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 (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 (Figure 1). The birth weight distribution has thus broadened, putting greater numbers of babies at the extremes and at elevated risk of both perinatal morbidity8 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 BMI13 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
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.\(^\text{16}\) 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.\(^\text{17}\) 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\(_{\text{2max}}\)) in association with lower death rates across a wide range of ages from 20 to 82 years.\(^\text{18}\)

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.\(^\text{19,20}\) 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.\(^\text{21}\)

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.\(^\text{22-24}\) Adaptations in large artery biomechanical properties,\(^\text{25-27}\) conduit vessel endothelium dependent vasodilatation\(^\text{28-32}\) and autonomic function\(^\text{29,33-35}\) are also likely to contribute to improved outcomes.

In addition to greater life expectancy\(^\text{36}\) and a reduction in cardiovascular mortality, moderately and highly active individuals live more years free of diabetes than their sedentary counterparts.\(^\text{37-39}\) With regard to improvement in glycemic control, resistance training provides particular benefit for middle aged to elderly people with type 2 diabetes.\(^\text{40,41}\) 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.\(^\text{42,43}\) 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.\(^\text{41}\) In contrast, aerobic training enhances glucose disposal independently of changes in muscle mass or aerobic capacity, suggesting an intrinsic increase in muscle glucose consumption.\(^\text{42}\) Furthermore, both aerobic and resistance training likely increase insulin sensitivity through concomitant decreases in visceral and abdominal subcutaneous adipose tissue.\(^\text{44,45}\)

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). 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. 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, Juul et al. 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.

Consistent with human data, birth weight is unaffected when healthy well-nourished rodents participate in mild to moderate intensity exercise programs during pregnancy. Further, mild training in conjunction with malnourishment during pregnancy indicates that the effect of diet on birth weight predominates over the training effect. Training may, however, attenuate the impact of a low-protein diet on the growth rate of rat offspring. 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. Continuing vigorous weight-bearing exercise (running, aerobic dance and cross-country skiing) throughout pregnancy led to a reduction in mean birth weight of 509g and 310g 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. 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 but not in urban, low income, black women in the USA. 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. However, high intensity exercise in mid-pregnancy was associated with an increased SGA risk. This is supported by smaller cohorts in which well-conditioned recreational athletes 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, or did not change. 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). Strenuous exercise in pregnant animals has been well-documented to reduce fetal weight as shown in mice, rats, guinea pigs and goats. Animal studies provide mechanistic insight suggesting that intense exercise may restrict placental blood flow causing fetal nutrient restriction and hypoxia. 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. 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.

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. 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. 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. 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).

