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# Slow early growers have more muscle in relation to adult activity: Evidence from Cebu, Philippines

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# Abstract

**Background/objectives**—Adult skeletal muscle mass (SMM) protects against type 2 diabetes but little is known about its developmental antecedents. We examined whether pace of early weight gain predicted adult SMM in a birth cohort from Cebu City, Philippines. Additionally, we examined whether increases in SMM associated with adult muscle-building exercise varied according to early growth.

**Subjects/methods**—Data came from 1472 participants of the Cebu Longitudinal Health and Nutrition Survey. Weight was measured at birth and at 6-month intervals through age 24 months. Adult SMM was estimated from anthropometric measurements when participants were 20-22 years old. Interviews provided information on adult exercise/lifestyle habits.

**Results**—SMM (mean  $\pm$  SD) was 20.8  $\pm$  3.9 kg (men) and 13.6  $\pm$  3.4 kg (women). Faster early weight gain predicted higher adult SMM. After adjustment for height and lifestyle factors, strongest associations with SMM were found for 6-12 months growth in men ( $\beta$ =0.17, p=0.001) and for birth weight in women ( $\beta$ =0.14, p=0.001). Individuals who had grown slowly displayed greater SMM in association with adult weight lifting, basketball playing, and physically demanding forms of employment (men) or household chores (women).

**Conclusions**—These results suggest heightened sensitivity of activity-induced muscle hypertrophy among adults who were born light or who gained weight slowly as infants. Future research should test this finding by comparing responses of muscle mass to an intervention in slow v. fast early growers. Findings suggest that adults who display reduced SMM following

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suboptimal early growth may be good candidates for new anti-diabetes interventions that promote muscle-building activities.

#### Keywords

growth and development; body composition; developmental origins of health and disease

### Introduction

Type 2 diabetes (non-insulin dependent diabetes mellitus) is a global health crisis increasing in prevalence worldwide. Peripheral insulin resistance is a key driver of type 2 diabetes. It is among the earliest detectable indicators of future diabetes risk and has been mechanistically linked to hyperinsulinemia and other metabolic disorders  $[^{1}.^{2}]$ . As the primary site of insulin-mediated glucose disposal in the body, the mass of skeletal muscle may be an important determinant of glucose uptake and insulin sensitivity  $[^{1}]$ , and prior research has identified low muscle mass as a likely contributor to individual diabetes risk  $[^{3}.^{5}]$ . In addition, variation in the contribution of muscle mass to overall body size and composition may underlie population-level disparities in metabolic disease risk. This appears to be particularly relevant among some Asian populations (and populations of Asian descent worldwide), who tend to have less muscle mass and display reduced insulin sensitivity at a given BMI relative to Europeans and populations of European descent [<sup>6</sup>.<sup>8</sup>].

Although previous research suggests that early environment shapes individual and population variation in lifetime skeletal muscle mass (SMM), the specific developmental determinants of this variation remain poorly understood. A consistent finding of past research is a positive correlation between early weight and adult fat-free mass. Small birth size, reflecting growth-limiting conditions in utero, predicts reduced adult fat-free mass  $[9_{-14}]$ , grip strength  $[15_{-16}]$  and muscle area [17]. In studies that simultaneously consider birth size and early postnatal weight gain, postnatal growth typically has been found to predict adult grip strength and/or fat-free mass independent of birth size  $[18_{22}]$ . Among these observations, though, relatively few focused on populations in economic transition experiencing rapid onset of chronic metabolic disease [11, 20\_22]. Moreover, few studies have attempted to separate SMM from total fat-free mass when examining the impact of early growth conditions on adult body composition, and no study to date has investigated the potential impact of early growth conditions on adult responsiveness to muscle-building activities  $[^{23}]$ . These are important limitations because skeletal muscle is unique among the lean tissues in its contribution to insulin mediated glucose disposal  $[^{24}]$  such that variation in muscle gains associated with exercise and other lifestyle factors could mediate metabolic health benefits associated with strength training  $[25_26]$ .

Here we aimed to clarify the developmental determinants of SMM in a population living in the Philippines, where prior research has documented higher levels of adiposity and cardiovascular disease risk at lower levels of BMI [<sup>27</sup>]. Data came from participants in the Cebu Longitudinal Health and Nutrition Survey, a longitudinal population-based study of a birth cohort born during a period of rapid economic transition. We extend previous body composition research in this population [<sup>21</sup>-<sup>22</sup>] by focusing specifically on skeletal muscle,

and also evaluate the possibility that early growth conditions influence responsiveness to exercise- or activity-induced muscle hypertrophy in adulthood.

