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Rapid Communication

Does Sarcopenia Originate in Early Life? Findings From the Hertfordshire Cohort Study

Avan Aihie Sayer,[1,2] Holly E. Syddall,[1] Helen J. Gilbody,[1] Elaine M. Dennison,[1] and Cyrus Cooper[1]

[1]MRC Environmental Epidemiology Unit, and
[2]University Geriatric Medicine, University of Southampton, United Kingdom.

Background. Sarcopenia is defined as the loss of skeletal muscle mass and strength with aging. Recent epidemiological studies have shown that men and women who grew less well in early life have lower muscle strength. Our objective was to investigate the relationship between birth weight, infant growth, and the development of sarcopenia.

Methods. We studied 730 men and 673 women, of known birth weight and weight at 1 year, who were born in Hertfordshire, U.K., between 1931 and 1939. Participants completed a health questionnaire, and we measured their height, weight, and grip strength. Standard deviation scores for birth weight, and for infant growth conditional on birth weight, were analyzed in relation to grip strength before and after adjustment for adult size.

Results. Grip strength was most strongly associated with birth weight in men ($r = 0.19$, $p < .001$) and women ($r = 0.16$, $p < .001$). These relationships remained significant after adjustment for adult height and weight. In contrast, the associations with infant growth were weakened after allowing for adult size. Adjustment for age, current social class, physical activity, smoking, and alcohol did not affect these results.

Conclusions. Birth weight is associated with sarcopenia in men and women, independently of adult height and weight. The influence of infant growth on long-term muscle strength appears to be mediated through adult size. Sarcopenia may have its origins in early life, and identifying influences operating across the whole life course may yield considerable advances in developing effective interventions.

SARCOPENIA is defined as the loss of skeletal muscle mass and strength with aging (1). There is increasing recognition of the serious health consequences of sarcopenia both in terms of disability, morbidity, and mortality (2,3), and in terms of significant healthcare costs (4). Important influences including age, gender, size, and physical activity have been well described, and there have been estimates of moderate heritability (5) with a number of candidate genes proposed (6–8), but there remains considerable unexplained variation in both the muscle mass and strength of men and women in later life. Not surprisingly, sarcopenia was recently cited as one of the top 10 hot topics in aging (9).

Novel research suggests that early environmental influences may be important. A study of 717 men and women aged 64–74 years demonstrated that birth weight and weight at 1 year were significantly positively associated with adult grip strength (10). The findings for birth weight have been replicated in a U.K. national birth cohort of men and women born in 1946, which showed strong relationships between size at birth and grip strength in midlife (11). There is also evidence that muscle mass in older people is positively associated with their birth weight independent of current size (12,13). The findings are consistent with a growing body of work demonstrating that poor early growth has important long-term sequelae for human health including an increased risk of developing coronary heart disease, type 2 diabetes, and osteoporosis (14).

These associations have been explained by the phenomenon of programming, which is the persisting influence of exposures occurring at critical periods of early development on long-term organ structure, function, and regulation (15). Programming of muscle has been documented in animal models, for example, in the field of animal husbandry where prenatal nutritional manipulation of muscle growth and quality is of particular interest to the meat industry. Prenatal undernutrition has been associated with reduced neonatal muscle weight but not fiber number in the sheep (16) and a reduction in postnatal muscle fiber number in the pig (17), guinea pig (18), and rat (19). There is evidence that these effects persist (20,21). A recent review of the impact of manipulation of myogenesis in utero on the performance of adult skeletal muscle in animal models concluded that the effect was predominantly on secondary muscle fibers formed later in embryonic and fetal development (22). There is evidence that the muscle phenotype can also be influenced by postnatal nutrition (23).