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Country (ref. no.)</th>
<th>Study design</th>
<th>Total no. of participants (no. exercisers if applicable)</th>
<th>Timing of exercise during pregnancy</th>
<th>Controls</th>
<th>Exercise modality</th>
<th>Effect of exercise on mean birth weight vs control or as stated (P value)</th>
<th>Exercise/PA duration, frequency, intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleten (2010) Norway13</td>
<td>Cross-sectional Observation</td>
<td>43,705</td>
<td>2nd trimester</td>
<td>Sedentary</td>
<td>Brisk walking, running, cycling, weight training, gym, aerobics, dancing, skiing, ball games, swimming</td>
<td>↓ 2.9g/unit (1×/mo) exercise</td>
<td>1-3×/mo 1×/wk 2×/wk 3+/wk</td>
<td></td>
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<tr>
<td>Hatch (1993) USA22</td>
<td>Cross-sectional Observation</td>
<td>462 (277)</td>
<td>Throughout</td>
<td>Sedentary</td>
<td>Strenuous: Aerobics, running; Non-strenuous: Gardening, antenatal exercise class</td>
<td>↑ 165g (ns) Heavy ↑ 325g (P&lt;0.05)†</td>
<td>20min/session Level I: 3+/wk - vigorous walking Level II: 1×/wk + vigorous walking</td>
<td></td>
</tr>
<tr>
<td>Sternfeld (1995) USA24</td>
<td>Cross-sectional Observation</td>
<td>361 (119)</td>
<td>Throughout</td>
<td>Sedentary/Low activity</td>
<td>Aerobics, cycling, running, swimming</td>
<td>↓ 84g (ns) Level I @36wks ↑ 121g</td>
<td>Level I: ≤1,000kcal/wk Level II: &gt;1,000kcal/wk</td>
<td></td>
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<tr>
<td>Hopkins (2010) NZ</td>
<td>Intervention</td>
<td>84 (47)</td>
<td>2nd &amp; 3rd trimester</td>
<td>Sedentary</td>
<td>Stationary cycle</td>
<td>↓ 143g (ns)</td>
<td>≤5×/wk 40min/session 65% VO2max</td>
<td></td>
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<tr>
<td>Juhl (2010) Denmark32</td>
<td>Cross-sectional Observation</td>
<td>79,692 (29,763)</td>
<td>1st &amp; 2nd trimester</td>
<td>Sedentary</td>
<td>Swimming, aerobics/gymnastics, dance, walking/hiking, yoga, jogging, ball games, gym, cycling, horse riding</td>
<td>↓ 11g (ns) ↓ modest SGA risk</td>
<td>0 1h/wk 1-2h/wk 2-3h/wk 3-4h/wk 4-5h/wk &gt;5h/wk</td>
<td></td>
</tr>
<tr>
<td>Leiferman (2003) USA33</td>
<td>Cross-sectional Observation</td>
<td>9,089</td>
<td>Throughout</td>
<td>Active (Con Ex)</td>
<td>Regular leisure physical activity: “Did you exercise or play sports?”</td>
<td>Uncon Nex ↑ VLBW risk vs Con Ex (P&lt;0.05) Con Nex ↑ VLBW risk vs Con Ex (P&lt;0.01)</td>
<td>Before preg: Conditioned (Con-Exercise 3+/wk) Unconditioned (Uncon-Exercise &lt;3/wk) During preg: Exerciser (Ex-3+/wk) Non-exerciser (Nex-&lt;3/wk)</td>
<td></td>
</tr>
<tr>
<td>Clapp (1990) USA35</td>
<td>Cross-sectional Observation</td>
<td>132 (77)</td>
<td>Throughout</td>
<td>Active</td>
<td>Aerobics, running</td>
<td>↓ 30g (P&lt;0.05)</td>
<td>As for Clapp (1984) below</td>
<td></td>
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<tr>
<td>Clapp (1984) USA36</td>
<td>Cross-sectional Observation</td>
<td>228 (76)</td>
<td>Throughout</td>
<td>Sedentary = Group I</td>
<td>Aerobics, running, x-country skiing</td>
<td>Gp III ↑ 50g vs Gp I (P&lt;0.01) Gp II ↑ 59g vs Gp I (ns)</td>
<td>3×/wk 30min/session 50% age-adjusted max HR; Group II (n=47): Discontinued exercise by 28wks; Group III (n=29): Exercised throughout</td>
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<tr>
<td>Jackson (1995) USA38</td>