# **Participants And Methods**

#### **Participants and Data Collection**

Data were collected during the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a population-based study of a birth cohort born in 1983-84 to women residing within the Cebu City metropolitan area, Philippines [<sup>28</sup>]. Metro Cebu (pop. 2.6 million), on the east coast of Cebu Island in the central Philippines, comprises three cities (Cebu City, Mandaue, and Lapu-Lapu) and 7 municipalities in surrounding peri-urban and rural areas. The urban core extends along the seacoast and to the base of nearby mountains. The study area is ecologically diverse with densely populated *barangays* (neighborhoods) in the cities, less dense peri-urban areas, rural towns, and more isolated mountain and island rural areas.

The original cohort included 3080 singletons enrolled at birth. Birth weight was measured by trained homebirth attendants using Salter dial faced hanging scales, or by medical staff at health facilities using the facility's scales. Gestational age was estimated from date of last menstrual cycle reported by the mother. If pregnancy complications occurred, including low birth weight (<2500g), gestational age was estimated by trained nurses using the Ballard method [<sup>29</sup>]. Infant weights were measured by trained interviewers using Salter hanging scales during home visits that occurred every 2 months for the first 24 months of life.

A follow-up study conducted in 2005 recorded information on participants' physical activity. Dichotomous variables were constructed based on survey responses (S-Table 1). Two questions asked participants to rate the level of physical strength demanded by their work and household activities. Participants were also asked whether they regularly perform muscle-building exercises (e.g., lift weights, sit-ups, push-ups), or play basketball at least once a month.

The 2005 study also included body composition assessment. Employing standard anthropometric techniques [ $^{30}$ ], trained technicians measured weight (portable digital scale), height (portable stadiometer), upper-arm circumference (non-stretch tape), and triceps skinfold thickness (Smedley-style calipers). Arm measurements were taken in triplicate and the mean value was used for analysis. As detailed elsewhere [ $^{28}$ ], quality control measures included extensive training and periodic inter-observer reliability assessments. Completed questionnaires were reviewed for consistency, and data entry included range checks. Interviewers returned to the respondent's household if questionable responses were noted.

Adult SMM was estimated from height and upper-arm muscle area using the sex-specific equations developed by Heymsfield *et al.* [<sup>31</sup>]. Because these equations were calibrated to tomography and 24-hr creatinine data (gold standard measures of muscle mass) generated from American men and women, we compared the estimates they produced to published body composition data from other Asian populations (S-Table 2). SMM estimates from Cebu appear consistent with other Asian populations. To control for expected differences in SMM attributable to lifestyle factors, potential confounder variables were coded to reflect

This study was approved by human subjects review boards at the University of North Carolina at Chapel Hill, USA and the University of San Carlos at Cebu City, Philippines. Participants provided written informed consent.

# **Study Participants**

Of the 3080 members of the original birth cohort, 61% participated in the 2005 follow-up study. The leading causes of attrition were migration out of metro Cebu and mortality, accounting for 70% and 20% of those lost to follow-up, respectively [<sup>32</sup>]. The sample (N=1472) included members of the original birth cohort for whom complete data were recorded on gestational age, birth weight, and infant weight at ages 6, 12, 18, and 24 months (S-Table 3). The sample was additionally limited to participants who were interviewed and had anthropometric measures obtained in 2005. Due to body composition changes that accompany pregnancy and lactation, women who were pregnant (assessed by hCG assay) or breastfeeding at the time of adult anthropometric data collection were excluded from analysis.

### Early Growth Measures

Birth weight was adjusted for gestational age prior to analyses. Early postnatal weight gain was used as a proxy for infant growth conditions, and is described in terms of 'conditional weight' at 6, 12, 18, and 24 months. The methods for calculating and interpreting conditional weights have been described previously [<sup>33</sup>-<sup>34</sup>]. Briefly, conditional weight at a given age reflects an individual's deviation from his or her own predicted weight trajectory as informed by subject sex, age (days since birth), age<sup>2</sup> (relevant if growth arced across centiles during the preceding interval), birth weight (corrected for gestational age), and conditional weights at all previous observation points. Conditional weights ensure linear independence between all growth variables so they may be simultaneously included in multiple regression analyses, and may be interpreted roughly akin to growth velocities during that interval.

#### **Statistical Analyses**

Analyses were conducted in STATA 13.0 (College Station, TX). Descriptive statistics were calculated by sex, bivariate plots relating adult SMM to each independent variable were examined for linearity, then multiple regression was employed to characterize relationships between adult SMM, early growth intervals, and potential confounders. Separate models were fit for unadjusted SMM and SMM adjusted for height. All continuous variables were standardized prior to analysis to allow direct unitless comparison of the coefficients. Within each sex, all models were selected from an identical sample. For all models presented, residual plots, formal normality tests (Kolmogorov-Smirnov tests), and robust regression methods were used to evaluate potential breaches of the assumptions of multiple regression. For the models reported, residuals did not statistically deviate from normality and outliers did not influence the significance of coefficients.

