An obesogenic postnatal environment is more important than the fetal environment for the development of adult adiposity: a study of female twins[1–3]

Paula ML Skidmore, Aedin Cassidy, Ramasamyiyer Swaminathan, J Brent Richards, Massimo Mangino, Tim D Spector, and Alex J MacGregor

ABSTRACT

Background: A relation between birth weight and adult body composition has been reported in singleton populations, especially when more accurate measures of body composition, such as dual-energy X-ray absorptiometry (DXA) were used. It remains uncertain whether this is mediated by a direct effect of fetal nutrition, through factors in the shared environment, or through genetic factors.

Objective: The objective was to investigate the relation between birth weight and body composition with the use of a co-twin design.

Design: DXA measurements and birth weights were available for 2228 dizygotic and 842 monozygotic female twins aged between 18 and 80 y. Multivariate regression models were used to identify both individual specific relations and those mediated through the shared environment.

Results: Significant relations were found between birth weight and DXA measures for individuals. A 1-kg increase in birth weight was associated with a 1.72-kg increase in lean mass, a 0.25-kg increase in fat mass, and a 0.05-unit increase in the lean:fat mass ratio. Within twin pairs, the analysis showed that associations between birth weight and absolute levels of lean and fat mass were mediated through individual-specific effects, whereas the relation between birth weight and the proportion of lean to fat mass was mediated purely through factors common to twin pairs.

Conclusions: A higher birth weight is associated with a higher proportion of lean to fat mass as adults. However, these analyses suggest that this association is not determined by individual specific factors in utero (eg, fetal nutrition) but through factors in the shared common environment of the twins. *Am J Clin Nutr* 2009;90:401–6.

INTRODUCTION

Levels of overweight and obesity have risen sharply in Europe, the United States, and other developed and developing countries in the past 20 y (1–3). This in turn has contributed to increased levels of chronic disease, including type 2 diabetes, cardiovascular disease, and hypertension (3). The fetal and early postnatal environment are recognized to be critical periods for the development of overweight and obesity in adult life (4, 5), and it has been suggested that the reported association between low birth weight and diseases related to obesity might be the result of a deficit of lean mass at birth due to fetal programming (6). If this impaired fetal growth is then followed by accelerated childhood weight gain, the risk of disease in adulthood might increase further (7).

However, evidence to support a relation between size at birth and subsequent body mass remains inconsistent in epidemiologic studies, particularly for measures of body fat. This may be because most previous studies have relied on anthropometric measures, which depend on both lean tissue and fat mass, which in turn may obscure any true birth weight relation with either fat deposition or lean mass (5, 8, 9). The use of more accurate measures of body composition, including dual-energy X-ray absorptiometry (DXA) (10), have provided more consistent evidence of an association. In particular, fat-free mass in adulthood has been shown to be positively associated with birth weight (11, 12). Studying the relation between birth weight and variables in adult life is also particularly difficult because of the scope for confounding from numerous factors, such as genetic background and a range of shared environmental variables, including maternal smoking, maternal dietary intake during pregnancy, and childhood socioeconomic status.

In this study we examined the association between birth weight and fat and lean mass as measured by DXA in a large group of monozygotic (MZ) and dizygotic (DZ) twins from the St Thomas' Twins UK Registry. The aim was to investigate whether those who are born small have a more detrimental body composition as adults as a result of fetal programming effects. The natural matching of twin pairs for age, genetic factors, and a range of shared environmental covariates, allows an analysis of the extent to which any association can be attributed to differ-

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[1] From the Department of Human Nutrition, University of Otago, Dunedin, New Zealand (PMLS); the School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, United Kingdom (PMLS, AC, and AJM); and the Department of Twin Research and Genetic Epidemiology, Kings College London, London, United Kingdom (RS, JBR, MM, TDS, and AJM).

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[3] Address correspondence to PML Skidmore, Department of Human Nutrition, University of Otago, Union Place, PO Box 56, Dunedin, New Zealand. E-mail: paula.skidmore@otago.ac.nz.

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ences in birth weight within pairs (that might, for instance, arise from differences in fetal nutrition) independently of influences that are common to both members of the pair (eg, through external confounding factors in the shared twin environment). Comparison of the degree of association in MZ and DZ twins additionally gives an indication of the extent to which any observed association might be mediated genetically.

