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The Developmental Origins of Sarcopenia: Using Peripheral Quantitative Computed Tomography to Assess Muscle Size in Older People

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Background. A number of studies have shown strong graded positive relationships between size at birth, grip strength, and estimates of muscle mass in older people. However no studies to date have included direct measures of muscle size.

Methods. We studied 313 men and 318 women born in Hertfordshire, United Kingdom between 1931 and 1939 who were still resident there and had historical records of growth in early life. Information on lifestyle was collected, and participants underwent peripheral quantitative computed tomography to directly measure forearm and calf muscle size.

Results. Birth weight was positively related to forearm muscle area in the men ($r = 0.24$, $p < .0001$) and women ($r = 0.17$, $p = .003$). There were similar but weaker associations between birth weight and calf muscle area in the men ($r = 0.13$, $p = .03$) and in the women ($r = 0.17$, $p = .004$). These relationships were all attenuated by adjustment for adult size.

Conclusion. We present first evidence that directly measured muscle size in older men and women is associated with size at birth. This may reflect tracking of muscle size and is important because it suggests that benefit may be gained from taking a life course approach both to understanding the etiology of sarcopenia and to developing effective interventions.

Key Words: Sarcopenia—Muscle—Aging—Development.

SARCOPENIA is defined as the loss of muscle mass and strength with age. The loss of muscle function in particular is associated with profound consequences for older people in terms of increased risk of morbidity, disability, and mortality. However, it remains poorly understood. A number of studies have shown strong graded positive relationships between size at birth and grip strength in older people, and there is growing interest in the effects of developmental influences on muscle in later life (1–4). The underlying mechanisms are unknown, but there is some evidence from animal models that prenatal undernutrition is associated with a reduced number of muscle fibers (5,6). It has been proposed that the relationship between low birth weight and impaired adult muscle strength reflects reduced muscle size.

Adult body composition studies involving indirect measures of fat-free or lean mass suggest associations between small size at birth and lower muscle mass (7–9). However, no studies to date have included direct measures of muscle size. Recent technological advances in imaging allowed us to use peripheral quantitative computed tomography (pQCT) to directly measure muscle cross-sectional area (CSA) in our clinic. We addressed the hypothesis that low birth weight was associated with smaller muscle size in older men and women participating in the Hertfordshire Cohort Study.

Methods

Study Population

In the late 1990s, 3000 men and women aged 59–72 years were recruited to take part in the Hertfordshire Cohort Study, which was designed to investigate the relationship between developmental, genetic, and adult lifestyle influences on long-term health, aging, and disease (10). These individuals had historical records of early growth and had been traced through the National Health Service Central Registry. They participated in a baseline study that included a home interview at which trained nurses collected information including self-reported walking speed (response options: unable to walk; very slow; stroll at an easy pace; normal speed; fairly brisk; fast) as a marker of physical activity (11) and social class. Men and women who were willing subsequently attended a clinic for a number of investigations including measurement of grip strength (12). A subgroup of 498 men and 468 women who were residents of East Hertfordshire also underwent dual x-ray absorptiometry (DXA) scans for assessment of bone mineral content and density (13).

Study Group

In 2004–2005, a follow-up study was performed in East Hertfordshire. The family doctors of participants in the

Table 1. Participant Characteristics

Participant Characteristic	Men ($N = 313$)	Women ($N = 318$)
pQCT forearm muscle cross-sectional area (mm^2)*	4033 (518)	2555 (370)
pQCT calf muscle area cross-sectional area (mm^2)*	8035 (1204)	6212 (981)
Birth weight, kg*	3.5 (0.5)	3.4 (0.5)
Age at pQCT scan, y*	69.2 (2.5)	69.5 (2.6)
Height, cm*	173.7 (6.5)	160.5 (6.1)
Weight, kg*	81.1 (1.2)	70.5 (1.2)
Walking speed†		
Very slow	3.5	3.8
Stroll at an easy pace	19.5	19.2
Normal speed	39.9	45.9
Fairly brisk	32.6	25.2
Fast	4.5	6.0
Social class†		
I–IIINM	40.9	42.8
IIM-V	54.0	57.2
Unclassified	5.1	0.0
Alcohol consumption†		
≤21 (men)/≤14 (women) units per week	83.7	96.8
>21 (men)/>14 (women) units per week	16.3	3.2
Smoking status†		
Never	38.3	63.2
Ex	53.4	31.4
Current	8.3	5.4

Notes: *Shown as mean and *SD*.

