Accuracy of Six Anthropometric Skinfold Formulas Versus Air Displacement Plethysmography for Estimating Percent Body Fat in Female Adolescents with Phenylketonuria

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Abstract *Background:* The reliability of studies investigating biological and therapeutic factors that influence body composition in PKU patients depends on accurate anthropometric measurements.

Objective: To determine the precision of six anthropometric skinfold equations versus air displacement plethysmography (ADP) for predicting body fat (BF) percentage in female adolescents with PKU.

Design: Skinfold and ADP measurements were recorded from a cross section of 59 female patients with PKU, ages 10–19 years. Anthropometric measures were used to calculate percent BF using equations published by Peterson et al., Loftin et al. (TAAG), Slaughter et al., Wilmore and Behnke, Durnin and Womersley, and Jackson et al. Bland-Altman agreement analysis and Lin's concordance correlation coefficient (ρ_c) were used to determine the precision of each equation compared with percent BF determined by ADP.

Results: Adolescent females with PKU had a mean BF content of 33% measured by ADP, with an inverse association to birth cohort ($r = -0.3$, $P = 0.016$). Based

on the Bland-Altman method for evaluating agreement, only Peterson's equation did not differ significantly from ADP percent BF results ($P = 0.23$). Peterson's skinfold equation yielded percent BF estimates with the smallest mean difference from ADP and the smallest standard deviation (0.76 ± 4.8), whereas Slaughter's equation had the largest (-7.7 ± 7.4). Loftin's TAAG equation had the least mean percent error (2.2%), while Slaughter's equation had the highest (19%). Both TAAG and Peterson's equations had the highest concordance correlation coefficients ($\rho_c = 0.8$, $\rho_c = 0.8$), while Slaughter's equation had the lowest ($\rho_c = 0.3$).

Conclusions: Peterson's equation is a precise surrogate for ADP when estimating percent BF in female adolescents with PKU, though Loftin's TAAG equation is also effective. Observed decreases in adiposity correlating with birth cohort could reflect steady improvements in patient nutrition care.

Abbreviations

ADP	Air displacement plethysmography
BF	Body fat
DXA	Dual-energy x-ray absorptiometry
PKU	Phenylketonuria
UWW	Underwater weighing

Introduction

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism characterized by the inability of phenylalanine hydroxylase to efficiently convert phenylalanine (Phe) into tyrosine. To prevent permanent neurological damage from high blood Phe concentrations, patients with PKU are instructed to follow a lifelong dietary regimen of

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low-Phe foods along with amino acid-rich medical food as a primary source of protein nutrition (Santos et al. 2006).

The effects that PKU, and the corresponding dietary regimen, may have on weight gain have been the subject of prior studies, including some that indicate a higher risk of overweight in those diagnosed with PKU (White et al. 1982; McBurnie et al. 1991; Acosta et al. 2003). This trend has been seen for inborn errors of protein metabolism in general (Wilcox et al. 2005). Other research has specifically investigated body composition in early-treated patients with PKU. A study using total body electrical conductivity found a positive association between grams per kilogram of natural protein intake and fat-free mass, even when no mean difference in body composition could be found between subjects with PKU and controls (Huemer et al. 2007). However, other studies have reported significantly less lean body mass (Allen et al. 1995) and greater percent body fat (BF) (Albersen et al. 2010) in PKU pediatric and adolescent females versus controls. The lack of significant body composition difference between patients and controls in the Huemer study, while relevant findings occurred for Albersen and Allen, may be attributed to the different measurement approaches used: skinfold measures for the Allen study and air displacement plethysmography (ADP) for the Albersen comparison, as opposed to Huemer's use of body electrical conductivity; although other cohort variables may also have been contributory. The significant differences the Albersen and Allen studies found within their female child and adolescent subgroups led us toward selecting this demographic for our analysis.

Precise analytical methods and measurement tools are essential when conducting body composition research. ADP is a widely accepted approach for measuring body composition (McCrory et al. 1995; Nunez et al. 1999; Ginde et al. 2005), but is not always feasible due to space, technician, and monetary requirements. In research designs and clinical settings where technologies such as DXA, UWW, or ADP are impractical, it is important to have an economical yet comparably accurate alternative for determining body composition. Alternatively, interpretive equations that calculate percent BF or fat-free mass from skinfold measurements are easily performed, low in cost, and have been used for decades (Sloan et al. 1962; Brook 1971; Katch and McArdle 1973; Lohman 1981). The reliability of such equations, however, is often limited to the populations from which they originate (Brandon 1998; Michener et al. 2000; Kohli et al. 2009). Research has shown that unique medical populations, such as patients with congenital adrenal hyperplasia, cystic fibrosis, Crohn's disease, or who require antipsychotic medications, all conditions affecting nutrient utilization, may require customized interpretive measurement protocols or equations to obtain accurate body composition information (Dung et al.