# Results

The current sample differs from the remaining members of the birth cohort in several ways. Because the mothers of the current sample are more likely to have remained in the same barangay since enrollment in 1983/84, the children located for follow-up have experienced relative residential stability [<sup>28</sup>]. Individuals in the current sample were more likely to live in rural areas (26% in current sample vs. 21% in remaining cohort, p<0.001), were exclusively breastfed longer (78 vs. 71 days, p<0.001), and tended to be heavier at birth and all postnatal check-ups (S-Table 4). The current sample did not differ from other members of the birth cohort, however, in average household income at baseline or average maternal weight at parturition.

At the time of adult SMM estimation, the average age of participants was  $21.5 (\pm 0.3)$  yr and they tended to be lean (Table 1). Men and women reported different lifestyle and leisure activities. While men and women reported equal rates of employment, men were more likely to participate in physically demanding work (e.g., fishing, mining, welding) while women more frequently reported office, service, and professional work (e.g., bookkeeping, housekeeping, nursing, teaching). On average, women completed more years of school and were more likely to report participating in physically demanding household chores. Few men and women reported intentional weightlifting exercise (e.g., push-ups, weightlifting at a gym). Women infrequently reported participation in physically demanding leisure activities (e.g., dancing, jogging) and the most frequent leisure activity reported by men was playing basketball.

In men, adult SMM was positively and significantly correlated with birth weight (adjusted for gestational age) and conditional weights at all intervals examined (Table 2). The association between early growth and adult SMM was strongest for weight gained during the interval between birth and age 6 months (Figure 1). These positive associations were weakened but most remained statistically significant in a model that adjusted SMM for height (Model 3).

While controlling for all other simultaneous effects in Model 2, greater SMM was observed among men who reported weightlifting, working in physically demanding jobs, and playing basketball. Adjusting SMM for height (Model 4) did not substantially alter the relationships between SMM and participation in these activities. However, each coefficient was adjusted due to differences in height between men who participated in activities versus those who did not. The relationship between demanding work and adult SMM was marginally strengthened, likely because men in demanding jobs tended to be shorter (mean height of men in demanding work=162.5 cm, non-demanding work=163.2 cm,  $\rho$ =0.049). Similarly, adjusting SMM for height marginally weakened the relationships between basketball player or weightlifter status and adult SMM, likely because basketball players and weightlifters tended to be taller (mean height of basketball players=164 cm, non-players=163 cm,  $\rho$ =0.033; mean height of weightlifters=165 cm, non-lifters=163,  $\rho$ =0.014).

As in men, women's SMM was positively correlated with birth weight (adjusted for gestational age) and conditional weight at all intervals examined (Table 3). In women,

however, the association between early growth and adult SMM was strongest for birth weight, followed by weight gained during the interval between birth and age 6 months (Figure 1). The positive correlation between SMM and conditional weight did not achieve statistical significant (at the  $\rho$ <0.05 level) at 18, or 24 months. As in men, the positive associations between early growth and women's adult SMM were weakened in models that adjusted SMM for height (Model 3).

While controlling for all other simultaneous effects in Model 2, greater SMM was observed among women with demanding chores. Adjusting SMM for height (Model 4) did not change the relationship between demanding chores and SMM, likely because there was no difference in height among women who did vs. did not report physically demanding chores (mean height of both groups=151 cm,  $\rho$ =0.448).

We next evaluated whether the relationships between adult lifestyle factors and SMM varied on the basis of early growth history. Examination of interactions between infant conditional weights and adult lifestyle factors revealed that men who gained weight more slowly in infancy tended to have greater SMM in association with weightlifting, basketball playing, and participation in demanding work, while women who gained weight slowly early on tended to have more SMM in association with demanding chores (Table 4). However, despite greater SMM associated with adult muscle-building lifestyle factors, men and women who experienced slower weight gain during infancy still tended to have lower absolute SMM compared to peers who gained weight faster during infancy (Figure 2).

# Discussion

We found that early weight gain was positively associated with adult SMM at every interval from conception to age 24 months, although the association was generally strongest with earlier growth intervals (birth weight and conditional weight at 6 months) relative to later intervals (conditional weights at 18 and 24 months). This is consistent with previously reported associations between early growth history and adult lean or fat-free mass within this and other populations [ $^{21}$ - $^{22}$ ,  $^{35}$ ]. The positive associations between early growth intervals and adult SMM were weakened but some remained statistically significant in models that adjusted SMM for height, suggesting that some—but not all—variation in SMM attributable to early weight gain occurs in association with changes in height and overall body frame. Since those with faster weight gain in infancy had more SMM per unit height, it is expected that they will have relatively more SMM at a given level of BMI, which could contribute to population-level differences in metabolic disease risk associated with BMI and other body composition indices [ $^{7}$ - $^{8}$ ].