SUBJECTS AND METHODS

Subjects and study design

The study subjects comprised a sample of female twins enrolled in the Twins UK Registry, a national sample of adult twin volunteers recruited through successive media campaigns. The twins were not selected for disease-specific studies and are representative of the UK population with respect to their frequency of common traits (13) and dietary habits (14). Zygosity was derived by questionnaire and confirmed by multiplex DNA fingerprinting (PE Applied Biosystems, Foster City, CA). Ethical approval for this study was obtained from St Thomas' Hospital Research Ethics Committee, and informed consent was obtained from all subjects.

Twins included in this sample were female and between the ages of 18 and 80 y. All subjects were clinically assessed at St Thomas' Hospital between 1996 and 2000. At assessment, twins completed a questionnaire detailing their medical history and lifestyle factors. Birth weight was recalled by participants. Total fat and central body fat were obtained by DXA body composition scans (Hologic QDR-2000; Vertec, Waltham, MA) (15). Central abdominal fat was determined by scan reanalysis by a single-blinded investigator. The region was defined by cursor manipulation as that extending from the upper border of the second lumbar vertebra to the lower border of the fourth and laterally to the inner border of the rib cage. Central abdominal fat (mass and percentage) was calculated by using the standard software calculation.

Statistical methods

In the analysis, age, total lean mass, total fat mass, and central fat mass were all normally distributed. All analyses were adjusted for age. We also further adjusted for body mass index (BMI; in kg/m^2) to account for current body composition.

A linear regression analysis was first undertaken in which the twins were treated as individuals, which allowed a direct comparison with findings in singleton populations.

$$E(Y_{ij}) = b_0 + b_c X_{ij} \qquad (1)$$

where Y_{ij} and X_{ij} represent the body composition (Y) and birth weight (X) of twin j from pair i, respectively, and β_c represents the expected change in body composition per 1-kg increase in birth weight in individuals. The regression analysis took into account the correlated structure of the data.

Second, following the approach described in detail by Carlin et al (16), the effect of birth weight of each individual twin on body composition was examined in a model parameterized with birth weight included as *1*) a variable representing the mean birth weight of the pair from which the twin is derived and *2*) a variable representing the individual twin's difference from the pair mean. This approach provides a simultaneous estimation of within-pair and between-pair influences of birth weight on body composition:

$$E(Y_{ij}) = \mathrm{b}_0 + \mathrm{b}_\mathrm{w}(X_{ij} - X_i) + \mathrm{b}_\mathrm{B} X_i \qquad (2)$$

where X_i is the mean value of X for twin pair i. The within-pair coefficient β_w gives the expected change in Y for a 1-unit change in the difference between individual X and the twin-pair average X value. The between-pair coefficient β_B gives the expected change in Y for a 1-unit change in the twin-pair average X, while holding the individual deviation from the average constant. The within-pair effect β_w represents an association that is free of confounding due to factors that are common to the twin pair. The between-pair effect β_B reflects further variation in Y that can be explained by variation in the twin-pair mean of X. Variation due to confounding from the maternal environment would be expected to be detected in β_B but not in β_w (16).

We also repeated the analysis only in those women aged $\geq$60 y. Because we did not have complete data on menopausal status in this cohort, age 60 y was used as a cutoff to identify those who were postmenopausal. These analyses were conducted because body fat levels may be higher in postmenopausal than in premenopausal women (17). All statistical analyses were performed by using STATA version 10 (StataCorp, College Station, TX).

RESULTS

Birth weight and body-composition data were available for 3170 women (1114 DZ pairs and 471 MZ pairs) (**Table 1**). The mean birth weight was 2.44 kg, which is slightly lower than the value in comparable singleton populations, and was lower in MZ (2.36 kg) twins than in DZ twins (2.47 kg). MZ twins were older (47.5 y) than DZ twins (46.7 y). DZ twins were taller than MZ twins, and they had a higher BMI. DZ twins had higher absolute lean mass than MZ twins. There were no significant differences between total fat mass, central fat mass, and the ratio of lean to fat mass between MZ and DZ twins. Scatter plots for birth weight and measures of body composition are shown in **Figure 1**.

