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Translational Article

Special Issue on Muscle Function and Sarcopenia

Developmental Influences, Muscle Morphology, and Sarcopenia in Community-Dwelling Older Men

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Background. Sarcopenia is associated with disability, morbidity, and mortality. Lower birth weight is associated with reduced muscle mass and strength in older people, suggesting that developmental influences are important in sarcopenia. However, underlying mechanisms are unknown. Our objective was to determine whether low birth weight is associated with altered skeletal muscle morphology in older men.

Methods. Ninety-nine men with historical records of birth weight (≤3.18 kg and ≥3.63 kg), aged 68–76 years, consented for detailed characterization of muscle, including a biopsy of the vastus lateralis. Tissue was processed for immunohistochemical studies and analyzed to determine myofibre density, area, and score.

Results. Muscle fibre score (fibres kilograms per square millimeter) was significantly reduced in those with lower birth weight: 1.5×10^3 vs 1.7×10^3, $p = .04$ unadjusted; $p = .09$ adjusted for age, height, and physical activity. In addition, there was a trend for reduced myofibre density (fibres per square millimeter) in those with lower birth weight: total fibre density: 176 vs 184, type I myofibre density: 77 vs 80, and type II myofibre density: 99 vs 105. Types I and II myofibre areas (square micrometers) were larger in those with lower birth weight: type I: 4903 vs 4643 and type II: 4046 vs 3859. However, none of these differences were statistically significant.

Conclusions. This is the first study showing that lower birth weight is associated with a significant decrease in muscle fibre score, suggesting that developmental influences on muscle morphology may explain the widely reported associations between lower birth weight and sarcopenia. However, the study may have been underpowered and did not include women supporting replication in larger cohorts of older men and women.

Key Words: Development—Muscle morphology—Sarcopenia.

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SARCOPENIA, as defined by the European Working Group on Sarcopenia in Older People (EWGSOP), is the loss of muscle mass and strength or physical performance with age (1) and is associated with impaired mobility (2), morbidity from impaired glucose tolerance, diabetes (3), falls (4), fractures (5), and increased mortality (6). In the context of increasing numbers of older people, it is a major contributor to rising health care costs (7). Estimates for the decline in muscle mass between the ages of 40 and 80 years range from 30%–50% (8,9). Loss of muscle mass and strength with age is caused by a global reduction in myofibre number as well as size (10,11), and there is increasing interest in understanding the etiology of this muscle loss, particularly at a cellular level, in order to develop effective preventive and treatment strategies (12).

Well-recognized adult influences on muscle mass and strength include age, gender, heritability, adult body size, physical activity, and nutrition (13–15), although less is known about influences operating at a cellular level. Loss of muscle mass does not necessarily correlate with loss of strength. Longitudinal as well as cross-sectional studies show that younger individuals can be stronger and older individuals weaker than would be predicted by their muscle mass alone (16). For example, in a longitudinal study (17),

follow-up measurements of a cohort of 1,880 older participants over 3 years showed that decreases in isokinetic knee-extension strength were more rapid than those in lean muscle mass. The discrepancies can be explained by a decrease in muscle quality in which innervation constitutes the biggest component and may account for some of the variability in muscle mass and strength between older people. However, there still remains considerable unexplained variation in both muscle mass and strength between older people, and it has been proposed that influences operating throughout the life course should be considered. The life course model suggests that muscle mass and strength in older people reflects not only the current rate of loss but also the peak mass and strength attained earlier in life; this approach therefore focuses attention on influences acting during growth and development (18).

Evidence that developmental influences are operating in sarcopenia has come from epidemiological studies showing that lower birth weight, as a marker of an adverse intrauterine environment, is associated with reduced muscle mass and strength in adult life (19–23). The developmental origins of health and disease hypothesis states that early environmental conditions can induce permanent changes in tissue structure and function that have long-term effects on human health. The underlying mechanism is thought to be the universal biological phenomenon of developmental plasticity, whereby a single genotype can produce different forms of structure or function depending on early environmental conditions (24,25).