The documented associations between size at birth, weight at 1 year, and adult muscle strength suggest that similar mechanisms may be operating in human muscle development but little is known about the relative importance of prenatal and postnatal size and growth. We

Table 1. Subject Characteristics

Mean (*SD*)	Men	Women
Grip strength (kg)	44.2 (7.2)	27.2 (5.6)
Age (y)	64.3 (2.6)	65.7 (2.5)
Height (cm)	174.1 (6.6)	160.8 (5.9)
Weight (kg)	82.0 (12.4)	71.1 (13.6)
Birth weight (lb)	7.8 (1.2)	7.4 (1.1)
Weight at 1 year (lb)	22.6 (2.4)	21.3 (2.3)
Activity score (%)	62.8 (15.4)	59.6 (16.0)
Percentage		
Social class:		
I-IIINM	36.2%	39.2%
IIIM-V	58.1%	60.8%
Unclassified	5.8%	0.0%
Smoker status:		
Never	32.5%	60.3%
Ex	50.6%	29.2%
Current	17.0%	10.6%
Alcohol		
≦21/≦14 units per week men/women	76.2%	96.9%
>21/>14 units per week men/women	23.8%	3.1%

Table 2. Adult Determinants of Grip Strength

Correlation Coefficient, *p* Value*	Men	Women
Age (y)	−0.22	−0.09
	$p < .0001$	$p = .02$
Height (cm)	0.40	0.25
	$p < .0001$	$p < .0001$
Weight (kg)	0.24	0.07
	$p < .0001$	$p < .09$
Activity score (%)	0.05	0.22
	$p = .20$	$p < .0001$
Mean (*SD*), *p* Value**		
Social class:		
I-IIINM	45.2 (6.5)	27.3 (5.4)
IIIM-V	43.4 (7.6)	27.1 (5.7)
Unclassified	45.6 (5.9)	—
	$p = .002$	$p = .74$
Smoker status:		
Never	44.4 (7.1)	27.5 (5.4)
Ex	44.2 (7.4)	26.4 (5.7)
Current	43.9 (6.9)	27.5 (5.6)
	$p = .83$	$p = .05$
Alcohol		
≦21/≦14 units per week men/women	44.0 (7.3)	27.1 (5.6)
>21/>14 units per week men/women	44.8 (7.0)	28.4 (5.1)
	$p = .17$	$p = .32$

Note: *Pearson's correlation coefficient for each adult variable vs grip strength.

***P* value from one way analysis of variance for grip strength vs adult variable.

have used a conditional statistical approach to investigate the relative contribution of birth weight, weight at 1 year, and growth in the first year of life independent of birth weight, to adult grip strength.

Methods

Study Population

From 1911 to 1948, midwives collected detailed records, including information on birth weight and weight at 1 year, on infants born in the county of Hertfordshire, U.K. The records for people born 1911–1930 have been used in a series of studies linking early growth to health in later life. In 1998, a younger cohort was recruited to participate in studies examining the interactions between early life, diet, adult lifestyle, and genetic factors as determinants of adult disease. A total of 1760 men and 1447 women born in Hertfordshire between 1931 and 1939 and still living in East Hertfordshire were traced with the aid of the National Health Service (NHS) central registry in Southport and confirmed as currently registered with a general practitioner in Hertfordshire.

Permission to contact 1397 (79%) men and 1364 (94%) women was obtained from their general practitioners. A total of 768 (55%) men and 714 (52%) women agreed to take part in a home interview where trained nurses collected information on their medical and social histories. A total of 737 (96%) of the men and 675 (95%) of the women interviewed at home subsequently attended a clinic for a number of investigations. Anthropometry included measurement of height and weight. Grip strength was measured three times on each side using a Jamar handgrip dynamometer (Promedics, Blackburn, U.K.) (24). Grip strength and height measurements were obtained for 730 (99%) men and 673 (99%) women. Intraobserver and interobserver studies were carried out at regular intervals during the fieldwork to ensure comparability of measurements within and between observers. The study had ethical approval from the North and East Hertfordshire Local Research Ethics Committee, and all participants gave written informed consent.

Statistical Methods

Early size and growth were characterized by calculating sex-specific standard deviation (*SD*) scores for birth weight, weight at 1 year, and infant growth conditional on birth weight (25). The *SD* score for infant growth conditional on birth weight was free of the artefactual effects of regression to the mean, and could be included in a regression model simultaneously with birth weight without multicolinearity problems.