Total lean mass

The results from the individual-level regression analysis showed a significant positive relation between total lean mass and birth weight (a 1.85-kg increase per 1-kg increase in birth weight; 95% CI: 1.51, 2.19) (**Table 2**); the relation remained significant after adjustment for BMI. Lean mass was positively associated both within and between twin pairs (**Table 3**), which indicated that both individual-specific in utero factors plus shared environmental factors exert an influence, but the within-pair effect was significantly larger than the between-pair effect. After adjustment for BMI, the between- and within-pair effects were of similar size.

Total fat mass

There was a significant relation between total fat mass and birth weight in individual level analyses (a 0.49-kg increase per 1-kg increase in birth weight; 95% CI: 0.00, 0.99), which remained significant after adjustment for BMI. There were also significant positive within-pair differences, both before and after adjustment for BMI, which is consistent with the relation being mediated by individual, specific, in utero factors.

TABLE 1
Characteristics of the study population

	All subjects (*n* = 3170)			Mean ± SD[1]	
	Mean ± SD	Minimum	Maximum	MZ only (*n* = 942)	DZ only (*n* = 2228)
Birth weight (kg)	2.44 ± 0.61	0.54	5.40	2.36 ± 0.65	2.47 ± 0.58[2]
Age (y)	46.9 ± 12.8	18	79	47.5 ± 13.9	46.7 ± 12.3[2]
Height (cm)	162 ± 6.14	143	183	162 ± 6.11	163 ± 6.15[2]
BMI (kg/m^2)	24.8 ± 1.18	13.9	52.4	24.5 ± 1.18	25.0 ± 1.18[2,3]
Total lean mass (kg)	39.8 ± 5.51	20.9	67.8	39.1 ± 5.46	40.0 ± 5.51[2]
Total fat mass (kg)	23.1 ± 8.44	5.0	77.1	22.6 ± 8.13	23.4 ± 8.57[2]
Central fat mass (kg)	1.34 ± 0.71	0.09	4.83	1.29 ± 0.69	1.36 ± 0.72
Total lean:fat mass ratio	1.92 ± 0.70	0.68	6.59	1.94 ± 0.72	1.92 ± 0.69

[1] Differences between monozygotic (MZ) and dizygotic (DZ) twins were measured with an unpaired *t* test.
[2] Significantly different from MZ twins, $P < 0.05$.
[3] Geometric mean.

Lean:total fat mass ratio

Results from the individual-level regression analysis showed a significant positive relation between the ratio of lean to fat mass and birth weight, even after adjustment for BMI (a 0.03-unit increase per 1-kg increase in birth weight; 95% CI: 0.00, 0.08). This positive relation was seen between pairs only, indicating that the association was mediated through the shared environment of the twin pairs.

Central fat mass

There were no consistent significant relations between any of these measures and birth weight in any of the analyses.

