.

48. Sternfeld B, Quesenberry CP, Jr., Eskenazi B, Newman LA. Exercise during pregnancy and pregnancy outcome. *Med. Sci. Sports Exerc.* 1995; **27**:634-40.

49. Hopkins SA, Baldi JC, Cutfield WS, McCowan L, Hofman PL. Exercise training in pregnancy reduces offspring size without changes in maternal insulin sensitivity. *J. Clin. Endocrinol. Metab.* 2010; **95**:2080-8.

50. Kramer MS, McDonald SW. Aerobic exercise for women during pregnancy. *Cochrane Database Syst. Rev.* 2006; **3**:CD000180.

51. Alderman BW, Zhao H, Holt VL, Watts DH, Beresford SA. Maternal physical activity in pregnancy and infant size for gestational age. *Ann. Epidemiol.* 1998; **8**:513-9.

52. Juhl M, Olsen J, Andersen PK, Nohr EA, Andersen AM. Physical exercise during pregnancy and fetal growth measures: a study within the Danish National Birth Cohort. *Am. J. Obstet. Gynecol.* 2010; **202**:63 e1-8.

53. Leiferman JA, Evenson KR. The effect of regular leisure physical activity on birth outcomes. *Matern. Child Health J.* 2003; **7**:59-64.

54. Rosa BV, Firth EC, Blair HT, Vickers MH, Morel PC. Voluntary exercise in pregnant rats positively influences fetal growth without initiating a maternal physiological stress response. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2011; **300**:R1134-41.

55. Monteiro AC, Paes ST, dos Santos JA, de Lira KD, de Moraes SR. Effects of physical exercise during

pregnancy and protein malnutrition during pregnancy and lactation on the development and growth of the offspring's femur. *J. Pediatr. (Rio J.)* 2010; **86**:233-8.

56. Amorim MF, dos Santos JA, Hirabara SM, Nascimento E, de Souza SL, de Castro RM, Curi R, Leandro CG. Can physical exercise during gestation attenuate the effects of a maternal perinatal low-protein diet on oxygen consumption in rats? *Exp. Physiol.* 2009; **94**:906-13.

57. Clapp JF, 3rd, Capeless EL. Neonatal morphometrics after endurance exercise during pregnancy. *Am. J. Obstet. Gynecol.* 1990; **163**:1805-11.

58. Clapp JF, 3rd, Dickstein S. Endurance exercise and pregnancy outcome. *Med. Sci. Sports Exerc.* 1984; **16**:556-62.

59. Jackson MR, Gott P, Lye SJ, Ritchie JW, Clapp JF, 3rd. The effects of maternal aerobic exercise on human placental development: placental volumetric composition and surface areas. *Placenta* 1995; **16**:179-91.

60. Clapp JF, 3rd, Simonian S, Lopez B, Appleby-Wineberg S, Harcar-Sevcik R. The one-year morphometric and neurodevelopmental outcome of the offspring of women who continued to exercise regularly throughout pregnancy. *Am. J. Obstet. Gynecol.* 1998; **178**:594-9.

61. Marquez-Sterling S, Perry AC, Kaplan TA, Halberstein RA, Signorile JF. Physical and psychological changes with vigorous exercise in sedentary primigravidae. *Med. Sci. Sports Exerc.* 2000; **32**:58-62.

62. Rao S, Kanade A, Margetts BM, Yajnik CS, Lubree H, Rege S, Desai B, Jackson A, Fall CH. Maternal activity in relation to birth size in rural India. The Pune Maternal Nutrition Study. *Eur. J. Clin. Nutr.* 2003; **57**:531-42.

63. Dwarkanath P, Muthayya S, Vaz M, Thomas T, Mhaskar A, Mhaskar R, Thomas A, Bhat S, Kurpad A. The relationship between maternal physical activity during pregnancy and birth weight. *Asia Pac. J. Clin. Nutr.* 2007; **16**:704-10.