There is good evidence from animal studies that an adverse intrauterine environment can affect the development of myofibres, particularly during the secondary wave of myogenesis (26). For example, results from a recent study in sheep showed that peri-implantation and late gestation maternal undernutrition differentially affected myofibre density and function in fetal triceps muscle (27). There is also evidence that the effects on myofibre number persist into later life (28). However, few studies have investigated the effect of early environmental influences on myofibre composition in human muscle. A study of 27 women showed no association between low birth weight and muscle myofibre density, capillary density, or muscle enzymatic activity (29). However, a study of 20 low birth weight and 20 higher birth weight men aged 19 years demonstrated a change in muscle fibre composition and size with a decrease in percentage type IIa fibres, an increase in type IIa fibre area, and an increase in percentage type IIx fibres in low birth weight individuals (30). There have been no studies to date linking birth weight and muscle morphology in older men.

The aim of this study was therefore to investigate the relationship between low birth weight as a marker of an adverse intrauterine environment, and muscle morphology in a group of well-characterized community-dwelling older men already taking part in the Hertfordshire Cohort Study (HCS).

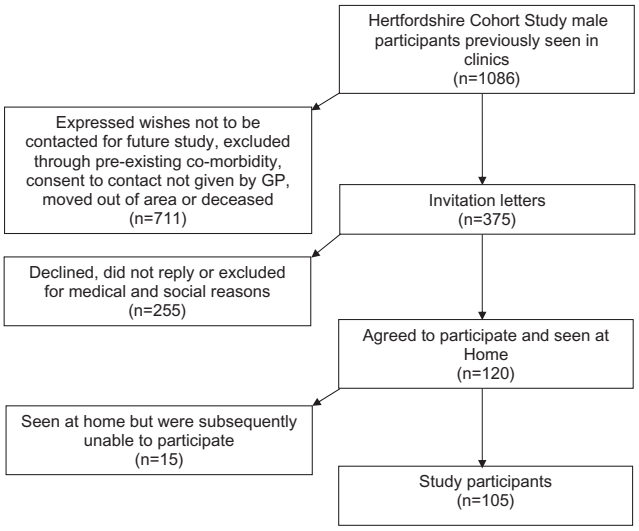

Figure 1. Flow chart for the recruitment into the current study.

Methods

Study Participants

The study received ethical approval from the Hertfordshire Research Ethics Committee (number 07/Q0204/68), and each participant gave written informed consent (31). All participants have previously been studied in the HCS (32). Briefly, the HCS comprised 2,997 men and women born between 1931 and 1939 in the UK county of Hertfordshire who had their birth weight recorded by a team of dedicated midwives. The objective of the HCS was to evaluate interactions between the genome, intrauterine and postnatal environment, and adult diet and lifestyle in the etiology of chronic disorders in later life and has been described in detail (32). From the 2,997 participants, 1,086 men who were seen in HCS clinics were identified as potential participants for this current study. Exclusion criteria for the study included diagnoses of ischemic heart disease, type 2 diabetes, neuromuscular comorbidity, or myopathy. Also, any participants on long-term anticoagulants or medication that could compromise wound healing were excluded. After several tiers of exclusion (Figure 1), a total of 375 men were invited. Each participant's General Practitioner was approached to obtain consent to contact their patient. One hundred and twenty participants were visited at home by the study physician where requirements for the study were explained in detail (Figure 1). An appointment was then made to attend the Wellcome Trust Clinical Research Facility in Southampton General Hospital for further investigations that involved an overnight stay. One hundred and five men aged 68–76 years with historical records of birth weight ($\leq$3.18 kg, 7 lb and $\geq$3.63 kg, 8 lb) agreed to take part in this retrospective cohort study.

The 105 men were fasted overnight prior to their arrival to the research facility. Body composition and lean mass

Table 1. Participant Characteristics

	Birth Weight					
	Lower (≤3.18 kg)		Higher (≥3.63 kg)			
	n = 51		*n* = 48			
	Mean	*SD*	Mean	*SD*	*p* Value	*p* Value*
Age (years)	72.4	2.5	72.5	2.4	—	
Height (cm)	173.3	6.2	174.9	6.7	NS	
Weight (kg)	80.9	12.0	84.5	13.0	NS	
Total lean mass (kg) $_{DxA}$	55.1	6.1	57.8	6.7	.04	.06
Body fat (%) $_{DxA}$	27.1	5.1	26.6	4.9	NS	
Birthweight (kg)	2.9	0.3	4.2	0.4	<.001	
Grip strength (kg)	37.8	8.7	39.5	7.4	.30	.47

Notes: DXA = dual-energy x-ray absorptiometry; NS = nonsignificant.
*Adjusted for age, height (cm), and physical activity.

were assessed by dual-energy x-ray absorptiometry scanning (Hologic Discovery, auto whole-body software version 12.5). Isometric grip strength was measured three times in each hand using a Jamar handheld hydraulic dynamometer (Promedics, Blackburn, UK). The maximum of the six measurements was used in subsequent analyses. Isometric grip strength has been shown to correlate with total body strength and has been advocated as a simple, valid, and reliable measurement in epidemiological studies of sarcopenia (1). All participants completed a health and activity questionnaire detailing current diet, smoking and alcohol intake, self-reported physical function, comorbidity, and medication use.