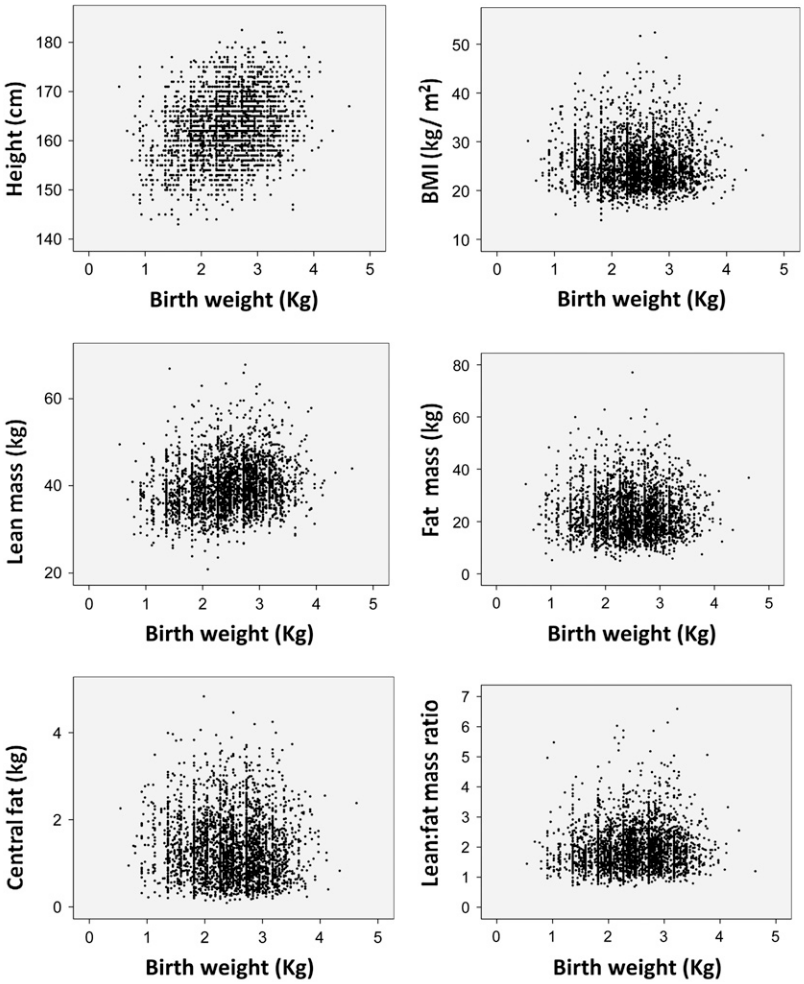

FIGURE 1. Scatter plot of Pearson correlation coefficients between measures of body composition and birth weight in 3170 female twins.

TABLE 2
Regression analyses of birth weight and measures of body size by dual-energy X-ray absorptiometry, with monozygotic (MZ) and dizygotic (DZ) twins treated as individuals (n = 3170)

	βc[1]	
	β (per kg birth weight)	(95% CI)
Total lean mass (kg)		
All twins		
Adjusted for age	1.853	(1.51, 2.19)
Adjusted for age and BMI	1.721	(1.46, 1.98)
MZ only		
Adjusted for age	1.676	(1.19, 2.16)
Adjusted for age and BMI	1.452	(1.11, 1.79)
DZ only		
Adjusted for age	1.964	(1.54, 2.39)
Adjusted for age and BMI	1.833	(1.50, 2.17)
Total fat mass (kg)		
All twins		
Adjusted for age	0.489	(0.00, 0.99)
Adjusted for age and BMI	0.249	(0.02, 0.48)
MZ only		
Adjusted for age	0.499	(−0.33, 1.32)
Adjusted for age and BMI	0.239	(−0.13, 0.61)
DZ only		
Adjusted for age	0.533	(−0.09, 1.16)
Adjusted for age and BMI	0.239	(−0.03, 0.51)
Central fat mass (kg)		
All twins		
Adjusted for age	0.003	(−0.04, 0.05)
Adjusted for age and BMI	−0.002	(−0.04, 0.01)
MZ only		
Adjusted for age	−0.004	(−0.07, 0.06)
Adjusted for age and BMI	−0.002	(−0.06, 0.02)
DZ only		
Adjusted for age	0.005	(−0.05, 0.06)
Adjusted for age and BMI	−0.002	(−0.05, 0.02)
Total lean:fat mass ratio		
All twins		
Adjusted for age	0.034	(0.00, 0.08)
Adjusted for age and BMI	0.049	(0.02, 0.08)
MZ only		
Adjusted for age	0.018	(−0.05, 0.09)
Adjusted for age and BMI	0.028	(−0.03, 0.09)
DZ only		
Adjusted for age	0.037	(−0.01, 0.09)
Adjusted for age and BMI	0.054	(0.02, 0.09)

[1] Regression coefficients from generalized estimating equations expressed as the change in outcome (per stated unit) for a 1-kg change in birth weight.

Postmenopausal women

When the analyses were restricted to those women aged ≥60 y, the patterns of association did not differ from those seen in the group overall (not shown). There were no important differences in the magnitude of either β_C (Table 2) or β_B (Table 3) between the MZ and DZ twins in any analyses. The fact that the 95% CI for β_C and β_B for both the MZ and DZ overlap in all models indicated that any significant relations were not mediated through genetic factors. When zygosity was added to the regression models for all twins, it had no significant effect on any relations. Age had a negative influence on all regression models. In the individual-level regression models, the β coefficient for age was approximately −0.005 and was statistically significant in all models.