†Shown as percentage.

pQCT = peripheral quantitative computed tomography; *SD* = standard deviation; I-IIINM = social classes one to three nonmanual of the 1990 Office of Population Census and Surveys (OPCS) standard occupational classification scheme for occupation and social class; IIIM-V = classes three manual to five.

baseline survey were contacted to ask if we could approach their patients again. Of the original 498 men and 468 women who had undergone a DXA scan, 8 had died, 6 had moved away, we were unable to obtain general practitioner (GP) permission to approach 4 people, 47 were no longer on family doctor lists, and 17 were unavailable. Hence, we were able to invite 437 men and 447 women to take part in the follow-up study. Of these, 322 men (74%) and 320 women (72%) agreed to attend a follow-up clinic, and 313 (97%) of the men and 318 (99%) of the women also underwent a pQCT scan.

Follow-Up Clinic Visit

At the follow-up clinic visit, a detailed health and lifestyle questionnaire was again administered to update the medical and social histories. Information was specifically collected on current smoking status and alcohol consumption. Anthropometry included measurement of height to the nearest 0.1 cm using a Harpenden pocket stadiometer (Chasmors Ltd, London, U.K.) and weight to the nearest 0.1 kg on a SECA floor scale (Chasmors Ltd).

Determination of Muscle Size

We performed pQCT to determine the muscle CSA of the nondominant forearm and lower leg using a Stratec XCT-2000 instrument (Stratec, Pforzheim, Germany). Data presented here were derived from 2.3 mm-thick transverse scans obtained at a standard position 66% along the length of the humerus and tibia (14,15). Previous studies have shown that this is the region with the largest outer diameter and little variability across individuals (16).

The total dose of radiation administered to the participants was 0.03 mSv (below that of a standard hand x-ray), and reproducibility, expressed as a coefficient of variation, has been reported as 1.93% for muscle CSA (17). The muscle area and bone cortical area were separated by a built-in software algorithm (18).

Ethics Approval

The East and North Hertfordshire Ethics Committee granted ethics approval for the study, and all participants provided written informed consent.

Statistical Analysis

Weight was positively skewed and $\log_e$ transformed to a normal distribution. Social class was coded from most recent full-time occupation according to the 1990 Office of Population Census and Surveys (OPCS) standard occupational classification scheme for occupation and social class. Social class for ever-married women was coded from the husband's most recent full-time occupation. Variables were summarized using means and standard deviation (*SD*) or frequency and percentage distributions. Geometric means and *SD* values were calculated for weight. Relationships between potential adult determinants of forearm and calf muscle CSA were explored using Pearson correlation coefficients and one-way analysis of variance (ANOVA). Mutually adjusted relationships were subsequently explored using linear regression. Height and weight were strongly correlated ($r = 0.39$, $p < .0001$ for men; $r = 0.40$, $p < .0001$ for women); to avoid multicolinearity problems, these variables were included as predictors in regression models in turn.

Pearson's pairwise and partial correlation coefficients were used to describe the relationships between muscle CSA and birth weight without, and with, adjustment for the adult determinants of muscle CSA. For presentational purposes, means and confidence intervals of muscle CSA were derived according to quintiles of birth weight. However, statistical tests of association with muscle CSA were based on the continuously distributed birth weight variable throughout.

All analyses were carried out for men and women separately, using the Stata statistical software package, release 8.0 (Stata Corp, College Station, TX).

Results

Participant Characteristics

The characteristics of the study group are shown in Table 1.

Adult Determinants of Muscle CSA

Univariate analyses showed that older age was associated with lower forearm muscle CSA in men and women;