Muscle Biopsy

Muscle morphology was characterized using tissue obtained from a percutaneous muscle biopsy of the vastus lateralis carried out with a Weil–Blakesley conchotome (33) with the participant fasted. Participants were aged 68–76 years at the time of the muscle biopsy. One hundred and two participants were eligible for the procedure; the three participants who did not have the muscle biopsy were on treatment that could have influenced wound healing ($n = 2$) or predispose to hematoma formation ($n = 1$). Samples for immunohistochemical analyses were viewed under a dissecting microscope and orientated longitudinally prior to immersion in a 5 mL solution of cold acetone, phenylmethylsulphonyl fluoride, and iodoacetamide. The samples were allowed to fix overnight at −20°C before being embedded in glycol methacrylate resin. Serial cross-sections at 7 m were cut and stained for type II fast-twitch myofibres using the monoclonal antimyosin fast antibody (clone MY-32; Sigma-Aldrich, Dorset, UK). Thereafter, sections were counterstained with Mayer's hematoxylin to identify type I slow-twitch fibres. Stained sections were examined under a photomicroscope (Zeiss Axioskop II, Carl Ziess Ltd., Welwyn Garden City, UK) coupled to KS 400 image analysis software (Image Associates, Bicester, UK). All sections were viewed at a ×5 magnification and digitized to obtain tissue area, myofibre composition (type I vs type II), and myofibre cross-sectional areas. All samples were analyzed twice by the same blinded observer. Three samples were deemed unsuitable for fibre composition or myofibre area determination; thus, the final analysis sample comprised 99 participants. Myofibre number was normalized to section area to account for the variability in biopsy size and was expressed as myofibre density (fibres per square millimeter). Fibre score (fibres kilograms per square millimeter) as an alternative to total fibre number was derived from the product of myofibre density and leg lean mass.

Statistical Analysis

Statistical analyses were performed using STATA release 10 (StataCorp, College Station, Texas). The data were normally distributed and summarized using means and standard deviations (mean ± *SD*). The relationships between size in early life and myofibre morphology, muscle mass, and strength were examined using a Student's *t* test and linear regression unless stated. Adult height has been shown to be the strongest anthropometric predictor of muscle strength; therefore, multiple linear regression was used to adjust for the potential confounding influences of adult height as well as age and physical activity. A *p* value of .05 or less was considered statistically significant.

Results

Participant Characteristics

Fifty-one participants had birth weight that was less than or equal to 3.18 kg and 48 had birth weight that was equal to or higher than 3.63 kg (Table 1). Participants with lower birth weight were shorter, lighter, weaker, and had a higher body fat percentage. However, none of these differences were statistically significant apart from total lean mass, which was significantly reduced in lower birth weight individuals (55.1 vs 57.8 kg, $p = .04$; Table 1). This difference was slightly attenuated ($p = .06$) after adjustment for age, height, and physical activity.

Table 2. Univariate and Multivariate Analysis Between Birth Weight Groups and Myofibre Morphology

	Birth Weight									
	Lower (≤3.18 kg)			Higher (≥3.63 kg)						
	n	Mean	*SD*	*n*	Mean	*SD*	Regression Coefficient	95% CI	*p* Value*	Regression Coefficient	95% CI	*p* Value†
Myofibre density (fibres/mm^2)												
Total myofibre density	51	176	47.9	48	184	38.9	7.7	–9.7, 25.2	0.38	7.7	–10.3, 25.7	0.40
Type I slow myofibre density	51	77	30.3	48	80	25.5	2.4	–8.8, 13.7	0.67	2.2	–9.4, 13.9	0.71
Type II fast myofibre density	51	99	42.8	48	105	33.1	5.3	–10.0, 20.7	0.49	5.5	–10.4, 21.3	0.50
Myofibre area (m^2)												
Type I slow myofibre area	48‡	4903	1354	47§	4644	1022	–259	–749, 230	0.30	–363	–856, 130	0.15
Type II fast myofibre area	48‡	4046	1166	47§	3859	1127	–188	–655, 279	0.43	–154	–634, 326	0.53
Myofibre score (fibres kg/mm^2)												
Total fibre score	51	1.5×10^3	420	48	1.7×10^3	342	160	6.3, 313	0.04	138	–19.6, 296.2	0.09
Type I slow myofibre score	51	663	268	48	723	226	60	–39, 159	0.23	48	–53.8, 150.0	0.35
Type II fast myofibre score	51	854	354	48	954	302	100	–320, 231	0.14	90	–47.0, 227.3	0.20