DISCUSSION

In our twin cohort, we found that the absolute amounts of fat and lean tissue in adult life were determined in the fetal period to some degree and that twins with a higher birth weight also had a more favorable body composition in adulthood. This higher ratio of lean to fat tissue was determined through the shared common environment, which indicated that although smaller infants had a lower fat mass at birth, it was accompanied by a much larger deficit in lean mass, which led to a propensity to accumulate fat throughout the life cycle. Relevant factors in the shared environment that might explain these effects include maternal smoking and diet during pregnancy (directly influencing both fetuses) and factors in the shared postnatal family environment, such as childhood nutrition and physical activity. Lean mass also appeared to be related to individual specific undernutrition in utero, as was the case for total fat mass, because of a diminished supply of nutrients reaching the fetus, regardless of shared maternal factors in each twin pair.

Our study had the advantage of focusing on DXA measurements of body composition, which provide more accurate data compared with BMI or waist circumference. We observed no consistent relations between birth weight and less accurate measures of body composition in these data (data not shown). BMI is generally used as a proxy for body fat in epidemiologic studies. Whereas BMI was found to correlate with measures of fat by DXA in this population (15), it was not a sufficiently accurate measure to reflect the subtle differences in total fat between MZ and DZ twins (15) that can be detected by DXA. The accuracy of BMI as a marker may also decrease after menopause, because of height shrinkage and a potential decrease in muscle mass (18), which also emphasizes the need for more precise measures of body composition.

Whereas the use of cross-sectional data allowed us to show that common environmental factors play a role in the relation between birth weight and adult body composition, it did not allow us to resolve at which point these factors might be acting. For example, maternal characteristics such as socioeconomic level or smoking status may play a role both pre- and postnatally. It is possible that postnatal factors such as nutrition and physical activity levels, which may differ in families with twins as compared with singletons, smoking or alcohol intake, or other lifestyle factors may play a role, but we were unable to identify what the specific factors involved were. We were also unable to determine from these data at which point in the life course this accelerated growth in body size occurs, but it may be that infancy is a critical time.

An alternative explanation was that the relation was mediated by an effect of gestational age, because twins are born ≈3–4 wk earlier in the gestation period than are singletons. We were also unable to distinguish those who were premature from those who exhibited impaired fetal growth, because we had no measure of gestational age in this cohort. Previous research has shown that infants born small-for-gestational age have higher proportions of fat mass and lower levels of lean mass when compared with infants of appropriate gestational age with the same birth weight (19). However, there is a lack of data concerning the role of gestational age in the relation between birth weight and health

TABLE 3
Regression analyses of birth weight and measures of body size by dual-energy X-ray absorptiometry, with estimation of within- and between-pair differences[1]

	βw[2]		β_B[3]	
	β (per kg birth weight)	(95% CI)	β (per kg birth weight)	(95% CI)
Total lean mass (kg)				
All twins				
Adjusted for age	2.339	(1.80, 2.88)	1.542	(1.11, 1.98)
Adjusted for age and BMI	1.969	(1.57, 2.37)	1.542	(1.21, 1.88)
MZ only				
Adjusted for age	2.047	(1.41, 2.67)	1.092	(0.34, 1.85)
Adjusted for age and BMI	1.534	(1.08, 1.99)	1.322	(0.76, 1.89)
DZ only				
Adjusted for age	2.449	(1.75, 3.15)	1.709	(1.18, 2.23)
Adjusted for age and BMI	2.141	(1.62, 2.66)	1.639	(1.22, 2.06)
Total fat mass (kg)				
All twins				
Adjusted for age	1.381	(0.52, 2.24)	0.039	(−0.60, 0.68)
Adjusted for age and BMI	0.582	(0.24, 0.93)	0.031	(−0.27, 0.33)
MZ only				
Adjusted for age	1.449	(0.20, 2.70)	−0.382	(−1.46, 0.69)
Adjusted for age and BMI	0.349	(−0.13, 0.83)	0.096	(−0.48, 0.67)
DZ only				
Adjusted for age	1.356	(0.26, 2.45)	0.164	(−0.63, 0.95)
Adjusted for age and BMI	0.673	(0.23, 1.11)	0.001	(−0.35, 0.35)
Central fat mass (kg)				
All twins				
Adjusted for age	0.071	(−0.01, 0.15)	−0.030	(−0.08, 0.02)
Adjusted for age and BMI	0.011	(−0.03, 0.06)	−0.030	(−0.06, 0.00)
MZ only				
Adjusted for age	0.057	(−0.05, 0.16)	−0.056	(−0.14, 0.03)
Adjusted for age and BMI	−0.082	(0.03, 0.37)	−0.019	(−0.07, 0.03)
DZ only				
Adjusted for age	0.076	(−0.02, 0.17)	−0.026	(−0.09, 0.04)
Adjusted for age and BMI	0.026	(−0.03, 0.08)	−0.038	(−0.04, −0.08)
Total lean:fat mass ratio				
All twins				
Adjusted for age	−0.018	(−0.09, 0.05)	0.059	(0.01, 0.11)
Adjusted for age and BMI	0.026	(−0.03, 0.08)	0.059	(0.02, 0.10)
MZ only				
Adjusted for age	−0.072	(−0.17, 0.03)	0.082	(−0.01, 0.17)
Adjusted for age and BMI	−0.090	(0.07, 0.81)	0.054	(−0.02, 0.13)
DZ only				
Adjusted for age	0.003	(−0.08, 0.09)	0.051	(−0.01, 0.11)
Adjusted for age and BMI	0.040	(−0.03, 0.11)	0.060	(−0.02, 0.11)