Table 2. Adult Determinants of pQCT Forearm and Calf Muscle CSA

Adult Determinant	Forearm Muscle CSA		Calf Muscle CSA	
	Men	Women	Men	Women
Age at pQCT scan, y*	−0.17	−0.14	−0.10	−0.09
	$p = .002$	$p = .01$	$p = .09$	$p = .12$
Height, cm*	0.17	0.25	0.17	0.25
	$p = .002$	$p < .0001$	$p = .004$	$p < .0001$
Weight, kg*	0.59	0.52	0.60	0.57
	$p < .0001$	$p < .0001$	$p < .0001$	$p < .0001$
Walking speed†				
Very slow	4255 (535)	2507 (435)	8061 (1332)	5885 (858)
Stroll at an easy pace	4072 (570)	2658 (392)	8222 (1269)	6422 (966)
Normal	4011 (526)	2516 (345)	7898 (1163)	6190 (957)
Fairly brisk	4020 (484)	2524 (356)	8103 (1250)	6085 (923)
Fast	4001 (441)	2691 (448)	7992 (850)	6431 (1385)
	$p = .64$	$p = .05$	$p = .53$	$p = .23$
Social class†				
I-IIINM	3946 (492)	2540 (410)	7956 (1255)	6132 (1022)
IIIM-V	4097 (538)	2566 (337)	8078 (1160)	6275 (946)
Unclassified	4068 (410)	$p = .54$	8196 (1280)	$p = .21$
	$p = .05$		$p = .61$	
Alcohol consumption†				
≤21 (men)/≤14 (women) units per week	4033 (535)	2555 (372)	8019 (1217)	6201 (977)
>21 (men)/>14 (women) units per week	4033 (421)	2538 (342)	8113 (1144)	6367 (1052)
	$p = .99$	$p = .89$	$p = .62$	$p = .60$
Smoking status†				
Never	3936 (507)	2516 (360)	8053 (1225)	6121 (940)
Ex	4082 (514)	2589 (360)	8052 (1179)	6313 (1015)
Current	4160 (539)	2747 (445)	7853 (1288)	6655 (1136)
	$p = .03$	$p = .02$	$p = .73$	$p = .05$

Notes: *Pearson correlation coefficient for each adult variable versus muscle CSA, then p value.

†Mean (standard deviation, *SD*), then p value from one-way analysis of variance for muscle CSA versus adult variable.

pQCT = peripheral quantitative computed tomography; CSA = cross-sectional area; I-IIINM = social classes one to three nonmanual of the 1990 Office of Population Census and Surveys (OPCS) standard occupational classification scheme for occupation and social class; IIIM-V = classes three manual to five.

associations between age and calf muscle area were similar, but not statistically significant. Adult size was strongly related to muscle CSA. Taller height and heavier weight were both significantly associated with increased forearm and calf muscle CSA in men and women. There were no associations between forearm or calf muscle CSA and walking speed or alcohol intake in men or women. Average forearm muscle CSA was higher among men of manual (4097 mm^2) compared with nonmanual social class (3946 mm^2, $p = .05$); there were no other associations between muscle CSA and social class in men or women. Men and women who were current smokers had higher forearm muscle CSA in comparison with those who were ex- or never-smokers ($p = .03$ for men, $p = .02$ for women). Current smoking was also associated with increased calf muscle area in women ($p = .05$) but not men ($p = .73$). These results are summarized in Table 2.

Age, height or weight, social class, and smoking were subsequently included as predictors of muscle CSA in mutually adjusted regression models; all of the significant univariate relationships described above remained significant after mutual adjustment. Hence, age, height or weight, social class, and smoking were taken forward as adjustment variables for the analyses of birth weight in relation to muscle CSA. Adult height and weight were the strongest influences on muscle CSA, so their individual effects on the relationship between birth weight and muscle CSA were ascertained prior to a multivariate model determining the effect of all the adult influences.

Relationship Between Birth Weight and Adult Muscle CSA

Lower birth weight was associated with reduced forearm muscle area in the men ($r = 0.24$, $p < .0001$, Figure 1) and women ($r = 0.17$, $p = .003$, Figure 1). These associations were attenuated but remained significant after adjustment for height alone, or collectively for height, age, social class, and smoking status in the men but not the women (Table 3). There were similar but weaker associations between calf muscle area and birth weight in the men ($r = 0.13$, $p = .03$, Figure 1) and in the women ($r = 0.17$, $p = .004$, Figure 1), but these did not remain significant after adjustment for height, or for height, age, social class, and smoking status (Table 3). Adjustment for adult weight alone fully explained the associations between lower birth weight and reduced muscle area at the forearm for women, and the calf for men and women (Table 3); the relationship between birth weight and calf muscle area in men was also substantially