Notes: CI = confidence interval.
*p value for unadjusted univariate relationship between myofibre morphology values and higher birth weight compared with the lower birth weight group (baseline).
†p value after adjusting for current age, height (cm), and physical activity.
‡Area measurements not available for three further participants.
§Area measurements not available for one further participant.

Relationships Between Birth Weight and Myofibre Density, Size, and Score

Table 2 shows data on the relationships between birth weight and myofibre density (fibres per square millimeter) as well as myofibre area (square micrometers) and fibre score (fibres kilograms per square millimeter). There was a tendency for reduced total, type I slow-twitch, and type II fast twitch fibre densities in lower birth weight individuals (total: 176 vs 184, type I: 77 vs 80 and type II: 99 vs 105). Both type I and type II fibres were larger in lower birth weight individuals (type I: 4903 vs 4644 m^2 and type II: 4046 vs 3859 m^2). These differences were not statistically significant both in univariate and multivariate analyses (Table 2). The leg fibre score was significantly reduced in lower birth weight individuals (1.5×10^3 vs 1.7×10^3, $p = .04$), but this effect was attenuated after adjustment for current age, height, and physical activity ($p = .09$; Table 2). Both type I and type II fibre scores were reduced in lower birth weight individuals, but these differences were not statistically significant.

Discussion

This is the first study to investigate the relationship between birth weight and muscle morphology, mass, and strength in community-dwelling older men. The birth weight cutpoints used represent the lower and higher ranges of birth weight within the HCS database and were chosen to maximize sample heterogeneity and the potential to detect differences in muscle outcomes between the birth weight groups. We have shown that low birth weight is associated with a significantly lower fibre score and nonsignificant trends for decreased fibre density and increased fibre size. Men in the lower birth weight group had significantly lower lean mass. There were also nonsignificant trends for them to be shorter and lighter and have lower grip strength.

There is strong evidence from animal studies for the effect of an adverse intrauterine environment on the subsequent number of myofibres in the fetus (27,28,34,35). The majority of studies have use models of prenatal nutritional manipulation, the observed effects on myofibres being dependent on the timing, nature, and severity of the nutritional insult. Results from an ovine study showed that periimplantational and late gestational maternal undernutrition differentially affected myofibre density and function in fetal triceps muscle (27). Both nutritional insults resulted in decreased myofibre and capillary density with late gestational undernutrition predominantly causing a reduction in type I slow-twitch myofibre density. The effect of undernutrition on myofibre development and birth weight has been seen in other animal models, and there is evidence that the effect of fewer myofibres has detrimental effects on muscle mass in postnatal life (28,34,35).

The existing literature for developmental influences on human muscle morphology is limited. A study of 27 women

approximately 55 years old showed no association between low birth weight and muscle morphology (myofibre or capillary density), muscle enzyme histochemistry, or blood flow (29). In contrast, a more recent study by Jensen and colleagues (30), involving 20 low birth weight (2702 ± 2.2 g) and 20 normal birth weight (3801 ± 101 g) young men aged 19 years, demonstrated a change in muscle fibre composition and size. The low birth weight young men had fewer type IIa fibres and an increase in type II fibre mean area. No statistically significant differences were seen in type I fibre number, but type I fibres tended to be larger in the lower birth weight group. Similar nonsignificant changes in morphology were seen in our study, although direct comparisons cannot be made between myofibre areas obtained from young and old muscles because of myofibre size differences (36).

