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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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Abstract

Background—A number of studies have shown strong graded positive relationships between size at birth and 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 UK 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 ($r = 0.24$ $p < 0.0001$) and women ($r = 0.17$ $p = 0.003$). There were similar but weaker associations between birth weight and calf muscle area in the men ($r=0.13$, $p=0.03$) and in the women ($r=0.17$, $p=0.004$). 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 aetiology of sarcopenia and to developing effective interventions.

Introduction

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 yet 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 life1-4. The underlying mechanisms are unknown but there is some evidence from animal models that prenatal undernutrition is associated with a reduced number of muscle fibres5;6 and 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 mass7-9. However no studies to date have included direct measures of muscle size. Recent technological advances in

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imaging allowed us to utilise peripheral quantitative computed tomography (pQCT) to directly measure muscle cross-sectional area 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, ageing and disease10. 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 which 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 activity11 and social class. Men and women who were willing, subsequently attended a clinic for a number of investigations including measurement of grip strength12. A subgroup of 498 men and 468 women who were resident in East Hertfordshire also underwent dual x-ray absorptiometry (DXA) scans for assessment of bone mineral content and density13 .

Study group

In 2004-5, a follow-up study was performed in East Hertfordshire. The family doctors of participants in the 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 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 0.1cm using a Harpenden pocket stadiometer (Chasmors Ltd, London, UK) and weight to the nearest 0.1kg on a SECA floor scale (Chasmors Ltd, London, UK).

Determination of muscle size

Peripheral quantitative computed tomography (pQCT) was performed to determine the muscle cross-sectional area (CSA) of the non-dominant 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 tibia14 15. Previous studies have shown that this is the region with the largest outer diameter and little variability across individuals16. 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 cross-sectional area17. The muscle area and bone cortical area were separated by a built-in software algorithm18.

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 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 summarised using means and standard deviations (SD's) or frequency and percentage distributions. Geometric means and standard deviations were calculated for weight. Relationships between potential adult determinants of forearm and calf muscle cross-sectional area (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 ($r=0.39$, $p<0.0001$ for men; $r=0.40$, $p<0.0001$ for women); to avoid multi-collinearity 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.

Results

Participant characteristics

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

Adult determinants of muscle cross-sectional area

Univariate analyses showed that older age was associated with lower forearm muscle cross-sectional area (CSA) in men and women; 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 ($4097mm^2$) compared with non-manual social class ($3946mm^2$, $p=0.05$); 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 ($p=0.03$ for men, $p=0.02$ for men). Current smoking was also associated with increased calf muscle area in women ($p=0.05$) but not men ($p=0.73$). These results are summarised 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 cross-sectional area

Lower birth weight was associated with reduced forearm muscle area in the men ($r = 0.24$ $p < 0.0001$, Figure 1) and women ($r = 0.17$ $p = 0.003$, 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 ($r=0.13$, $p=0.03$, Figure 1) and in the women ($r=0.17$, $p=0.004$, 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 attenuated although 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. This is the first study investigating developmental influences on sarcopenia to utilise direct imaging of muscle with pQCT. However the findings are consistent with previous studies showing relationships between poor early growth and lower lean or non-fat mass as estimated by urinary creatinine excretion, anthropometry and dual x-ray absorptiometry7-9. 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 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 could represent a chance finding although the consistency in findings across studies using different methodologies to characterise 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 comes from a number of studies linking early growth to muscle size in children and young people19-23 and recognition that the ageing muscle phenotype reflects not only loss of muscle in later life but also the peak reached in early adulthood24.

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 development5;6;25-32. It appears that muscle fibre number is largely complete by the time of birth suggesting that prenatal influences may be particularly important for long-term muscle quantity and possibly quality33. There has been one human metabolic study linking small size at birth with alteration in adult muscle fibre composition in young adults34 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 those who did not take part in a number of ways10. There were no substantial differences in birth weight or weight at one 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 attend 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 clinic. However there was evidence for a healthy participant bias in those who attended 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 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 aetiology of sarcopenia and to developing effective interventions.

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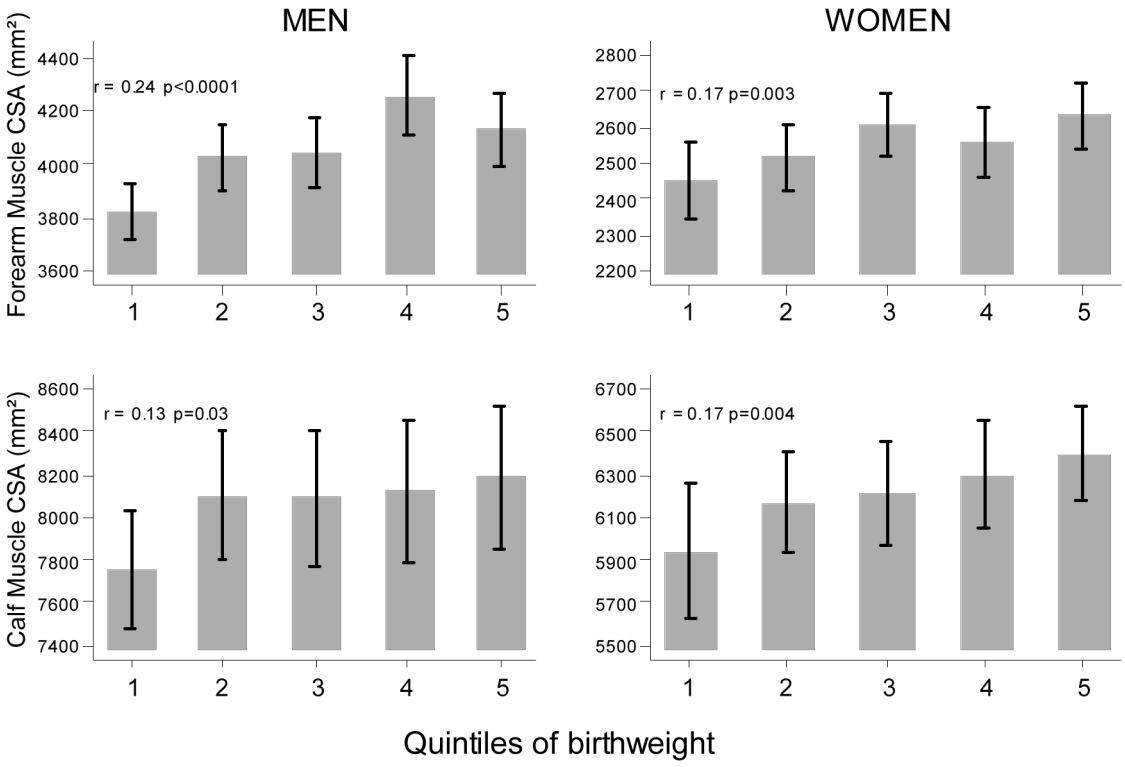