Among men, increased SMM was also observed in association with weightlifting, physically demanding forms of employment, and playing basketball (as reported previously for this population [<sup>36</sup>]). Among women, physically demanding household chores predicted greater SMM. After adjusting for height, the associations between lifestyle factors and SMM changed relatively little, suggesting that weightlifting (men) and demanding chores (women) impact SMM largely independent of height. For men, the relationship of SMM to demanding work was likely confounded by the socioeconomic distribution of manual vs.

non-manual employment. At Cebu, physically demanding work is more common among men of lower SES who also tend to be shorter. Thus, the association of demanding work with SMM was strengthened after adjusting for height. In contrast, basketball player status was no longer a statistically significant predictor of SMM in the model adjusting for height, suggesting that the taller mean stature of basketball players explained much of the difference between their higher SMM compared to non-players. In general, the effect of early-life weight gain on adult SMM was larger in men than in women (S-Figure 1).

Our findings suggest that young adults who were born small or who experienced slower weight gain in infancy tended to gain more SMM in relation to physically demanding activities, although not all interaction terms evaluating these relationships achieved statistical significance. Among young adults, variation in the increase of muscle mass in response to activities like resistance training is known to depend on genetic [<sup>37\_39</sup>] and hormonal factors [40], as well as the intensity of training regimens performed [41]. Although the current study does not control for frequency, duration, or intensity of muscle-building tasks (for example if individuals who grew slowly early on, who tend to be of lower SES, perform higher intensity or more frequent physical tasks in association with physically demanding work), it is unlikely that this explains the consistent trend across all activities surveyed in both sexes (work, basketball, and weightlifting in men; household chores in women). Alternatively, greater sensitivity of muscle hypertrophy could mirror greater sensitivity of anabolic hormone responses to physical tasks. For example, in young men and women, strength training is known to induce increases in unbound testosterone  $[^{42}_{-44}]$  and growth hormone  $[^{45}]$ , concentrations of which predict degree of exercise-induced gain in muscle mass [<sup>46</sup>]. In this cohort, we recently showed that weight gain specific to the first 6 months of life was a significant predictor of adult testosterone production, muscle size, and strength, with effects primarily limited to men [47]. While this study points to possible "programming" effects of early postnatal nutrition or growth on adult biology and body composition, it is currently unknown whether the hypertrophic response of muscle to anabolic hormones, or to exercise, might also vary according to early-life weight gain. Future research is needed to evaluate the mechanistic bases of the findings reported here, which will clarify their potential importance as a pathway linking early growth conditions to adult variation in SMM and metabolic disease risk.

If confirmed in other populations, the heightened sensitivity of SMM to adult lifestyle habits among slow early-growers at Cebu could indicate that their health would benefit more from physical activities aimed at increasing SMM. This could operate, for instance, through the role of muscle mass in total-body insulin sensitivity and glucose homeostasis. Musclebuilding exercise is known to protect against type 2 diabetes independent of other forms of activity [ $^{25}$ ] and, consistent with our result, at least one prior study reports that the positive impact of exercise on glucose tolerance was greatest among those who grew slowest *in utero* [ $^{48}$ ]. If future research confirms that slow early growth predicts greater muscle gains in association with adult muscle-building activities, one public health strategy to combat the rising worldwide incidence of type 2 diabetes would be targeting of muscle-building interventions to adults who gained weight relatively slowly early in life. It is important to note, however, that despite the possible enhanced muscle hypertrophy response to the observed lifestyle factors, individuals who had gained weight slowly early in life tended to

remain at an absolute SMM deficit compared to their faster early-growing peers (S-Figure 1) —reaffirming the importance of policies aimed at ensuring favorable early development in order to preserve health across the life course [<sup>49</sup>].

Several limitations of this study warrant discussion. First, although valuable for its separation of skeletal muscle from other components of the fat-free tissues, our method of SMM estimation was based on arm muscle measurements and therefore may not reflect muscle gains in other regions. This may be especially important among women, who display narrower inter-individual variation in arm muscle area than men [<sup>50</sup>]. Second, because SMM was observed at only one timepoint, it was not possible to directly assess the impact of lifestyle factors on changing SMM. Controlled intervention studies comparing SMM before and after hypertrophy-inducing regimens are needed to confirm whether early growth histories predict variation in responsiveness of muscle mass to strength training. An alternative possibility is that among individuals who experienced slow early weight gain, those with the most SMM in adulthood self-selected into physically demanding forms of labor and leisure activities (with weaker self-selection bias among individuals who experienced faster early weight gain). This might occur if a minimum strength is required to initiate participation in such activities and this threshold excludes more slow than fast early growers. In this instance, the slow early growers who happened to be more muscular at the outset might end up over-represented among participants of more intensive activities.

This study is the first to demonstrate that adults who were born small or gained weight slowly during infancy had more SMM in association with adult muscle-building activities. Although those who grew slowly early on had more to gain from muscle-building activities in adulthood, they generally remained at a SMM deficit compared to their peers who experienced faster early weight gain. These findings help clarify the developmental determinants of body composition and suggest a new approach for targeting adult interventions that are aimed at curbing elevated metabolic disease risks associated with early-life undernutrition or growth faltering.

# Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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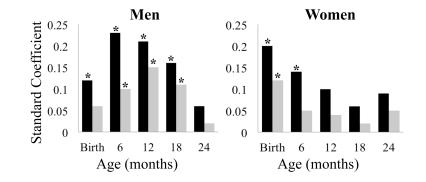
# **Literature Cited**

1. DeFronzo RA, Tripathy D. Skeletal Muscle Insulin Resistance Is the Primary Defect in Type 2 Diabetes. Diabetes Care. 2009; 32:S157–S163. [PubMed: 19875544]

- Petersen KF, Dufour S, Savage DB, Bilz S, Solomon G, Yonemitsu S, et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. PNAS. 2007; 104:12587– 12594. [PubMed: 17640906]
- Srikanthan P, Karlamangla AS. Relative Muscle Mass Is Inversely Associated with Insulin Resistance and Prediabetes. Findings from The Third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab. 2011; 96:2898–2903. [PubMed: 21778224]
- Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia Exacerbates Obesity-Associated Insulin Resistance and Dysglycemia: Findings from the National Health and Nutrition Examination Survey III. PLoS ONE. 2010; 5:e10805. [PubMed: 22421977]
- Atlantis E, Martin SA, Haren MT, Taylor AW, Wittert GA. Inverse associations between muscle mass, strength, and the metabolic syndrome. Metabolism. 2009; 58:1013–1022. [PubMed: 19394973]
- Bakker LEH, Sleddering MA, Schoones JW, Meinders AE, Jazet IM. Mechanisms in endocrinology: Pathogenesis of type 2 diabetes in South Asians. Eur J Endocrinol. 2013; 169:R99–R114. [PubMed: 23939919]
- 7. Chan JC, Malik V, Jia W, Kadowaki R, Yajnik CS, Yoon KH, et al. Diabetes in Asia: Epidemiology, Risk Factors, and Pathophysiology. JAMA. 2009; 301:2129–2140. [PubMed: 19470990]
- Yajnik CS. Early Life Origins of Insulin Resistance and Type 2 Diabetes in India and Other Asian Countries. J Nutr. 2004; 134:205–210. 2004. [PubMed: 14704320]
- 9. Yliharsila H, Kajantie E, Osmond C, Forsen T, Barker DJP, Eriksson JG. Birth size, adult body composition and muscle strength later in life. Int J Obes. 2007; 31:1392–1399.
- Kensara OA, Wooton SA, Phillips DI, Patel M, Jackson AA, Elia M. Fetal programming of body composition: relation between birth weight and body composition measure with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. Am J Clin Nutr. 2005; 82:980– 987. [PubMed: 16280428]
- Li H, Stein AD, Barnhart HX, Ramakrishnan U, Martorell R. Associations between prenatal and postnatal growth and adult body size and composition. Am J Clin Nutr. 2003; 77:1498–1505. [PubMed: 12791630]
- 12. Loos RJF, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young adult men—a prospective twin study. Int J Obes. 2001; 25:1537–1545.
- 13. Loos RJF, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young women: a prospective twin study. Am J Clin Nutr. 2002; 75:676–682. [PubMed: 11916753]
- Weyer C, Pratley RE, Lindsay RS, Tataranni PA. Relationship Between Birth Weight and Body Composition, Energy Metabolism, and Sympathetic Nervous System Activity Later in Life. Obes Res. 2000; 8:559–565. [PubMed: 11156431]
- 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. [PubMed: 17697158]
- Kuh D, Bassey J, Hardy R, Sayer AA, 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. [PubMed: 12244031]
- 17. Kahn HS, Narayan KM, Williamson DF, Valez R. Relation of birth weight to lean and fat thigh tissue in young men. Int J Obes. 2000; 24:667–672.
- Euser AM, Finken MJ, Keijzer-Veen MF, Hille ET, Wit JM, Dekker FW. Associations between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm. Am J Clin Nutr. 2005; 81:480– 487. [PubMed: 15699238]
- Sayer AA, Syddall HE, Dennison EM, Gilbody HJ, Duggleby SL, Cooper C, et al. Birth weight, weight at 1 y of age, and body composition in older men: findings form the Hertfordshire Cohort Study. Am J Clin Nutr. 2004; 80:199–203. [PubMed: 15213049]
- 20. Sachdev HS, Fall CH, Osmond C, Lakshmy R, Biswas SKD, Leary SD, 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. [PubMed: 16087993]