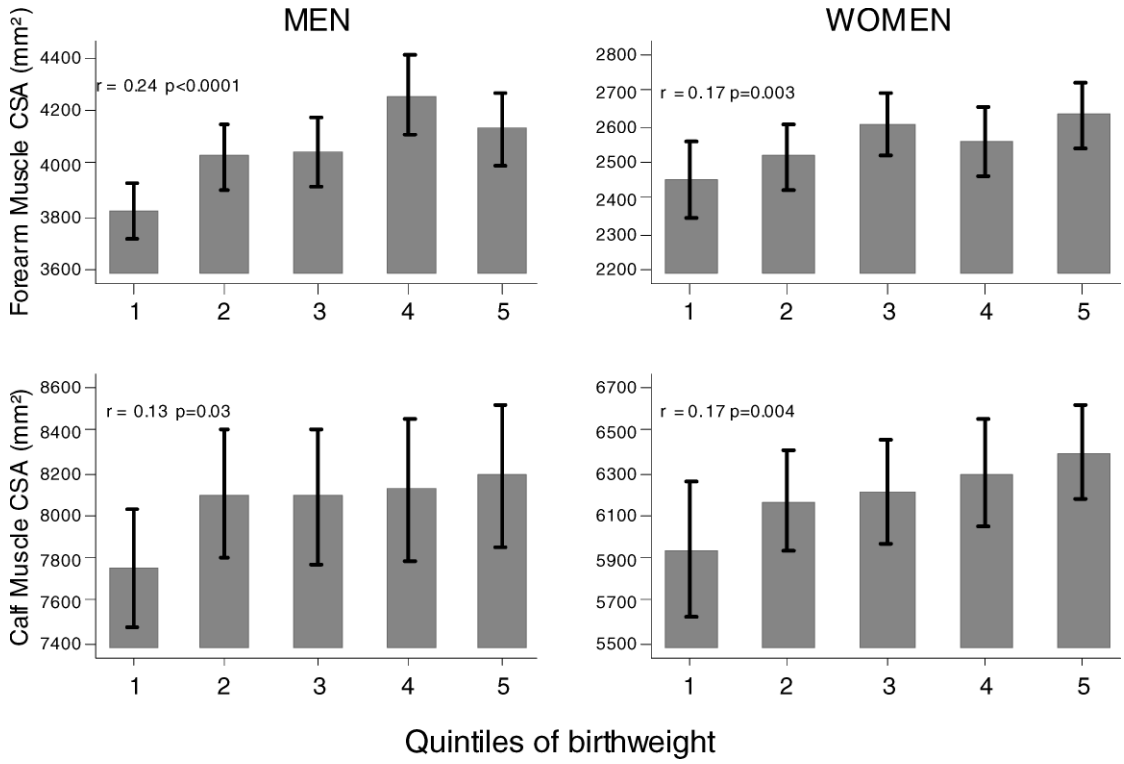

Figure 1. Relationships between birth weight and adult muscle cross-sectional area (CSA). Muscle cross-sectional area presented according to quintiles of birthweight correlation coefficients (r) and *p* values based on continuously distributed variables.

attenuated although it remained statistically significant. Adjustment for age, social class, and smoking status in addition to weight had little further impact on the results.

Discussion

We have shown that directly measured muscle size in older men and women is positively associated with size at birth. To our knowledge, this is the first study investigating developmental influences on sarcopenia to utilize direct imaging of muscle with pQCT. However, the findings are consistent with previous studies showing relationships between poor early growth and lower lean or nonfat mass as estimated by urinary creatinine excretion, anthropometry, and DXA (7–9). There was evidence of regional variation in the strength of the associations with a stronger correlation between muscle size and birth weight at the forearm than the calf. This finding might reflect the greater contribution of adult influences such as voluntary activity to muscle size in the lower limb.

There may be a number of explanations for the relationship between birth weight and adult muscle size. It

Table 3. Relationships Between Birth Weight and Adult Muscle CSA

	Forearm Muscle CSA		Calf Muscle CSA	
Birth Weight and Other Determinants	Men	Women	Men	Women
Unadjusted	0.24	0.17	0.13	0.17
	$p < .0001$	$p = .003$	$p = .03$	$p = .004$
Adjusted for adult size				
Height	0.22	0.11	0.11	0.11
	$p < .001$	$p = .06$	$p = .06$	$p = .07$
Weight	0.17	0.07	0.02	0.05
	$p = .003$	$p = .25$	$p = .72$	$p = .42$
Adjusted for adult size and other determinants				
Adjusted for height, age, social class, and smoking status	0.19	0.08	0.10	0.08
	$p = .001$	$p = .14$	$p = .09$	$p = .16$
Adjusted for weight, age, social class, and smoking status	0.14	0.05	0.03	0.03
	$p = .01$	$p = .40$	$p = .67$	$p = .63$

Notes: Values shown are correlation coefficients with *p* value.
CSA = cross-sectional area.

could represent a chance finding, although the consistency in findings across studies using different methodologies to characterize muscle suggests a true association. The association was largely explained by measures of adult size, particularly adult weight, and tracking of muscle size and weight from early life could underlie a causal association. Support for this explanation comes from a number of studies linking early growth to muscle size in children and young people (19–23) and recognition that the aging muscle phenotype reflects not only loss of muscle in later life but also the peak reached in early adulthood (24).