<td>Cross-sectional Observation</td>
<td>60 (40)</td>
<td>2nd &amp; 3rd trimester</td>
<td>Active</td>
<td>Aerobics, running, x-country skiing</td>
<td>2nd trimester ↓ 220g (ns) 3rd trimester ↓ 24g (ns)</td>
<td>3×/wk 30min/session &gt;50% max capacity</td>
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<tr>
<td>Clapp (1998) USA39</td>
<td>Cross-sectional Observation</td>
<td>104 (52)</td>
<td>Throughout</td>
<td>Sedentary</td>
<td>Step aerobics, stair stepper, treadmill</td>
<td>200g (P=0.05) @ birth ↓ 70g (ns) @ 1 year</td>
<td>3×/wk 20min/session &gt;50% max capacity</td>
<td></td>
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<tr>
<td>Marquez-Sterling (2000) USA41</td>
<td>Intervention</td>
<td>15 (9)</td>
<td>2nd &amp; 3rd trimester</td>
<td>Sedentary</td>
<td>Cycling, rowing, running, walking</td>
<td>↓ 207g (ns)</td>
<td>3×/wk 60min/session 150-156rpm</td>
<td></td>
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<tr>
<td>First author (Year)</td>
<td>Study design</td>
<td>Total no. of participants</td>
<td>Timing of exercise during pregnancy</td>
<td>Controls</td>
<td>Exercise modality</td>
<td>Effect of exercise on mean birth weight vs control or as stated (P value)</td>
<td>Exercise/PA duration, frequency, intensity</td>
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<tr>
<td>Rao (2003) India(^{86})</td>
<td>Cross-sectional Observation</td>
<td>62</td>
<td>2nd &amp; 3rd trimester</td>
<td>Active (low activity)</td>
<td>Agricultural &amp; domestic activities: Cooking, washing, sweeping, fetching water, farm work, resting</td>
<td>High PA @18wks ↓69g (P=0.05) High PA @28wks ↓69g (P=0.02) High PA @18wks ↑LBW risk (P&lt;0.05)</td>
<td>Activity score: Low Medium High See ref. for more detail</td>
<td></td>
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<tr>
<td>Dwarkanath (2007) India(^{87})</td>
<td>Cross-sectional Observation</td>
<td>63</td>
<td>Throughout</td>
<td>Sedentary activities (&gt;165min/day)</td>
<td>Occupational, exercise, housework, hobbies, sleep</td>
<td>Highest PA tertile in 1st trimester ↑LBW risk Relative maternal physical activity level (Tertiles)</td>
<td>2×/wk 60min/session</td>
<td></td>
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<tr>
<td>Haakstad (2011) Norway(^{64})</td>
<td>Intervention</td>
<td>105 (52)</td>
<td>2nd trimester</td>
<td>Sedentary</td>
<td>Aerobic dance &amp; strength training; plus 30min self-imposed physical activity</td>
<td>100% exercise adherence ↓232g (ns) NB: n=14 only</td>
<td>2×/wk 60min/session 5×/wk 60min/session</td>
<td></td>
</tr>
<tr>
<td>Orr (2006) USA(^{65})</td>
<td>Cross-sectional Observation</td>
<td>922</td>
<td>Throughout</td>
<td>Sedentary</td>
<td>Self-reported physical activity</td>
<td>↑LBW risk (ns) Strenuous vs Non-strenuous exercise</td>
<td>See ref. for details</td>
<td></td>
</tr>
<tr>
<td>Gollenberg (2011) USA(^{66})</td>
<td>Cross-sectional Observation</td>
<td>1,040</td>
<td>1st &amp; 2nd trimester</td>
<td>Low activity quartile</td>
<td>Sports/exercise, household, occupational, active living (Categorized in quartiles)</td>
<td>High PA mid-preg ↓SGA risk; High sports/ exercise ↑SGA risk</td>
<td>See ref. for details</td>
<td></td>
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<tr>
<td>Clapp (2000) USA(^{76})</td>
<td>Intervention</td>
<td>46 (22)</td>
<td>Throughout</td>
<td>Sedentary</td>