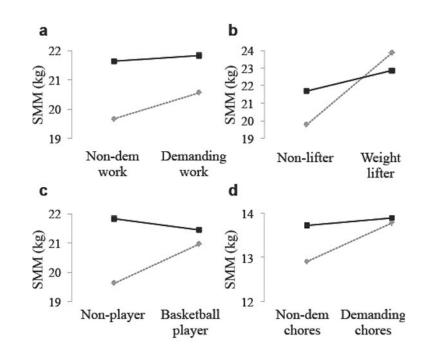
- 21. Kuzawa CW, McDade TW, Adair LS, Lee N. Rapid weight gain after birth predicts life history and reproductive strategy in Filipino males. PNAS. 2010; 107:16800–16805. [PubMed: 20837542]
- 22. Kuzawa CW, Hallal PC, Adair LS, Bhargava SK, Fall CH, Lee CH, et al. Birth weight, postnatal weight gain and adult body composition in five low and middle income countries. Am J Hum Biol. 2012; 24:5–13. [PubMed: 22121058]
- 23. Siebel AL, Carey AL, Kingwell BA. Can exercise training rescue the adverse cardiometabolic effects of low birth weight and prematurity? Proc Aust Physiol Soc. 2012; 43:101–116.
- DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose, results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes. 1981; 30:1000–1007. [PubMed: 7030826]
- Grontved A, Rimm EB, Willett CW, Andersen LB, Hu FB. A Prospective Study of Weight Training and Risk of Type 2 Diabetes Mellitus in Men. Arch Intern Med. 2012; 172:1306–1312. [PubMed: 22868691]
- 26. Croymans DM, Paparisto E, Lee MM, Brandt N, Le BK, Lohan D, et al. Resistance training improves indices of muscle insulin sensitivity and β-cell function in overweight/obese, sedentary young men. J Appl Physiol. 2013; 115:1245–1253. [PubMed: 23970530]
- Colin, Bell A.; Adair, LS.; Popkin, BM. Ethnic Differences in the Association between Body Mass Index and Hypertension. Am J Epidemiol. 2002; 155:346–53. [PubMed: 11836199]
- Adair LS, Popkin BM, Akin JS, Guilkey DK, Gultiano S, Borja J, et al. Cohort profile: the Cebu longitudinal health and nutrition survey. Int J Epidemiol. 2011; 40:619–625. [PubMed: 20507864]
- 29. Ballard J, Novak H, Driver M. A simplified score for assessment of fetal maturation in newly born infants. J Pediatr. 1979; 95:769–74. [PubMed: 490248]
- Lohman, TG.; Roche, AF.; Martorell, R. Anthropometric Standardization Reference Manual. Human Kinetics Books; Champaign, IL, USA: 1988.
- Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measures of muscle mass: revised equations for calculating bone-free arm muscle area. Am J Clin Nutr. 1982; 36:680– 690. [PubMed: 7124671]
- 32. Perez, TLL.; Borja, JB.; Bas, IN. Attrition in the Cebu Longitudinal Health and Nutrition Survey. Cebu City, Philippines: USC-Office of Population Studies Foundation, Inc., University of San Carlos; 2014. OPS Report Series No. 1
- 33. Adair LS, Martorell R, Stein AD, Hallal PD, Sachdev HS, Prabhakaran D, et al. Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low- and middle-income-country cohorts: when does weight gain matter? Am J Clin Nutr. 2009; 89:1983–1392.
- 34. Norris SA, Osmond C, Gigante D, Kuzawa CW, Ramakrishnan L, Lee NR, et al. Size at Birth, Weight Gain in Infancy and Childhood, and Adult Diabetes Risk in Five Low- or Middle-Income Country Birth Cohorts. Diabetes Care. 2012; 35:72–79. [PubMed: 22100968]
- Wells JCK, Hallal PC, Wright A, Singhal A, Victora CG. Fetal, infant and childhood growth: relationships with body composition in Brazilian boys aged 9 years. Int J Obes. 2005; 29:1192– 1198.
- Gettler LT, Agustin SS, Kuzawa CW. Testosterone, Physical Activity, and Somatic Outcomes Among Filipino Males. Am J Phys Anth. 2010; 142:590–599.
- Ivey FM, Roth SM, Ferrel RE, Tracy BL, Lemmer JT, Hurlbut DE, et al. Effects of Age, Gender, and Myostatin Genotype on the Hypertrophic Response to Heavy Resistance Strength Training. J Gerontol. 2000; 55:M641–M648.
- Clarkson PM, Devaney JM, Gordish-Dressman H, Thompson PD, Hubal MJ, Urso M, et al. ACTN3 genotype is associated with increases in muscle strength and response to resistance training in women. J Appl Physiol. 2005; 99:564–569. [PubMed: 15817725]
- Pescatello LS, Kostek MA, Gordish-Dressman H, Thompson PD, Seip RL, Price TB, et al. ACE ID genotype and the muscle strength and size response to unilateral resistance training. Med Sci Sports Exerc. 2005; 38:1074–1081. [PubMed: 16775548]
- Deschenes MR, Kraemer WJ. Performance and Physiologic Adaptations to Resistance Training. Am J Phys Med Rehabil. 2002; 81:S3–S16. [PubMed: 12409807]