Studies in a wide range of animal models have shown that early environmental influences, such as prenatal and postnatal nutrition, are important determinants of early muscle growth and development (5,6,25–32). It appears that muscle fiber number is largely complete by the time of birth, suggesting that prenatal influences may be particularly important for long-term muscle quantity and possibly quality (33). There has been one human metabolic study linking small size at birth with alteration in adult muscle fiber composition in young adults (34), and these findings now need to be replicated in older men and women.

Our study has a number of potential limitations. There have been losses to follow-up both in the tracing process and through gaining consent to take part in the study. However, we have been able to characterize people who did not take part in a number of ways (10). There were no substantial differences in birth weight or weight at 1 year between those who were traced and eligible to take part and those who chose not to. There were also no differences in terms of early life measurements between those who attended the home visit but chose not to attend a clinic appointment. Furthermore, there were no statistical differences in social class distribution in the home-interviewed participants who did not attend the clinic. However, there was evidence for a healthy participant bias in those who attended the clinic. For example, they were less likely to smoke or drink. However, our comparisons are internal; unless the relationship between early size, growth, and muscle size differed between those who did and did not take part in the study, no bias should have been introduced.

We present the first evidence that directly measured muscle size in older men and women is associated with size at birth. This may reflect tracking of muscle size and is consistent with the aging muscle phenotype representing peak muscle attained as well as subsequent loss. This is important because it suggests that benefit may be gained from taking a life course approach both to understanding the etiology of sarcopenia and to developing effective interventions.

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References

1. Sayer AA, Cooper C, Evans JR, et al. Are rates of ageing determined in utero? *Age Ageing*. 1998;27:579–583.
2. Kuh D, Bassey J, Hardy R, Aihie Sayer A, Wadsworth M, Cooper C. Birth weight, childhood size, and muscle strength in adult life: evidence from a birth cohort study. *Am J Epidemiol*. 2002;156: 627–633.
3. Sayer AA, Syddall HE, Gilbody HJ, Dennison EM, Cooper C. Does sarcopenia originate in early life? Findings from the Hertfordshire Cohort Study. *J Gerontol A Biol Sci Med Sci*. 2004;59:930–934.
4. Yliharsila H, Kajantie E, Osmond C, Forsen T, Barker DJ, Eriksson JG. Birth size, adult body composition and muscle strength in later life. *Int J Obes (Lond)*. 2007;31:1392–1399.
5. Maltin CA, Delday MI, Sinclair KD, Steven J, Sneddon AA. Impact of manipulations of myogenesis in utero on the performance of adult skeletal muscle. *Reproduction*. 2001;122:359–374.
6. Costello P, Rowlerson A, Braddick L, et al. Fetal skeletal muscle fibre number and type are altered by early and late gestation maternal undernutrition in sheep. *Proc Physiol Soc*. 2006;3:C116.
7. Phillips DIW. Relation of fetal growth to adult muscle mass and glucose tolerance. *Diab Med*. 1995;12:686–690.
8. Gale CR, Martyn CN, Kellingray S, Eastell R, Cooper C. Intrauterine programming of adult body composition. *J Clin Endocrinol Metab*. 2001;86:267–272.
9. Sayer AA, Syddall HE, Dennison EM, et al. Birth weight, weight at one year and body composition in older men: findings from the Hertfordshire Cohort Study. *Am J Clin Nutr*. 2004;80:199–203.
10. Syddall HE, Sayer AA, Dennison EM, Martin HJ, Barker DJ, Cooper C. Cohort profile: The Hertfordshire Cohort Study. *Int J Epidemiol*. 2005;34:1234–1242.
11. Bendall MJ, Bassey EJ, Pearson MB. Factors affecting walking speed of elderly people. *Age Ageing*. 1989;18:327–332.
12. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil*. 1985;66:69–74.
13. Dennison EM, Syddall HE, Sayer AA, Gilbody HJ, Cooper C. Birth weight and weight at 1 year are independent determinants of bone mass in the seventh decade: the Hertfordshire cohort study. *Pediatr Res*. 2005;57:582–586.
14. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol*. 2003;95:1851–1860.
15. McDermott MM, Hoff F, Ferrucci L, et al. Lower extremity ischemia, calf skeletal muscle characteristics, and functional impairment in peripheral arterial disease. *J Am Geriatr Soc*. 2007;55:400–406.
16. Rittweger J, Beller G, Ehrig J, et al. Bone-muscle strength indices for the human lower leg. *Bone*. 2000;27:319–326.
17. Neu CM, Rauch F, Rittweger J, Manz F, Schoenau E. Influence of puberty on muscle development at the forearm. *Am J Physiol Endocrinol Metab*. 2002;283:E103–E107.
18. Schoenau E, Neu CM, Mokov E, Wassmer G, Manz F. Influence of puberty on muscle area and cortical bone area of the forearm in boys and girls. *J Clin Endocrinol Metab*. 2000;85:1095–1098.
19. Ford GW, Kitchen WH, Doyle LW. Muscular strength at 5 years of children with a birthweight under 1500 g. *Aust Paediatr J*. 1988;24:295–296.
20. Rogers M, Fay TB, Whitfield MF, Tomlinson J, Grunau RE. Aerobic capacity, strength, flexibility, and activity level in unimpaired extremely low birth weight (< or = 800 g) survivors at 17 years of age compared with term-born control subjects. *Pediatrics*. 2005; 116:e58–e65.
21. Martorell R, Ramakrishnan U, Schroeder DG, Melgar P, Neufeld L. Intrauterine growth retardation, body size, body composition and physical performance in adolescence. *Eur J Clin Nutr*. 1998;52 Suppl 1:S43–S52.
22. Sachdev HS, Fall CH, Osmond C, et al. Anthropometric indicators of body composition in young adults: relation to size at birth and serial measurements of body mass index in childhood in the New Delhi birth cohort. *Am J Clin Nutr*. 2005;82:456–466.
23. Inskip HM, Godfrey KM, Martin HJ, Simmonds SJ, Cooper C, Aihie Sayer A. Size at birth and its relation to muscle strength in young adult women. *J Intern Med*. 2007;262:368–374.