64. Haakstad LA, Bo K. Exercise in pregnant women and birth weight: a randomized controlled trial. *BMC Pregnancy Childbirth* 2011; **11**:66.

65. Orr ST, James SA, Garry J, Prince CB, Newton ER. Exercise and pregnancy outcome among urban, low-income, black women. *Ethn. Dis.* 2006; **16**:933-7.

66. Gollenberg AL, Pekow P, Bertone-Johnson ER, Freedson PS, Markenson G, Chasan-Taber L. Physical activity and risk of small-for-gestational-age birth among predominantly Puerto Rican women. *Matern. Child Health J.* 2011; **15**:49-59.

67. Clapp JF, 3rd, Kim H, Burciu B, Lopez B. Beginning regular exercise in early pregnancy: effect on fetoplacental growth. *Am. J. Obstet. Gynecol.* 2000; **183**:1484-8.

68. Zavorsky GS, Longo LD. Exercise guidelines in pregnancy: new perspectives. *Sports Med.* 2011;

41:345-60.

69. Gorski J. Exercise during pregnancy: maternal and fetal responses. A brief review. *Med. Sci. Sports Exerc.* 1985; **17**:407-16.

70. Terada M. Effect of physical activity before pregnancy on fetuses of mice exercised forcibly during pregnancy. *Teratology* 1974; **10**:141-4.

71. Levitsky LL, Kimber A, Marchichow JA, Uehara J. Metabolic response to fasting in experimental intrauterine growth retardation induced by surgical and nonsurgical maternal stress. *Biol. Neonate.* 1977; **31**:311-5.

72. Oliveira AO, Fileto C, Melis MS. Effect of strenuous maternal exercise before and during pregnancy on rat progeny renal function. *Braz. J. Med. Biol. Res.* 2004; **37**:907-11.

73. Nelson PS, Gilbert RD, Longo LD. Fetal growth and placental diffusing capacity in guinea pigs following long-term maternal exercise. *J. Dev. Physiol.* 1983; **5**:1-10.

74. Dhindsa DS, Metcalfe J, Hummels DH. Responses to exercise in the pregnant pygmy goat. *Respir. Physiol.* 1978; **32**:299-311.

75. Lumbers ER. Exercise in pregnancy: physiological basis of exercise prescription for the pregnant woman. *J. Sci. Med. Sport* 2002; **5**:20-31.

76. Clapp JF, 3rd, Kim H, Burciu B, Schmidt S, Petry K, Lopez B. Continuing regular exercise during pregnancy: effect of exercise volume on fetoplacental growth. *Am. J. Obstet. Gynecol.* 2002; **186**:142-7.

77. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S: Births, final data for 2004. National vital statistics report. Statistics NCfH, Ed. Hyattsville, MD, 2006

78. Ananth CV, Joseph KS, Oyelese Y, Demissie K, Vintzileos AM. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. *Obstet. Gynecol.* 2005; **105**:1084-91.

79. Takito MY, Benicio MH. Physical activity during pregnancy and fetal outcomes: a case-control study. *Rev. Saude Publica.* 2010; **44**:90-101.

80. Domingues MR, Barros AJ, Matijasevich A. Leisure time physical activity during pregnancy and preterm birth in Brazil. *Int. J. Gynaecol. Obstet.* 2008; **103**:9-15.

81. Jukic AM, Evenson KR, Daniels JL, Herring AH, Wilcox AJ, Hartmann KE. A prospective study of the association between vigorous physical activity during pregnancy and length of gestation and birthweight. *Matern. Child Health J.* 2011.

82. Domingues MR, Matijasevich A, Barros AJ. Physical activity and preterm birth: a literature review. *Sports Med.* 2009; **39**:961-75.