The best of the six grip measurements was used in analyses. The relationships between grip and adult lifestyle variables were explored using Pearson's correlations and analysis of variance. Adult determinants of grip were included as adjustment variables in subsequent analyses.

For presentational purposes, means and *SD*s of grip strength were derived according to sex-specific quintiles of birth weight, weight at 1 year, and infant growth conditional on birth weight. However, statistical tests of association with grip strength were based on continuously distributed early life variables. Pearson's pair-wise and partial correlation coefficients were used to describe the relationships between grip strength and early size and growth without, and with, adjustment for adult determinants of grip.

The sex-specific regression coefficients for grip on adult height were used to calculate grip strength adjusted to

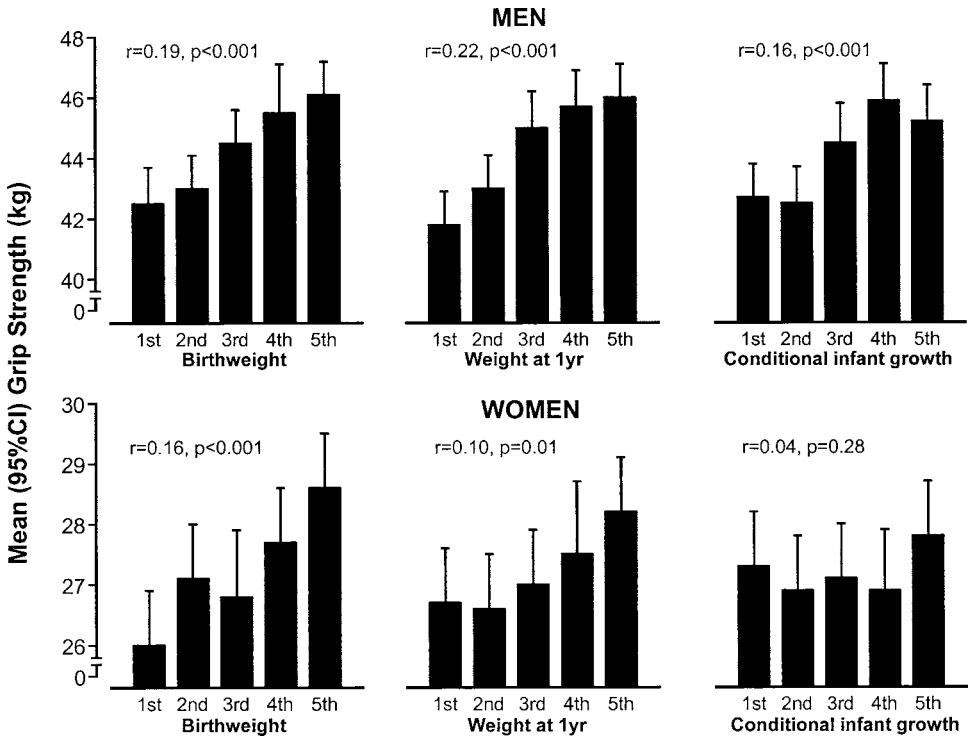

Figure 1. Relationships between early size and growth and adult grip strength. Grip strength is presented according to quintiles of birth weight, weight at 1 year, and conditional infant growth.

average adult height. Analyses were repeated using height-adjusted grip strength in order to assess the impact of adult anthropometry on the relationships between early size and growth and grip strength in later life. All analyses were carried out for men and women separately, using the Stata statistical software package, release 7.0 (Stata Corp, College Station, TX).

Results

Subject Characteristics

The characteristics of the 1403 study subjects are shown in Table 1.

Adult Determinants of Grip Strength

Univariate analyses showed that lower grip strength was associated with older age, shorter height, and lower adult weight in men and women, with lower physical activity score in women, and with manual social class in men (Table 2). There were no strong associations between grip strength and smoking habit or alcohol consumption in men or women. Subsequent analyses focused on height rather than weight, as height was the strongest anthropometric determinant of grip.