2007; Sharpe et al. 2008; Wells et al. 2008; Gonçalves et al. 2012). Though research validating skinfold techniques to ADP has been reported for select groups (Gonzalez-Aguero et al. 2011; Gomez-Ambrosi et al. 2012; Lingwood et al. 2012), the usability of such equations has yet to be evaluated for those affected by inborn errors of metabolism, including the PKU population. Thus, the aim of this comparative analysis was to determine the precision and accuracy of six anthropometric skinfold equations versus ADP in a group of female adolescents with PKU.

Subjects and Methods

Subjects

Subjects were a cross section of adolescent females with PKU who attended Emory University's Annual Metabolic Camp at least once from 1999 to 2006. All subjects were early diagnosed through newborn screening with access to traditional diet treatment from infancy. PKU phenotypes ranged from classic to mild. Each camper represents only one data point, since those returning to camp in consecutive years were not remeasured to avoid repeats in the data sample. Of the 69 study volunteers who met the age criteria of 10–19 years (mean $\pm$ SD = 14.4 ± 2.5), 59 (85%) agreed to measurement by both ADP and skinfold calipers. Data from the other ten subjects were excluded from comparative analysis due to a lack of either measure. Legal guardians and participants provided consent and assent, respectively, prior to participation in the research protocol. This protocol was approved by Emory University's Institutional Review Board.

Data Collection

ADP, a well-accepted and prevalent method for evaluating body composition (Fields et al. 2005), using the BOD POD® apparatus (Life Measurement Inc, Concord, CA), was selected as the reference standard because of convenience, availability, and comparability with the gold-standard methods of underwater weighing (UWW) (Nunez et al. 1999; Ginde et al. 2005) and dual-energy x-ray absorptiometry (DXA) (Nicholson et al. 2001; Ballard et al. 2004).

The Emory University Hospital Clinical Interaction Site (EUH CIS, formerly the EUH General Clinical Research Center) is a National Institutes of Health sponsored research site that provides trained professional research staff and quality standardized calibrated equipment for accurate measurement of anthropometric parameters. Licensed registered dietitians at the EUH CIS performed ADP body

Table 1 Female-specific body composition equations compared with ADP when calculating percent BF. Skinfold measurements in millimeters

Source	Formula	Age specificity
Peterson	%BF = 22.189 + 0.064 (age) + 0.604 (BMI) – 0.145 (height) + 0.309 (subscapular + triceps + thigh + suprailliac) – 0.001 (subscapular + triceps + thigh + suprailliac) ²	18–54 years
TAAG	%BF = –23.39 + 2.27 (BMI) + 1.94 (triceps) – 2.95 (race*) – 0.52 (age) – 0.06 (BMI × triceps)	10–15 years
Slaughter	%BF = 1.33 (subscapular + triceps) – 0.013 (subscapular + triceps) ² – 2.5	8–18 years
Wilmore/Behnke	BD = 1.062 – .001[0.68 (subscapular) – 0.39 (triceps) – 0.25 (thigh)]	17–47 years
Durnin/Womersley	BD = 1.152 – 0.069 × log(subscapular + triceps + suprailliac)	16–19 years
Jackson	BD = 1.096 – .001[0.695 (triceps + abdominal + thigh + suprailliac) + 0.001 (triceps + abdominal + thigh + suprailliac) ² – 0.071 (age)]	18–55 years

*Race is designated as 1 for African American and 0 for non-African American

density and skinfold caliper measurements. Height (cm) and weight (kg) were measured and recorded by a research nurse during the visit. Dietetic and nursing personnel all had prior experience and training in collection of anthropometric measures in accordance with well-established published standards (ACSM 2000, CDC 2000–2005). Anthropometric data collection occurred between 8am and 1pm each year on the day of arrival to camp, dependent upon the subject's time of arrival. All subjects were fasting for at least 8 hours at the time of data collection. Information about date of birth and demographics were obtained with a questionnaire. Birth cohort was determined by year born such that subjects born within the same year were considered to be of the same birth cohort. Plasma amino acids were analyzed by HPLC (Biochrom 30 Amino Acid Analyzer) at Emory Genetics lab.

Anthropometric Calculations

ADP uses air displacement to determine body volume. The subject's weight is divided by the measured volume to yield whole body density (BD) in grams per cubic centimeter (McCrory et al. 1998; Higgins et al. 2001).