83. Kramer MS. Aerobic exercise for women during pregnancy. *Cochrane Database Syst. Rev.* 2002:CD000180.

84. Duncombe D, Skouteris H, Wertheim EH, Kelly L, Fraser V, Paxton SJ. Vigorous exercise and birth

outcomes in a sample of recreational exercisers: a prospective study across pregnancy. *Aust. N. Z. J. Obstet. Gynaecol.* 2006; **46**:288-92.

85. Hegaard HK, Hedegaard M, Damm P, Ottesen B, Petersson K, Henriksen TB. Leisure time physical activity is associated with a reduced risk of preterm delivery. *Am. J. Obstet. Gynecol.* 2008; **198**:180 e1-5.

86. Grisso JA, Main DM, Chiu G, Synder ES, Holmes JH. Effects of physical activity and life-style factors on uterine contraction frequency. *Am. J. Perinatol.* 1992; **9**:489-92.

87. Barakat R, Stirling JR, Lucia A. Does exercise training during pregnancy affect gestational age? A randomised controlled trial. *Br. J. Sports Med.* 2008; **42**:674-8.

88. Cavalli AS, Tanaka T. Relationship between maternal physical activities and preterm birth. *Environ. Health Prev. Med.* 2001; **6**:74-81.

89. Petridou E, Salvanos H, Skalkidou A, Dessypris N, Moustaki M, Trichopoulos D. Are there common triggers of preterm deliveries? *BJOG* 2001; **108**:598-604.

90. Barker DJ. Early growth and cardiovascular disease. *Arch. Dis. Child.* 1999; **80**:305-7.

91. Hopkins SA, Cutfield WS. Exercise in pregnancy: weighing up the long-term impact on the next generation. *Exerc. Sport Sci. Rev.* 2011; **39**:120-7.

92. Clapp JF, 3rd. Exercise during pregnancy. A clinical update. *Clin. Sports Med.* 2000; **19**:273-86.

93. Clapp JF, 3rd. Morphometric and neurodevelopmental outcome at age five years of the offspring of women who continued to exercise regularly throughout pregnancy. *J. Pediatr.* 1996; **129**:856-63.

94. McGee SL, Fairlie E, Garnham AP, Hargreaves M. Exercise-induced histone modifications in human skeletal muscle. *J. Physiol.* 2009; **587**:5951-8.

95. Zhang FF, Cardarelli R, Carroll J, Zhang S, Fulda KG, Gonzalez K, Vishwanatha JK, Morabia A, Santella RM. Physical activity and global genomic DNA methylation in a cancer-free population. *Epigenetics* 2011; **6**:293-9.

96. Artal R, O'Toole M. Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period. *Br. J. Sports Med.* 2003; **37**:6-12; discussion

97. Brown W. The benefits of physical activity during pregnancy. *J. Sci. Med. Sport* 2002; **5**:37-45.

98. Bell BB, Dooley MMP: Exercise in Pregnancy. Royal College of Obstetricians & Gynaecologists, 2006

99. Davies GA, Wolfe LA, Mottola MF, MacKinnon C. Joint SOGC/CSEP clinical practice guideline: exercise in pregnancy and the postpartum period. *Can. J. Appl. Physiol.* 2003; **28**:330-41.

100. Hallal PC, Wells JC, Reichert FF, Anselmi L, Victora CG. Early determinants of physical activity in adolescence: prospective birth cohort study. *BMJ* 2006; **332**:1002-7.

101. Ridgway CL, Brage S, Sharp SJ, Corder K, Westgate KL, van Sluijs EM, Goodyer IM, Hallal PC, Anderssen SA, Sardinha LB, Andersen LB, Ekelund U. Does birth weight influence physical activity in youth? A combined analysis of four studies using objectively measured physical activity. *PLoS One* 2011; **6**:e16125.

102. Welsh L, Kirkby J, Lum S, Odendaal D, Marlow N, Derrick G, Stocks J. The EPICure study: maximal exercise and physical activity in school children born extremely preterm. *Thorax* 2010; **65**:165-72.