Relationship Between Early Size and Growth and Grip Strength

Lower adult grip strength was related to a lower *SD* score for birth weight and weight at 1 year in men and women (Figure 1). Lower grip strength was related to poorer infant growth conditional on birth weight in men only. The relatively weaker relationship between grip and conditional infant growth among men in comparison with that between grip and weight at 1 year, suggested that the extent of the relationship between grip and size reached at 1 year partly reflected the fact that achieved size at 1 year is a combination of size at birth, and infant growth, both of which were related to grip in men. These results were unaltered by adjustment for age, physical activity, social class, smoking, and alcohol (partial correlations of grip with birth weight and with conditional infant growth were 0.19, $p < .001$ and $r = 0.15$, $p < .001$ for men, and 0.16, $p < .001$ and $r = 0.04$, $p = .26$ for women). These results were little altered by adjusting for adult weight.

Relationship Between Early Size and Growth and Height-Adjusted Grip Strength

The relationships between height-adjusted grip strength and early size and growth are shown in Figure 2. Comparison of Figure 2 with Figure 1 reveals that adjustment for height weakened all of the relationships between size and growth in early life and adult grip. However, adjustment for adult size had the least impact on the relationship between birth weight and adult grip, which remained statistically significant ($r = 0.12$, $p = .001$ in men, $r = 0.09$, $p = .03$ in women). Figure 2 also provides some evidence for a residual link between weight at 1 year and adult grip in men after adjustment for height ($r = 0.08$, $p = .02$). However, the absence of a relationship between height-adjusted grip and conditional infant growth in men

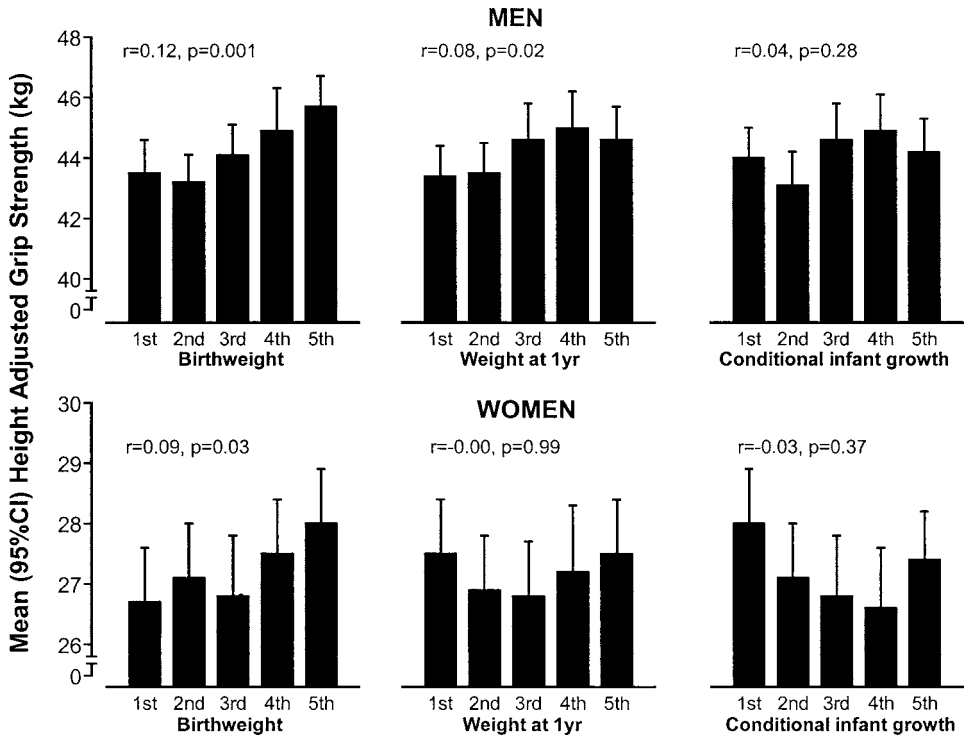

Figure 2. Relationships between early size and growth and adult height-adjusted grip strength. Height-adjusted grip strength is presented according to quintiles of birth weight, weight at 1 year, and conditional infant growth.

suggested that any remaining correlation between weight at 1 year and grip was a reflection of the robust relationship between birth weight and grip after height adjustment. As above, these results were unaltered by adjustment for age, physical activity, social class, smoking, and alcohol (partial correlations of height-adjusted grip with birth weight and with conditional infant growth were $r = 0.12$, $p = .001$ and $r = 0.03$, $p = .51$ in men, and $r = 0.09$, $p = .02$ and $r = -0.03$, $p = .38$ in women).