The six equations selected for this comparative analysis (Table 1) incorporate anthropometric and demographic predictors that can be observed easily in a clinical environment and had to be gender specific. Slaughter's (Slaughter et al. 1988), TAAG (Trial of Activity for Adolescent Girls) (Loftin et al. 2007), Durnin/Womersley (Durnin and Womersley 1974), Peterson's (Peterson et al. 2003), Wilmore/Behnke (Wilmore and Behnke 1970), and Jackson's (Jackson et al. 1980) skinfold equations met this criterion. Since adolescent-specific equations were sparse in the literature, and nonexistent for the full age spectrum of our study sample, equations for age groups below and above 18 years were included in the analysis.

Triplicate caliper measurements for each skinfold site were averaged for each person. Averaged values were then used for the six selected equations. Peterson's, TAAG, and

Slaughter's equations calculate percent BF directly, whereas the Wilmore/Behnke, Durnin/Womersley, and Jackson equations calculate BD.

BD determined either by ADP or skinfold equations was converted to percent BF values using the Siri formula (Siri 1993), and body mass index (BMI) was calculated from height and weight information. Sex- and age-specific BMI percentiles, and height-for-age percentiles, were determined from the Centers for Disease Control (CDC) 2000 growth charts (Kuczmarski et al. 2000). Percentile ranks for percent BF results in study participants were determined from published age-adjusted gender-specific US pediatric reference curves (Kelly et al. 2009). "Underfat" was identified at the 2nd percentile or less as set forth in the *International Journal of Obesity* (McCarthy et al. 2006). "Overfat" was identified when percent BF was at or above the 80th percentile per Flegal's NHANES-based recommendation (Flegal et al. 2010). Percentile values between these two adiposity classes were identified as being within the "healthy fat" range, respectively.

Statistical Analysis

The Bland-Altman method for assessing agreement (Bland and Altman 1986, 2003) was used to compare calculated percent BF from each skinfold equation against ADP. Statistical significance was set at $P = 0.05$. Further confirmation of agreement was performed using both Pearson correlation (r) and Lin's concordance correlation coefficient (ρ_c) (Lin 1989; Lin 2000).

The percent error of each skinfold equation for each individual was calculated with the following equation:

$$\frac{(\text{Equation percent BF result} - \text{ADP percent BF result}) \times 100}{\text{ADP percent BF result}}$$

Percent errors for all participants were then averaged to determine the mean percent error of each equation compared with ADP.

Linear regression in SPSS 17.0 was used to investigate covariate relationships with percent BF or with the precision error for each anthropometric formula.

Results

Demographics, BMI, and ADP Body Composition

Table 2 presents demographics and anthropometrics of the final study sample ($n = 59$). Table 3 provides the percentile ranks of the study sample for percent BF, BMI, and height-for-age. Mean height-for-age fell below the 50th percentile, but was still within the normal range. Seven (12%) study participants had a height-for-age below the 5th percentile. BMI percentiles ranged from 5th to 99th and averaged within the 71st (± 25 SD). Forty-four percent of the study group exceeded the CDC BMI-for-age healthy weight criterion (5th–84th percentiles). Percent BF, as measured by ADP, averaged 32.5% (± 9.5 SD) and ranged from 10.5% to 58.2%. Percentile values for ADP percent BF indicated 42% of study participants had body fat amounts above healthy fat criterion (3rd–79th percentiles). Neither BMI percentiles nor percent BF were associated with age or concurrent plasma Phe concentration; however, an inverse association between birth cohort (year of birth) and percent BF was observed ($P = 0.016$). This association remained significant ($P = 0.049$) even after controlling for periodic changes to dietetic staff. BMI percentiles were not associated with birth cohort.

Mean Values and Correlations

Table 4 provides mean BF results for each equation, as well as correlations with the ADP values. Percent BF calculated from Peterson's equation had the highest correlation to ADP ($r = 0.88$, $\rho_c = 0.80$), whereas Slaughter's equation had the lowest ($r = 0.67$, $\rho_c = 0.31$).

Bland-Altman Agreement

When calculated differences were plotted against individual averages for ADP and the specified equation to determine bias, Peterson's equation had an intercept closest to zero, with data points evenly distributed, while Slaughter's equation had an intercept far below zero with a steep inverse bias (Fig. 1).