<td>Step aerobics, stair stepper, treadmill</td>
<td>↓230g (P&lt;0.05)</td>
<td>3-5×/wk 20min/session 35-60% VO(_2) max</td>
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<tr>
<td>Clapp (2002) USA(^{75})</td>
<td>Intervention</td>
<td>75 (51)</td>
<td>Throughout</td>
<td>Active Mod-Mod (n=24): Moderate intensity throughout</td>
<td>Step aerobics, stair stepper, treadmill</td>
<td>Hi-Lo ↑460g vs Mod-Mod (P&lt;0.001) Lo-Hi ↓100g vs Mod-Mod (ns)</td>
<td>5×/wk Low=20min/session Mod=40min/session High=60min/session 55-60% VO(_2) max; Lo-Hi (n=26): Low int. 8-20wks; High int. 24-40wks; Hi-Lo (n=25): High int. 8-20wks; Low int. 24-40wks</td>
<td></td>
</tr>
<tr>
<td>Erkkola (1976) Finland(^{40})</td>
<td>Intervention</td>
<td>44 (23)</td>
<td>Throughout</td>
<td>Sedentary</td>
<td>Cycling, running, stair climbing, swimming, walking</td>
<td>↑88g (ns)</td>
<td>3×/wk 60min/session HR &gt;160bpm</td>
<td></td>
</tr>
<tr>
<td>Collings (1983) USA(^{141})</td>
<td>Intervention</td>
<td>20 (12)</td>
<td>2nd &amp; 3rd trimester</td>
<td>Sedentary</td>
<td>Cycling</td>
<td>↑243g (ns)</td>
<td>3×/wk for 7-19wks 50min/session 65-70% VO(_2) max</td>
<td></td>
</tr>
<tr>
<td>Zeana (1993) USA(^{142})</td>
<td>Cross-sectional Observation</td>
<td>173 (87)</td>
<td>3rd trimester</td>
<td>Active</td>
<td>Unknown</td>
<td>High intensity ↑255g vs Low intensity (ns); Long duration ↑17g vs short duration; ↑99g vs moderate duration (ns)</td>
<td>Duration: Long=40min/session Moderate=20-39min Short=≤19min Intensity: High=HR &gt;150bpm Moderate=HR 130-149bpm Low=HR ≤129bpm</td>
<td></td>
</tr>
<tr>
<td>Bell (1995) AUS(^{83})</td>
<td>Cross-sectional Observation</td>
<td>99 (58)</td>
<td>2nd trimester</td>
<td>Sedentary</td>
<td>Aerobics, swimming, running.</td>
<td>5+wk ↑315g (P&lt;0.02) 3+wk ↑318g (P&lt;0.05)</td>
<td>3+wk 30min/session 50% age-adj.max HR Grp 1 continued: 5+/wk Grp 2 reduced: 1-3+/wk</td>
<td></td>
</tr>
<tr>
<td>Bell (2000) AUS(^{84})</td>
<td>Intervention</td>
<td>43 (23)</td>
<td>2nd &amp; 3rd trimester</td>
<td>Active=Grp 2</td>
<td>Vigorous exercise</td>
<td>↑LBW risk (Adjusted OR 4.61) vs NBW, P&lt;0.05)</td>
<td>Structured exercise 3-4×/wk vs 5+/wk</td>
<td></td>
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<tr>
<td>Campbell (2001) USA(^{140})</td>
<td>Intervention</td>
<td>529 (164)</td>
<td>3rd trimester</td>
<td>Active (3-4×/wk)</td>
<td>Recreational exercise &amp; occupational activity</td>
<td>↑LBW risk (Adjusted OR 4.61) vs NBW, P&lt;0.05)</td>
<td>Structured exercise 3-4×/wk vs 5+/wk</td>
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</table>
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 and is the leading cause of neonatal and infant morbidity and mortality. The latest data from Australia reported that in 2009, 8.2% of babies were born pre-term. 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 as well as with first trimester vigorous activity. 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. 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. 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. 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. 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. Other studies have also shown no relationship between physical activity exercise and gestational age 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). 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.