103. Cameron AJ, Welborn TA, Zimmet PZ, Dunstan DW, Owen N, Salmon J, Dalton M, Jolley D, Shaw JE. Overweight and obesity in Australia: the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Med. J. Aust.* 2003; **178**:427-32.

104. Rogers M, Fay TB, Whitfield MF, Tomlinson J, Grunau RE. Aerobic capacity, strength, flexibility, and activity level in unimpaired extremely low birth weight (≤800 g) survivors at 17 years of age compared with term-born control subjects. *Pediatrics* 2005; **116**:e58-65.

105. Kajantie E, Strang-Karlsson S, Hovi P, Räikkönen K, Pesonen AK, Heinonen K, Järvenpää AL, Eriksson JG, Andersson S. Adults born at very low birth weight exercise less than their peers born at term. *J. Pediatr.* 2010; **157**:610-6, 6 e1.

106. Armstrong N, McManus AM. Physiology of elite young male athletes. *Med. Sport Sci.* 2011; **56**:1-22.

107. Eriksson JG, Yliharsila H, Forsen T, Osmond C, Barker DJ. Exercise protects against glucose intolerance in individuals with a small body size at birth. *Prev. Med.* 2004; **39**:164-7.

108. Miles JL, Landon J, Davison M, Krägeloh CU, Thompson NM, Triggs CM, Breier BH. Prenatally undernourished rats show increased preference for wheel running v. lever pressing for food in a choice task. *Br. J. Nutr.* 2009; **101**:902-8.

109. Finucane FM, Horton J, Purslow LR, Savage DB, Brage S, Besson H, Horton K, Rolfe Ede L, Sleigh A, Sharp SJ, Martin HJ, Sayer AA, Cooper C, Ekelund U, Griffin SJ, Wareham NJ. Randomized controlled trial of the efficacy of aerobic exercise in reducing metabolic risk in healthy older people: The Hertfordshire Physical Activity Trial. *BMC Endocr. Disord.* 2009; **9**:15.

110. Baraldi E, Zanconato S, Zorzi C, Santuz P, Benini F, Zacchello F. Exercise performance in very low birth weight children at the age of 7-12 years. *Eur. J. Pediatr.* 1991; **150**:713-6.

111. Kriemler S, Keller H, Saigal S, Bar-Or O. Aerobic and lung performance in premature children with and without chronic lung disease of prematurity. *Clin. J. Sport Med.* 2005; **15**:349-55.

112. Keller H, Ayub BV, Saigal S, Bar-Or O. Neuromotor ability in 5- to 7-year-old children with very low or extremely low birthweight. *Dev. Med. Child Neurol.* 1998; **40**:661-6.

113. Poulsen AA, Desha L, Ziviani J, Griffiths L, Heaslop A, Khan A, Leong GM. Fundamental movement

skills and self-concept of children who are overweight. *Int. J. Pediatr. Obes.* 2011; **6**:e464-71.

114. Joesaar H, Hein V. Psychosocial determinants of young athletes' continued participation over time. *Percept. Mot. Skills* 2011; **113**:51-66.

115. Keller H, Bar-Or O, Kriemler S, Ayub BV, Saigal S. Anaerobic performance in 5- to 7-yr-old children of low birthweight. *Med. Sci. Sports Exerc.* 2000; **32**:278-83.

116. Kilbride HW, Gelatt MC, Sabath RJ. Pulmonary function and exercise capacity for ELBW survivors in preadolescence: effect of neonatal chronic lung disease. *J. Pediatr.* 2003; **143**:488-93.

117. Vrijlandt EJ, Gerritsen J, Boezen HM, Grevink RG, Duiverman EJ. Lung function and exercise capacity in young adults born prematurely. *Am. J. Respir. Crit. Care Med.* 2006; **173**:890-6.

118. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, Sachdev HS. Maternal and child undernutrition: consequences for adult health and human capital. *Lancet* 2008; **371**:340-57.