[1] Regression coefficients from generalized estimating equations. MZ, monozygotic; DZ, dizygotic.

[2] Regression coefficients expressed as the change in outcome (per stated unit) for a 1-kg change in the difference between the individual birth weight and the twin-pair average birth weight.

[3] Regression coefficients expressed as the change in outcome (per stated unit) for a 1-kg change in the twin-pair average birth weight value.

later in life. Results from previous studies in which data were available indicate that it either does not play an independent role in the relation between birth weight and later health outcomes (20–22) or that the effect of adjustment for gestational age is inconsistent across cohorts (23). Also, whereas gestational age may theoretically affect estimates of β_b, it would not affect estimates of β_w.

Our results are also consistent with data showing that infants who were born small are more likely to experience rapid weight gain in the first 2 y of life (24) and that those experiencing rapid catch-up growth were already attaining a higher proportion of body fat. Rapid weight gain in infancy is strongly related to overweight and obesity in adulthood (25). Therefore, we suggest that while the absolute amounts of fat and lean tissue may be determined in the fetal period, the postnatal environment may play a more important role in the development of an unfavorable body composition in adulthood. The lack of any significant differences in the relation between MZ and DZ twins suggests that genetic factors do not play an important role in this relation, although, in the absence of data on chorionicity, a possible genetic influence cannot be fully excluded. Our results also suggest that the association between birth weight and body composition should be taken into account in studies seeking to estimate the heritability of these variables.

A limitation of this study was that our only measure of size at birth was birth weight. Birth weight may not be the ideal measurement of body composition in newborns because it does not discriminate between those infants of different sizes or body shapes. Recalled birth weights were used in this study; questions on recalled birth weight were supplied 2 wk before the clinical visit and participants were encouraged to consult their mother for answers. However, previous research has shown that, although there are some disadvantages in the use of recalled birth weight (26–28), mainly because of the underestimation of birth weight in smaller infants, most women (between 72% and 88%) can precisely recall the birth weight of their children. However, because there is no reason why there should be discordance in recall error within pairs, this should not have had any real influence on the relation within each twin pair.

The representativeness of the twins is a concern. Consistent with the association that we have shown with birth weight, our twins had a slightly lower adult weight than a comparative adult singleton population (13). It is also important to consider that the fetal growth pattern of twins is different from that of singletons and that fetal growth may be particularly compromised in MZ twins (29, 30), which leads to greater discordance in birth weight. However, in previous studies of body composition (10–12) and of other indicators of health (29–33), the magnitude of the relation between birth weight in twins was similar to that reported in singletons.

These epidemiologic findings are consistent with studies that have shown that the number of muscle cells in the body is determined before birth (34) and that increasing muscle mass throughout the life course can only be achieved by hypertrophy. In contrast, adipocytes undergo both hypertrophy and hyperplasia (35). Thus, it is conceivable that nutrition and physical activity have the greater potential to act in combination to affect the ratio of lean to fat tissue.

The authors' responsibilities were as follows— PMLS, AC, and AJM: developed the study concept; PMLS, AC, AJM, and TDS: designed the study; PMLS: conducted the statistical analysis and tabulated the data; PMLS, AC, and AJM: wrote the first draft of manuscript; and RS, JBR, and MM: contributed to and provided a critical review of the manuscript and agreed on the final version. No conflicts of interest were reported.

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