24. Aihie Sayer A, Cooper C. Aging, sarcopenia and the life course. *Rev Clin Gerontol*. 2007;16:265–274.
25. Zhu MJ, Ford SP, Means WJ, Hess BW, Nathanielsz PW, Du M. Maternal nutrient restriction affects properties of skeletal muscle in offspring. *J Physiol*. 2006;575:241–250.
26. Quigley SP, Kleemann DO, Kakar MA, et al. Myogenesis in sheep is altered by maternal feed intake during the peri-conception period. *Anim Reprod Sci*. 2005;87:241–251.
27. Fahey AJ, Brameld JM, Parr T, Buttery PJ. The effect of maternal undernutrition before muscle differentiation on the muscle fiber development of the newborn lamb. *J Anim Sci*. 2005;83:2564–2571.
28. Bayol S, Jones D, Goldspink G, Stickland NC. The influence of undernutrition during gestation on skeletal muscle cellularity and on the expression of genes that control muscle growth. *Br J Nutr*. 2004; 91:331–339.
29. Lefaucheur L, Ecolan P, Barzic YM, Marion J, Le Dividich J. Early postnatal food intake alters myofiber maturation in pig skeletal muscle. *J Nutr*. 2003;133:140–147.
30. Greenwood PL, Hunt AS, Hermanson JW, Bell AW. Effects of birth weight and postnatal nutrition on neonatal sheep: II. Skeletal muscle growth and development. *J Anim Sci*. 2000;78:50–61.
31. Dwyer CM, Stickland NC, Fletcher JM. The influence of maternal nutrition on muscle fiber number development in the porcine fetus and on subsequent postnatal growth. *J Anim Sci*. 1994;72:911–917.
32. Ward SS, Stickland NC. The effect of undernutrition in the early postnatal period on skeletal muscle tissue. *Br J Nutr*. 1993;69: 141–150.
33. Dauncey MJ, Gilmour RS. Regulatory factors in the control of muscle development. *Proc Nutr Soc*. 1996;55:543–559.
34. Jensen CB, Storgaard H, Madsbad S, Richter EA, Vaag AA. Altered skeletal muscle fiber composition and size precede whole-body insulin resistance in young men with low birth weight. *J Clin Endocrinol Metab*. 2007;92:1530–1534.

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