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.

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). 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. Furthermore, offspring of exercised mothers are leaner and have a better neurodevelopmental outcome at 5 years of age. 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 or via increased global DNA methylation. Physical activity has been shown to influence such epigenetic mechanisms to control gene expression. 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 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, or being born extremely pre-term (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. This finding is congruent with four separate, large and varied cohorts compiled by Ridgway et al., 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. 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. 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 and VLBW 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. VLBW young adults (~20-22 years of age) also exercised less than their NBW counterparts in a cohort of normal weight (BMI ≃22 kg/m²) 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. 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. 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. 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. 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.

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

<table>
<thead>
<tr>
<th>First author (year) (ref. no.)</th>
<th>Study design</th>
<th>Cohort age (yrs)</th>
<th>Cohort birth weight category</th>
<th>Habitual activity level compared to NBW</th>
<th>Exercise capacity compared to NBW</th>
<th>Physiological effects compared to NBW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallal (2006)</td>
<td>Observational</td>
<td>10-12</td>
<td>LBW</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridgway (2011)</td>
<td>Observational</td>
<td>12-15</td>
<td>Various LBW cohorts, VLBW, ELBW excluded</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welsh (2010)</td>
<td>Cross-sectional</td>
<td>11</td>
<td>ELBW</td>
<td>↓</td>
<td>↓ VO&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;</td>
<td>↓ aerobic fitness, muscular strength, power, endurance and flexibility</td>
</tr>
<tr>
<td>Rogers (2005)</td>
<td>Cross-sectional</td>
<td>16-20</td>
<td>ELBW</td>
<td>↓</td>
<td>↓ VO&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;, max HR, aerobic endurance</td>
<td>↓ mechanical efficiency (running), lung function</td>
</tr>
<tr>
<td>Kajantie (2010)</td>
<td>Cross-sectional</td>
<td>19-27</td>
<td>VLBW</td>
<td>↓</td>
<td>↓ VO&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;, max HR, aerobic endurance</td>
<td>↓ mechanical efficiency (running), ↓ lung function</td>
</tr>
<tr>
<td>Eriksson (2004)</td>
<td>Observational</td>
<td>65-75</td>
<td>LBW</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baraldi (1991)</td>
<td>Cross-sectional</td>
<td>7-12</td>
<td>VLBW-AGA</td>
<td>↔ VO&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;, max HR, aerobic endurance</td>
<td>↔ mechanical efficiency (running), lung function</td>
<td></td>
</tr>
<tr>
<td>Keller (1998, 2000)</td>
<td>Cross-sectional</td>
<td>5-7</td>
<td>ELBW</td>
<td>↓</td>
<td>↓ neuromuscular coordination, reaction time, anaerobic power</td>
<td>↓ lean mass, ↑ fat mass</td>
</tr>
<tr>
<td>Kilbride (2003)</td>
<td>Cross-sectional</td>
<td>5-7</td>
<td>VLBW</td>
<td>↓</td>
<td>↓ VO&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;, aerobic endurance</td>
<td>↓ lean mass, ↑ fat mass</td>
</tr>
<tr>
<td>Vrijlandt (2006)</td>
<td>Observational, Cross-sectional</td>
<td>9-15</td>
<td>ELBW</td>
<td>↓</td>
<td>↓ VO&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;, aerobic endurance</td>
<td>↓ lung function</td>
</tr>
<tr>
<td>Kriemler (2005)</td>
<td>Cross-sectional</td>
<td>5-7</td>
<td>ELBW to VLBW</td>
<td>↔ VO&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;</td>
<td>↓ mechanical efficiency (cycling), ↓ lung function</td>
<td></td>
</tr>
<tr>
<td>Sipola-Leppänen (2011)</td>
<td>Cross-sectional</td>
<td>22</td>
<td>VLBW</td>
<td>↓</td>
<td>↓ mechanical efficiency (cycling), ↓ lung function</td>
<td></td>
</tr>
<tr>
<td>Ozanne (2005)</td>
<td>Cross-sectional</td>
<td>19</td>
<td>LBW</td>
<td>↓</td>
<td>↔ lean, fat mass; ↓ insulin signalling proteins</td>
<td></td>
</tr>
</tbody>
</table>
VLBW children and adolescents include reduced aerobic capacity, whether expressed in absolute or relative terms or indirectly estimated via an incremental exercise test (Table 2). Multiple indices of muscular power and endurance are also reduced (Table 2). The common theme in these latter studies compared with an earlier study by Baraldi et al. is the presence, or not, of chronic bronchopulmonary disease in some participants, a common affliction, particularly in the lowest birth weight categories. 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. Studies of VLBW children support this reduction in mechanical efficiency while cycling, but only in those diagnosed with chronic lung disease.

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. In adult LBW rats both red and white muscle fibres are smaller (cross-sectional area) than in control animals. Corticosteroids used to treat chronic lung disease in LBW individuals may also induce muscle atrophy. While lower relative muscle mass may provide a simple explanation for the observation of reduced \( V_{O_2} \text{max} \) 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. 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 flexors and adult rat soleus 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. of a greater oxygen consumption per kg of body weight at a given submaximal workload in SGA children. It may also explain why LBW individuals can achieve a normal \( V_{O_2} \text{max} \) 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. This is supported by reductions in phosphocreatine concentration, phosphocreatine:ATP ratio and the ATP:ADP ratio in VLBW infant muscle.

LBW also influences metabolic signalling cascades affecting substrate utilisation. For example, the glucose transporter GLUT4 is reduced in skeletal muscle of LBW individuals. 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 and another in newborn mice following maternal protein restriction 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. 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. 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. 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. 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. 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. This is, however, not supported by a study in 9-15 year old ELBW individuals who had significantly (>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.

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. 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. 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. 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. 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. 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. 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.

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