- Wernbom M, Augustsson J, Thomee R. The Influence of Frequency Intensity Volume and Mode of Strength Training on Whole Muscle Cross-Sectional Area in Humans. Sports Med. 2007; 37:225– 264. [PubMed: 17326698]
- 42. Tremblay MS, Copeland JL, Van Helder W. Effect of training status and exercise mode on endogenous steroid hormones in men. J Appl Physiol. 2003; 96:531–539. [PubMed: 14514704]
- Kraemer WJ, Hakkinen K, Newton RU, Nindl BC, Vlok JS, McCormick M, et al. Effects of heavyresistance training on hormonal response patterns in younger vs older men. J Appl Physiol. 1999; 87:982–92. [PubMed: 10484567]
- Nindl BC, Kraemer WJ, Gotshalk LA, Marx JO, Volek JS, Bush FM, et al. Testosterone responses after resistance exercise in women: influence of regional fat distribution. Int J Sport Nutr Exerc Metab. 2001; 11:451–65. [PubMed: 11915780]
- Nindl BC, Kraemer WJ, Hymer WC. Immunofunctional vs immunoreactive growth hormone responses after resistance exercise in men and women. Growth Horm IGF Res. 2000; 10:99–103. [PubMed: 10931748]
- 46. McCall GE, Byrnes WC, Fleck SJ, Dickenson A, Kraemer WJ. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. Can J Appl Physiol. 1999; 24:96–107. [PubMed: 9916184]
- 47. Kuzawa CW, McDade TW, Adair LS, Lee N. Rapid weight gain after birth predicts life history and reproductive strategy in Filipino males. PNAS. 107:16800–16805. [PubMed: 20837542]
- Eriksson JG, Yliharsila H, Forsen T, Osmond C, Barker DJP. Exercise protects against glucose intolerance in individuals with a small body size at birth. Prev Med. 2004; 39:164–167. [PubMed: 15207998]
- Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter, et al. Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 2008; 371:340–357. [PubMed: 18206223]
- Gallagher D, Visser M, De Meersman RE, Sepulveda D, Baumgartner RN, Pierson RN, et al. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. J Appl Physiol. 1997; 83:229–239. [PubMed: 9216968]



### Figure 1.

Standard coefficients relating early conditional weights (at birth, 6, 12, 18, or 24 months) to adult skeletal muscle mass. Bars reveal the relative magnitudes of influence of early growth intervals on adult absolute skeletal muscle mass (black bars) or skeletal muscle mass adjusted for height (gray bars). Weight at birth was adjusted for gestational age prior to analysis. Relationships significant at p<0.05 indicated by asterisk (\*).



#### Figure 2.

Comparisons of mean skeletal muscle mass (kg) among adults in the lightest (dashed line) vs. heaviest (solid line) tertile of conditional weight. Steeper slopes indicate greater sensitivity of skeletal muscle mass to the lifestyle factor. Notice that despite greater gains associated with some activities, adults in the lowest tertile of conditional weight tended to remain at a skeletal muscle mass deficit relative to peers who had grown faster. Panel **a**, comparison among men by conditional weight at 6 mo. and physical demands of employed work; panel **b**, comparison among men by conditional weight at 12 mo. and weightlifting; panel **c**, comparison among men by conditional weight at 6 mo. and basketball playing; panel **d**, comparison among women by conditional weight at 6 mo. and physical demands of household chores.

#### Table 1

Descriptive statistics by sex, mean (SD).

	Men (n=864)	Women (n=608)
SMM (kg)	20.8 (3.9)	13.6 (3.4)
Height (cm)	163.0 (5.9)	151.2 (5.5)
Weight (kg)	56.0 (9.4)	46.3 (8.2)
BMI (kg/m <sup>2</sup> )	21.0 (3.1)	20.2 (3.2)
Age (yr)	21.5 (0.3)	21.5 (0.3)
BW (g)	3032 (324)	2994 (311)
CW 6 mo (g)	7139 (644)	6628 (560)
CW 12 mo (g)	8263 (504)	7687 (479)
CW 18 mo (g)	9128 (452)	8503 (431)
CW 24 mo (g)	10105 (468)	9483 (454)
School completed (yr)	9.5 (0.1)	11.2 (0.1)
Laborer (%)	40.9	21.7
Office worker (%)	49.1	68.1
Currently employed (%)	68.6	69.2
Weightlifter (%)	4.7	5.9
Demanding work (%)	34.4	27.1
Basketball Player (%)	30.8	2.1
Demanding chores (%)	19.4	51.5

Women were not pregnant or breastfeeding at the time of the study. SMM, skeletal muscle mass; BW, birth weight corrected for gestational age; BMI, body mass index; CW, conditional weight at the given age in months. Lifestyle factors are dichotomously coded with percent of sample participating in each activity reported. Laborer refers to current or past primary employment as a farmer, logger, fisher, miner, woodworker or other skilled trade; Office worker refers to current or past primary employment in sales, a service industry, office administration, degreed profession, or civil service. Author Manuscript

# Table 2

Multiple regression models relating men's skeletal muscle mass to early growth and lifestyle factors (n=864 in all models).