119. Kind KL, Moore VM, Davies MJ. Diet around conception and during pregnancy – effects on fetal and neonatal outcomes. *Reprod. Biomed. Online* 2006; **12**:532-41.

120. Wank V, Bauer R, Walter B, Kluge H, Fischer MS, Blickhan R, Zwiener U. Accelerated contractile function and improved fatigue resistance of calf muscles in newborn piglets with IUGR. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2000; **278**:R304-10.

121. Hediger ML, Overpeck MD, Kuczmarski RJ, McGlynn A, Maurer KR, Davis WW. Muscularity and fatness of infants and young children born small- or large-for-gestational-age. *Pediatrics* 1998; **102**:E60.

122. Sipola-Leppänen M, Hovi P, Andersson S, Wehkalampi K, Vääräsmäki M, Strang-Karlsson S, Järvenpää AL, Mäkitie O, Eriksson JG, Kajantie E. Resting energy expenditure in young adults born preterm--the Helsinki study of very low birth weight adults. *PLoS One* 2011; **6**:e17700.

123. Huber K, Miles JL, Norman AM, Thompson NM, Davison M, Breier BH. Prenatally induced changes in muscle structure and metabolic function facilitate exercise-induced obesity prevention. *Endocrinology* 2009; **150**:4135-44.

124. Nixon PA, Washburn LK, Schechter MS, O'Shea TM. Follow-up study of a randomized controlled trial of postnatal dexamethasone therapy in very low birth weight infants: effects on pulmonary outcomes at age 8 to 11 years. *J. Pediatr.* 2007; **150**:345-50.

125. Clarke BA, Drujan D, Willis MS, Murphy LO, Corpina RA, Burova E, Rakhilin SV, Stitt TN, Patterson C, Latres E, Glass DJ. The E3 Ligase MuRF1 degrades myosin heavy chain protein in dexamethasone-treated skeletal muscle. *Cell Metab.* 2007; **6**:376-85.

126. Colling-Saltin AS. Enzyme histochemistry on skeletal muscle of the human foetus. *J. Neurol. Sci.* 1978; **39**:169-85.

127. Bertocci LA, Mize CE, Uauy R. Muscle phosphorus energy state in very-low-birth-weight infants: effect of exercise. *Am. J. Physiol. Endocrinol. Metab.* 1992; **262**:E289-94.

128. Ozanne SE, Jensen CB, Tingey KJ, Storgaard H, Madsbad S, Vaag AA. Low birthweight is associated with specific changes in muscle insulin-signalling protein expression. *Diabetologia* 2005; **48**:547-52.

129. Wadley GD, Siebel AL, Cooney GJ, McConell GK, Wlodek ME, Owens JA. Uteroplacental insufficiency and reducing litter size alters skeletal muscle mitochondrial biogenesis in a sex-specific manner in the adult rat. *Am. J. Physiol. Endocrinol. Metab.* 2008; **294**:E861-9.

130. Mortensen OH, Olsen HL, Frandsen L, Nielsen PE, Nielsen FC, Grunnet N, Quistorff B. al. Gestational protein restriction in mice has pronounced effects on gene expression in newborn offspring's liver and skeletal muscle; protective effect of taurine. *Pediatr. Res.* 2010; **67**:47-53.

131. Brøns C, Jensen CB, Storgaard H, Alibegovic A, Jacobsen S, Nilsson E, Astrup A, Quistorff B, Vaag A. Mitochondrial function in skeletal muscle is normal and unrelated to insulin action in young men born with low birth weight. *J. Clin. Endocrinol. Metab.* 2008; **93**:3885-92.

132. Muhlhausler BS, Duffield JA, Ozanne SE, Pilgrim C, Turner N, Morrison JL, McMillen IC. et al. The transition from fetal growth restriction to accelerated postnatal growth: a potential role for insulin signalling in skeletal muscle. *J. Physiol.* 2009; **587**:4199-211.