Discussion

We have demonstrated that a higher birth weight is associated with better grip strength in later life in men and women. Adjustment for adult height weakens, but does not remove, these relationships. Similar associations were seen for weight at 1 year, but this appeared to reflect the fact that size achieved at 1 year is a combination of both size at birth and infant growth. When conditional infant growth was examined, which is growth in the first year of life independent of size at birth, a relationship with muscle strength was only seen in the men, and this became insignificant after adjustment for adult height. This suggests that the effect of infant growth is largely mediated through adult size but that other factors are also operating in the relationship between birth weight and adult muscle strength.

There are a number of potential caveats to the interpretation of our findings. Losses to follow-up occurred during tracing and in gaining consent to participate, and response bias may have been introduced. However, we were able to characterize those who did not take part in the study in a number of ways. There were no substantial differences in birth weight or weight at 1 year between participants who were traced and eligible to participate in the study but did not, and those who had a home interview. Furthermore, there were no major differences in age, social class, alcohol consumption, or activity level between interviewed participants who did or did not attend the clinic. The proportion of current smokers was lower among interview participants who did come to the clinic (16.8% men, 10.5% women) than those who declined (32.3% men, 28.2% women). This suggests that there may have been a ''healthy subject'' effect in this study. However, our comparisons were internal; therefore, unless the relationship between early size and adult grip strength differed between those who did and did not come to the clinic, no bias should have been introduced.

Research into the etiology of sarcopenia has focused on the adult determinants of muscle loss in older people. However, factors operating earlier in life to determine peak muscle mass and strength, and subsequent rate of loss, have been largely overlooked. Our findings suggest that it is important to consider determinants of early muscle growth. Human muscle development begins between 6 and 8 weeks of gestation with the formation of primary fibers followed by the laying down of secondary fibers between weeks 8 and 18 (26). There are genetic influences on fetal growth, but the importance of maternal factors, particularly nutrition, have long been recognized (27). There is evidence that secondary muscle fibers are sensitive to the prenatal environment, including nutritional and hormonal influences.

For example, prenatal undernutrition may be associated with permanent reduction in both fiber size and number (22).

Work on animal models suggests that this sensitivity may extend into the postnatal period (28). It has long been held that the number of muscle fibers is determined by the time of birth, and subsequent growth is achieved by an increase in size rather than in the number of fibers (29). However, there is now emerging evidence that postmitotic myonuclei lying within mature myofibers might be able to reform myoblasts or stem cells, and there is increasing recognition of the role that satellite cells play in postnatal muscle growth and regeneration (30). The relevance of these findings to the growth of human muscle is, as yet, unclear. However, the relationships we have demonstrated between birth weight, infant growth, and adult grip strength suggest that muscle growth in both the prenatal and postnatal periods, whether by an effect on fiber size or number, or an effect on satellite cell activity, may have long-term importance for muscle function.

Furthermore, the finding that the relationship between birth weight and grip strength remains after allowing for adult size provides evidence that early influences may affect more than muscle growth and final size. The mechanism is not known but may reflect altered muscle fiber type, proportion, and quality, and this may have consequences not only for peak strength attained but also for subsequent decline. The underlying mechanisms need to be explored. We would suggest that identifying factors operating across the life course to influence peak muscle mass and strength, as well as loss, may yield considerable advances in developing effective interventions for sarcopenia.