Figure 1. Relationships between birth weight and adult muscle cross-sectional area (CSA)
Foot note: Muscle cross-sectional area presented according to quintiles of birthweight; correlation coefficients (r) and p-values based on continuously distributed variables

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Table 1

Participant characteristics

Mean (SD)	MEN (n=313)	WOMEN (n=318)
pQCT Forearm muscle cross-sectional area (mm^2)	4033 (518)	2555 (370)
pQCT Calf muscle area cross-sectional (mm^2)	8035 (1204)	6212 (981)
Birth weight (kg)	3.5 (0.5)	3.4 (0.5)
Age at pQCT scan (years)	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)
Percentage		
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
IIIM-V	54.0	57.2
Unclassified	5.1	0.0
Alcohol ≤21/≤14 units per week men/women	83.7	96.8
>21/>14 units per week men/women	16.3	3.2
Smoker status Never	38.3	63.2
Ex	53.4	31.4
Current	8.3	5.4

SD: Standard deviation

I-IIINM represents social classes one to three non-manual of the 1990 OPCS standard occupational classification scheme for occupation and social class. IIIM-V represents classes three manual to five.

* Geometric mean and standard deviation

Table 2
Adult determinants of pQCT forearm and calf muscle cross-sectional area (CSA)

	Forearm muscle CSA		Calf muscle CSA	
Correlation coefficient, p-value*	**MEN**	**WOMEN**	**MEN**	**WOMEN**
Age at pQCT scan (years)	-0.17 *p=0.002*	-0.14 *p=0.01*	-0.10 *p=0.09*	-0.09 *p=0.12*
Height (cm)	0.17 *p=0.002*	0.25 *p<0.0001*	0.17 *p=0.004*	0.25 *p<0.0001*
Weight (kg)	0.59 *p<0.0001*	0.52 *p<0.0001*	0.60 *p<0.0001*	0.57 *p<0.0001*
Mean (SD), p-value**				
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) *p=0.64*	2691 (448) *p=0.05*	7992 (850) *p=0.53*	6431 (1385) *p=0.23*
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=0.05*	- *p=0.54*	8196 (1280) *p=0.61*	- *p=0.21*
Alcohol ≤21/≤14 units per week men/women	4033 (535)	2555 (372)	8019 (1217)	6201 (977)
>21/>14 units per week men/women	4033 (421) *p=0.99*	2538 (342) *p=0.89*	8113 (1144) *p=0.62*	6367 (1052) *p=0.60*
Smoker status Never	3936 (507)	2516 (360)	8053 (1225)	6121 (940)
Ex	4082 (514)	2589 (360)	8052 (1179)	6313 (1015)
Current	4160 (539) *p=0.03*	2747 (445) *p=0.02*	7853 (1288) *p=0.73*	6655 (1136) *p=0.05*

I-IIINM represents social classes one to three non-manual of the 1990 OPCS standard occupational classification scheme for occupation and social class. IIIM-V represents classes three manual to five.

* Pearson correlation coefficient for each adult variable vs muscle cross-sectional area.

** P-value from oneway ANOVA for muscle cross-sectional area vs adult variable

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Table 3
Relationships between birth weight and adult muscle cross-sectional area (CSA)

	Forearm muscle CSA		Calf muscle CSA	
Correlation coefficient, *p-value*	**MEN**	**WOMEN**	**MEN**	**WOMEN**
Unadjusted	0.24 *p<0.0001*	0.17 *p=0.003*	0.13 *p=0.03*	0.17 *p=0.004*
Adjusted for adult size:				
Adjusted for height	0.22 *p<0.001*	0.11 *p=0.06*	0.11 *p=0.06*	0.11 *p=0.07*
Adjusted for weight	0.17 *p=0.003*	0.07 *p=0.25*	0.02 *p=0.72*	0.05 *p=0.42*
Adjusted for adult size and other determinants:				
Adjusted for height, age, social class and smoking	0.19 *p=0.001*	0.08 *p=0.14*	0.10 *p=0.09*	0.08 *p=0.16*
Adjusted for weight, age, social class and smoking	0.14 *p=0.01*	0.05 *p=0.40*	0.03 *p=0.67*	0.03 *p=0.63*