133. De Blasio MJ, Gatford KL, Harland ML, Robinson JS, Owens JA. Placental restriction reduces insulin sensitivity and expression of insulin signaling and glucose transporter genes in skeletal muscle, but not liver, in young sheep. *Endocrinology* 2012; **153**:2142-51.

134. Laaksonen MS, Kalliokoski KK, Kyröläinen H, Kemppainen J, Teräs M, Sipilä H, Nuutila P, Knuuti J. Skeletal muscle blood flow and flow heterogeneity during dynamic and isometric exercise in humans. *Am. J. Physiol. Heart Circ. Physiol.* 2003; **284**:H979-86.

135. Ortega FB, Ruiz JR, Hurtig-Wennlöf A, Meirhaeghe A, González-Gross M, Moreno LA, Molnar D, Kafatos A, Gottrand F, Widhalm K, Labayen I, Sjöström M. Physical activity attenuates the effect of low birth weight on insulin resistance in adolescents: findings from two observational studies. *Diabetes* 2011; **60**:2295-9.

136. Ridgway CL, Brage S, Anderssen SA, Sardinha LB, Andersen LB, Ekelund U. Do physical activity and aerobic fitness moderate the association between birth weight and metabolic risk in youth?: the European Youth Heart Study. *Diabetes Care* 2011; **34**:187-92.

137. Bouchard C. Individual differences in the response to regular exercise. *Int. J. Obes. Relat. Metab. Disord.* 1995; **19 Suppl 4**:S5-8.
138. Laker RC, Gallo LA, Wlodek ME, Siebel AL, Wadley GD, McConell GK. Short-term exercise training early in life restores deficits in pancreatic β-cell mass associated with growth restriction in adult male rats. *Am. J. Physiol. Endocrinol. Metab.* 2011; **301**:E931-40.
139. Garg M, Thamotharan M, Oak SA, Pan G, Maclaren DC, Lee PW, Devaskar SU. Early exercise regimen improves insulin sensitivity in the intrauterine growth-restricted adult female rat offspring. *Am. J. Physiol. Endocrinol. Metab.* 2009; **296**:E272-81.
140. Erkkola R, Makela M. Heart volume and physical fitness of parturients. *Ann. Clin. Res.* 1976; **8**:15-21.
141. Collings CA, Curet LB, Mullin JP. Maternal and fetal responses to a maternal aerobic exercise program. *Am. J. Obstet. Gynecol.* 1983; **145**:702-7.
142. Zeanah M, Schlosser SP. Adherence to ACOG guidelines on exercise during pregnancy: effect on pregnancy outcome. *J. Obstet. Gynecol Neonatal Nurs.* 1993; **22**:329-35.
143. Bell RJ, Palma SM, Lumley JM. The effect of vigorous exercise during pregnancy on birth-weight. *Aust. N. Z. J. Obstet. Gynaecol.* 1995; **35**:46-51.
144. Bell R, Palma S. Antenatal exercise and birthweight. *Aust. N. Z. J. Obstet. Gynaecol.* 2000; **40**:70-3.
145. Campbell MK, Mottola MF. Recreational exercise and occupational activity during pregnancy and birth weight: a case-control study. *Am. J. Obstet. Gynecol.* 2001; **184**:403-8.
146. Magann EF, Evans SF, Weitz B, Newnham J. Antepartum, intrapartum, and neonatal significance of exercise on healthy low-risk pregnant working women. *Obstet. Gynecol.* 2002; **99**:466-72.
147. Leet T, Flick L. Effect of exercise on birthweight. *Clin. Obstet. Gynecol.* 2003; **46**:423-31.
148. De Ver Dye T, Fernandez ID, Rains A, Fershteyn Z. Recent studies in the epidemiologic assessment of physical activity, fetal growth, and preterm delivery: a narrative review. *Clin. Obstet. Gynecol.* 2003; **46**:415-22.

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