Human myogenesis is complete by Week 24 of gestation; thus, hypertrophy and not hyperplasia is responsible for any postnatal gain in muscle size (26). Myofibre development is determined by nutrient availability as well as the action of hormones and growth factors that affect regulatory and structurally important myogenesis-related genes. The number of muscle fibres formed prenatally, in part, determines the rate of postnatal hypertrophy. During postnatal development, individual muscle fibres generally grow more slowly when muscle fibre numbers are high and conversely grow rapidly when the fibre numbers are low (28). This has been seen in experimental animal models (28), and it is possible that this phenomenon could explain the pattern of fibre density and area seen in relation to low birth weight in this study: lower fibre density, as a result of fewer muscle fibres, leads to an increase in fibre area as a result of increased postnatal growth. The increase in fibre area may be myofibre dependent as studies conducted by Lexel and colleagues (11) suggest that muscle containing fewer fibres generally have larger type I fibres .

The differences in anthropometric measurements between birth weight groups observed in this study are consistent with findings from previous epidemiological studies showing smaller adult size in those with lower birth weight (21,23), although the findings in this small study were not statistically significant. Similarly, the significant decrease in total lean mass seen in those with lower birth weight is consistent with results previously obtained in the Hertfordshire Cohort (37) as well as other birth cohorts (19,23). Muscle strength measured by handheld dynamometry was also reduced in those with lower birth weight, but this relationship did not reach significance. The absence of a significant association with birth weight is surprising but may reflect lack of power due to the small study size as there have been consistent reports of significant positive associations between birth weight and muscle strength across the life course and indeed in the HCS from which this study group was drawn (19–21).

Strengths and Limitations

This is a novel study in human participants aged 68–76 years from a well-characterized birth cohort shown to be representative of the UK population (32). As far as we are aware, this is the first study integrating collection of muscle tissue and morphological studies into an established birth cohort study. The advantage is that participants have already been well characterized and there is potential for large study within the context of cellular and molecular work. Conversely, the sample size of 99 is small for epidemiological investigations and could have resulted in insufficient power to detect differences, also limiting generalizability. Residual confounding is also likely to exist. For example, we were unable to measure loss in motor unit function between the two birth weight groups to account for loss of myofibres (38). Lastly, our study did not include older women, and this is another area for future work.

In conclusion, our study is the first to demonstrate that lower birth weight is associated with a significant decrease in muscle fibre score. This suggests that developmental influences on muscle morphology may explain reported associations between lower birth weight and sarcopenia. The importance of this life course approach to sarcopenia is that positive findings widen the potential window for intervention from the current focus on later life, where the aim is to minimize loss, to preventative strategies that could be implemented early in life to maximize peak muscle mass and strength. A demonstrated link between low birth weight and sarcopenia can be exploited to identify high-risk individuals who may benefit from intervention and prevention strategies throughout life. The findings from this study now need replication in a larger cohort of older men and women.

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References

1. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People 692. *Age Ageing*. 2010;39(4):412–423.
2. Rantanen T, Avlund K, Suominen H, Schroll M, Frandin K, Pertti E. Muscle strength as a predictor of onset of ADL dependence in people aged 75 years. *Aging Clin Exp Res*. 2002;14(3 suppl):10–15.
3. Sayer AA, Syddall HE, Dennison EM, et al. Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. *QJM*. 2007;100(11):707–713.
4. Sayer AA, Syddall HE, Martin HJ, Dennison EM, Anderson FH, Cooper C. Falls, sarcopenia, and growth in early life: findings from the Hertfordshire cohort study. *Am J Epidemiol*. 2006;164(7):665–671.
5. Di Monaco M, Vallero F, Di Monaco R, Tappero R. Prevalence of sarcopenia and its association with osteoporosis in 313 older women following a hip fracture. *Arch Gerontol Geriatr*. 2011;52(1):71–74.

6. Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. *Int J Epidemiol*. 2006;36(1):228–235.
7. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc*. 2004;52(1): 80–85.
8. Faulkner JA, Larkin LM, Claflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. *Clin Exp Pharmacol Physiol*. 2007;34(11):1091–1096.
9. Lexell J. Human aging, muscle mass, and fiber type composition. *J Gerontol A Biol Sci Med Sci*. 1995;50 Spec No:11-6.
10. Brunner F, Schmid A, Sheikhzadeh A, Nordin M, Yoon J, Frankel V. Effects of aging on Type II muscle fibers: a systematic review of the literature. *J Aging Phys Act*. 2007;15(3):336–348.
11. Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci*. 1988;84(2–3):275–294.
12. Lynch GS. Update on emerging drugs for sarcopenia—age-related muscle wasting. *Expert Opin Emerg Drugs*. 2008;13(4):655–673.
13. Paddon-Jones D, Short KR, Campbell WW, Volpi E, Wolfe RR. Role of dietary protein in the sarcopenia of aging. *Am J Clin Nutr*. 2008; 87(5):1562S–1566S.
14. Reed T, Fabsitz RR, Selby JV, Carmelli D. Genetic influences and grip strength norms in the NHLBI twin study males aged 59–69. *Ann Hum Biol*. 1991;18(5):425–432.
15. Vincent KR, Braith RW, Feldman RA, et al. Resistance exercise and physical performance in adults aged 60 to 83. *J Am Geriatr Soc*. 2002; 50(6):1100–1107.
16. Reed RL, Pearlmutter L, Yochum K, Meredith KE, Mooradian AD. The relationship between muscle mass and muscle strength in the elderly. *J Am Geriatr Soc*. 1991;39(6):555–561.
17. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci*. 2006;61(10):1059–1064.
18. Aihie Sayer A, Cooper C. Aging, sarcopenia and the life course. *Rev Clin Gerontol*. 2007;16(4):265–274.
19. Gale CR, Martyn CN, Kellingray S, Eastell R, Cooper C. Intrauterine programming of adult body composition. *J Clin Endocrinol Metab*. 2001;86(1):267–272.
20. Kuh D, Hardy R, Butterworth S, et al. Developmental origins of midlife grip strength: findings from a Birth Cohort Study. *J Gerontol A Biol Sci Med Sci*. 2006;61(7):702–706.
21. 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 Med Sci*. 2004;59(9):M930–M934.
22. Sayer AA, Dennison EM, Syddall HE, Jameson K, Martin HJ, Cooper C. The developmental origins of sarcopenia: using peripheral quantitative computed tomography to assess muscle size in older people. *J Gerontol A Biol Sci Med Sci*. 2008;63(8):835–840.
23. 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(9):1392–1399.
24. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61–73.
25. Lucas A. Programming by early nutrition in man. *Ciba Found Symp*. 1991;156:38–50.
26. 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(3):359–574.
27. Costello PM, Rowlerson A, Astaman NA, et al. Peri-implantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. *J Physiol*. 2008;586(9): 2371–2379.
28. Rehfeldt C, Kuhn G. Consequences of birth weight for postnatal growth performance and carcass quality in pigs as related to myogenesis. *J Anim Sci*. 2006;84(suppl):E113–E123.
29. Thompson CH, Sanderson AL, Sandeman D, et al. Fetal growth and insulin resistance in adult life: role of skeletal muscle morphology. *Clin Sci (Lond)*. 1997;92(3):291–296.
30. 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(4):1530–1534.
31. Patel HP, Syddall HE, Martin HJ, Stewart CE, Cooper C, Sayer AA. Hertfordshire Sarcopenia Study: design and methods. *BMC Geriatrics*. 2010;10(1):43.
32. Syddall HE, Aihie SA, Dennison EM, Martin HJ, Barker DJ, Cooper C. Cohort profile: the Hertfordshire cohort study. *Int J Epidemiol*. 2005;34(6):1234–1242.
33. Patel HP, Syddall HE, Martin HJ, Stewart CE, Cooper C, Sayer AA. The feasibility and acceptability of muscle biopsy in epidemiological studies: findings from the Hertfordshire Sarcopenia Study (HSS). *J Nutr Health Aging*. 2011;15(1):10–15.
34. 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(4): 911–917.
35. Dwyer CM, Madgwick AJ, Ward SS, Stickland NC. Effect of maternal undernutrition in early gestation on the development of fetal myofibres in the guinea-pig. *Reprod Fertil Dev*. 1995;7(5): 1285–1292.
36. Kirkeby S, Garbarsch C. Aging affects different human muscles in various ways. An image analysis of the histomorphometric characteristics of fiber types in human masseter and vastus lateralis muscles from young adults and the very old. *Histol Histopathol*. 2000;15(1): 61–71.
37. Kensara OA, Wootton SA, Phillips DI, Patel M, Jackson AA, Elia M. Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. *Am J Clin Nutr*. 2005;82(5):980–987.
38. Campbell MJ, McComas AJ, Petito F. Physiological changes in ageing muscles. *J Neurol Neurosurg Psychiatr*. 1973;36(2):174–182.