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Address correspondence to Dr. Avan Aihie Sayer, MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO16 6YD, U.K. E-mail: aas@mrc.soton.ac.uk

References

1. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. *J Lab Clin Med*. 2001;137:231–243.
2. Rantanen T, Guralnik JM, Foley D, et al. Midlife hand grip strength as a predictor of old age disability. *JAMA*. 1999;281:558–560.
3. Rantanen T, Harris T, Leveille SG, et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol Med Sci*. 2000;55A:M168–M173.
4. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc*. 2004;52:80–85.
5. Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. *J Bone Miner Res*. 1997;12:2076–2081.
6. Seibert MJ, Xue QL, Fried LP, Walston JD. Polymorphic variation in the human myostatin (GDF-8) gene and association with strength measures in the Women's Health and Aging Study II cohort. *J Am Geriatr Soc*. 2001;49:1093–1096.
7. Geusens P, Vandevyver C, Vanhoof J, Cassiman JJ, Boonen S, Raus J. Quadriceps and grip strength are related to vitamin D receptor genotype in elderly nonobese women. *J Bone Miner Res*. 1997;12:2082–2088.
8. Roth SM, Schrager MA, Ferrell RE, et al. CNTF genotype is associated with muscular strength and quality in humans across the adult age span. *J Appl Physiol*. 2001;90:1205–1210.
9. Morley JE. The top 10 hot topics in aging. *J Gerontol Med Sci*. 2004; 59A:24–33.
10. Sayer AA, Cooper C, Evans JR et al. Are rates of ageing determined in utero? *Age Ageing*. 1998;27:579–583.
11. 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.
12. Gale CR, Martyn CN, Kellingray S, Eastell R, Cooper C. Intrauterine programming of adult body composition. *J Clin Endocrinol Metab*. 2001;86:267–272.
13. Phillips DIW. Relation of fetal growth to adult muscle mass and glucose tolerance. *Diab Med*. 1995;12:686–690.
14. Gluckman P, Bier D, Challis J, et al. Report on the 2nd World Congress on Fetal Origins of Adult Disease, Brighton, U.K. June 7-10, 2003. *Pediatr Res*. 2004;55:1–4.
15. Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J, eds. *The Childhood Environment and Adult Disease*. Ciba Foundation Symposium 156. Chichester: John Wiley; 1991:38–50.
16. 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.
17. 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.
18. 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;7:1285–1292.
19. Wilson SJ, Ross JJ, Harris AJ. A critical period for formation of secondary myotubes defined by prenatal undernourishment in rats. *Development*. 1988;102:815–821.
20. Prakash YS, Fournier M, Sieck GC. Effects of prenatal undernutrition on developing rat diaphragm. *J Appl Physiol*. 1993;75:1044–1052.
21. Pond WG, Yen JT, Mersmann HJ, Maurer RR. Reduced mature size in progeny of swine severely restricted in protein intake during pregnancy. *Growth Dev Aging*. 1990;54:77–84.
22. 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.
23. White P, Cattaneo D, Dauncey MJ. Postnatal regulation of myosin heavy chain isoform expression and metabolic enzyme activity by nutrition. *Br J Nutr*. 2000;84:185–194.
24. Weiner JS, Lourie JA, eds. *International Biology: A Guide to Field Methods*. Oxford: Blackwell Scientific Publications; 1969.
25. Cole TJ. Conditional reference charts to assess weight gain in British infants. *Arch Dis Child*. 1995;73:8–16.
26. Barbet JP, Thornell LE, Butler-Browne GS. Immunocytochemical characterisation of two generations of fibers during the development of the human quadriceps muscle. *Mech Dev*. 1991;35:3–11.
27. Walton A, Hammond J. The maternal effects on growth and conformation in Shire horse-Shetland pony crosses. *Proc Roy Soc Lond B*. 1938;125:311–335.
28. Desai M, Crowther NJ, Lucas A, Hales CN. Organ-selective growth in the offspring of protein-restricted mothers. *Br J Nutr*. 1996;76:591–603.
29. Grounds MD, White JD, Rosenthal N, Bogoyevitch MA. The role of stem cells in skeletal and cardiac muscle repair. *J Histochem Cytochem*. 2002;50:589–610.
30. Bailey P, Holowacz T, Lassar AB. The origin of skeletal muscle stem cells in the embryo and the adult. *Curr Opin Cell Biol*. 2001;13:679–689.

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