	2	Model 1	4	Model 2	4	Model 3	2	Model 4
	β	95% CI	β	95% CI	β	β 95% CI	β	95% CI
Birth weight	0.12	0.06, 0.19 0.13	0.13	0.06, 0.19	0.08	0.02, 0.14	0.08	0.02, 0.14
CW 6 mo	0.23	0.17, 0.29	0.23	0.17, 0.29	0.14	0.07, 0.21	0.14	0.08, 0.21
CW 12 mo	0.21	0.15, 0.27	0.21	0.15, 0.27	0.16	0.10, 0.23	0.17	0.10, 0.23
CW 18 mo	0.16	0.10, 0.22	0.16	0.09, 0.22	0.12	0.06, 0.18	0.12	0.06, 0.18
CW 24 mo	0.06	0.00, 0.12	0.05	-0.01, 0.11	0.03	-0.03, 0.09	0.02	-0.04, 0.08
Weightlifter			0.48	0.18, 0.77			0.43	0.15, 0.72
Demanding work			0.17	0.04, 0.30			0.18	0.05, 0.31
Basketball player			0.12	-0.01, 0.25			0.10	-0.03, 0.23
Height					0.25	0.18, 0.32	0.25	0.18, 0.32
Model R <sup>2</sup>		14.3%		16.3%		19.2%		20.9%

Birth weight was adjusted for gestational age. CW, conditional weights at age in months. All continuous variables were standardized prior to analysis. Weightlifter, Basketball, and Demanding work are dichotomously coded. Demanding work refers to employment requiring average-to-above average physical strength.

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# Table 3

Multiple regression models relating women's skeletal muscle mass to early growth and lifestyle factors (n=608 in all models).

	2	Model 1	2	Model 2	4	Model 3	2	Model 4
	β	95% CI	β	β 95% CI	ß	β 95% CI	β	β 95% CI
Birth weight	0.20		0.20	0.12, 0.27	0.14	0.12, 0.27 0.20 0.12, 0.27 0.14 0.06, 0.22 0.14	0.14	0.06, 0.22
CW 6 mo	0.14	0.06, 0.21	0.13	0.06, 0.21	0.08	0.00, 0.16 0.08	0.08	0.00, 0.16
CW 12 mo	0.10	0.02, 0.17	0.11	0.02, 0.18	0.06	-0.02, 0.14	0.07	-0.01, 0.14
CW 18 mo	0.06	-0.02, 0.17	0.05	-0.02, 0.13	0.03	-0.05, 0.12	0.03	-0.05, 0.11
CW 24 mo	0.09	0.01, 0.16	0.09	0.01, 0.16	0.06	-0.01, 0.14	0.06	-0.01, 0.14
Demanding chores			0.15	0.00, 0.31			0.15	0.00, 0.30
Height					0.17	0.17 0.08, 0.26 0.17 0.08, 0.26	0.17	0.08, 0.26
Model R <sup>2</sup>		7.7%		8.3%		9.9%		10.5%

Birth weight was adjusted for gestational age. CW, conditional weights at age in months. All continuous variables were standardized prior to analysis. Demanding chores dichotomously coded, referring to participation in household chores requiring average-to-above average physical strength

# Table 4

4. Negative interaction terms suggest that more muscle is gained in association with the lifestyle factor among those who had lesser conditional weight in Interactions observed between early growth and adult muscle-building lifestyle factors in the prediction of SMM, when added individually to Model 2 or infancy.

	Interactions	Model 2 β	Model 4 β	
	Weightlifter X Birth weight	-0.17	-0.14	
	Weightlifter X CW6mo	0.09	0.13	
	Weightlifter X CW12mo	-0.29	-0.29*	
	Weightlifter X CW18mo	0.16	0.17	
	Weightlifter X CW24mo	0.04	0.09	
	Demanding work X Birth weight	0.01	0.03	
	Demanding work X CW6mo	$-0.12^{*}$	-0.16**	
Men	Demanding work X CW12mo	0.02	0.04	
	Demanding work X CW18mo	-0.13 **	-0.11	
	Demanding work X CW24mo	0.06	0.05	
	Basketball X Birth weight	-0.13 *	-0.1	
	Basketball X CW6mo	-0.19	-0.19 ***	
	Basketball X CW12mo	0.08	0.1	
	Basketball X CW18mo	0.04	0.02	
	Basketball X CW24mo	-0.09	-0.09	
	Demanding chores X Birth weight	-0.04	-0.05	
	Demanding chores X CW6 mo	-0.04	-0.03	
Women	Demanding chores X CW12 mo	-0.04	-0.02	
	Demanding chores X CW18 mo	0.14	0.14	
	Demanding chores X CW24 mo	-0.09	-0.07	
* p<0.1,				
** p<0.05,				
*** <0.01,				

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Model 2 estimates unadjusted SMM, Model 4 estimates height-adjusted SMM.

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