Bland-Altman statistics for all six anthropometric equations compared with ADP are provided in Table 5. Peterson's equation had both the smallest mean difference

Table 2 Demographic and anthropometric distributions for 59 female patients with PKU

	N	%	Mean	$\pm$ SD	Range
<i>Age (years)</i>			14.2	2.3	10.6–19.8
10–14.9	37	63			
15–19.9	22	37			
<i>Ethnicity</i>					
African American	4	7			
Caucasian	53	90			
Other/unclassified	2	3			
<i>Height (cm)</i>			155.0	6.4	134.4–166.9
<i>Weight (kg)</i>			56.4	15.0	30.5–115.6
<i>BMI</i>			23.3	5.0	15.6–41.5
<i>Percent BF by ADP measurement</i>			32.5	9.5	10.5–58.2

Table 3 Growth percentile values for 59 female patients with PKU

	N	%	Mean	$\pm$ SD	Range
<i>Height-for-age percentiles</i>			38	25	1–84
<5th	7	12			
≥ 5 th	52	88			
<i>BMI-for-age percentiles</i>			71	25	5–99
<5th	0	0			
5th to <85th	33	56			
85th to <95th	16	27			
≥ 95 th	10	17			
<i>Percent BF percentiles</i>			63	31	0–99
<2nd	2	3			
3rd to <80th	32	55			
≥ 80 th	25	42			

Table 4 Percent BF central statistics for each anthropometric equation and correlations with ADP values. Pearson correlation is r ; ρ_c is Lin's concordance correlation coefficient

Method	Mean % BF $\pm$ SD	Range in % BF	r with ADP	ρ_c with ADP
Peterson	33 $\pm$ 6.3	20–48	0.88	0.80
TAAG	31 $\pm$ 7.9	15–45	0.84	0.80
Slaughter	25 $\pm$ 4.2	14–29	0.67	0.31
Wilmore/ Behnke	27 $\pm$ 4.2	20–38	0.84	0.50
Durnin/ Womersley	30 $\pm$ 5.6	17–39	0.84	0.69
Jackson	26 $\pm$ 6.6	11–37	0.86	0.61

Fig. 1 Diagram of bias for the Peterson and Slaughter skinfold equations compared with reference ADP. Dashed lines indicate upper and lower limits of agreement (mean $\pm$ 2SD). Centerline is mean difference of all points from ADP

from ADP and smallest standard deviation; it was the only equation with a nonsignificant P value, as well, revealing good agreement with ADP. All other equations had significant P values, indicating poor agreement with the reference ADP BF results. When percent error values for all participants were averaged, TAAG had the smallest mean percent error, followed by Durnin/Womersley and Peterson's equations. The Slaughter equation, along with the Wilmore/Behnke and Jackson equations, had the largest mean percent errors.

All six equations fulfilled the Bland-Altman criterion that at least 95% of the difference values fall within the limits of agreement (mean bias $\pm$ 2SD), with values outside these limits classified as outliers.

Variation in Percent Error

All equations showed variability in the percent error from ADP for individual body composition results (Fig. 2), with the Slaughter equation underestimating percent BF by as much as 58% and Peterson's equation overestimating percent BF by as much as 104%. All skinfold equations revealed a significant inverse association ($P < .0001$) between percent BF and percent error bias from ADP, indicating that individuals with lower BF were more likely to receive inflated percent BF results from the equations, whereas individuals with higher BF were more likely to

Table 5 Results from Bland-Altman analysis, evaluating difference of each body composition equation from ADP reference. Limits of agreement are mean difference $\pm$ 2 SD

Formula	Mean % error	Mean difference ($\pm$ SD)	P value	Limits of agreement
Peterson	+7.0 %	0.76 $\pm$ 4.8	$P = 0.230$	-8.8, 10.3
TAAG	-2.2 %	-1.58 $\pm$ 5.2	$P = 0.024$	-12.0, 8.9
Slaughter	-19.3 %	-7.70 $\pm$ 7.4	$P < 0.0001$	-22.5, 7.1
Wilmore/ Behnke	-10.4 %	-5.05 $\pm$ 6.2	$P < 0.0001$	-17.5, 7.4
Durnin/ Womersley	-3.0 %	-2.41 $\pm$ 5.7	$P = 0.002$	-13.8, 9.0
Jackson	-17.8 %	-6.32 $\pm$ 5.0	$P < 0.0001$	-16.4, 3.7

receive underestimates. Changes in clinical staff who collected skinfold measurements from 1999 to 2006 were not associated with the percent error from reference ADP.

Discussion

Agreement of Tested Equations with ADP Results

Though none of the equations tested is perfect for determining individual body composition, Peterson's skinfold equation proved superior at determining percent BF from anthropometric measurements in a female adolescent population with PKU in the clinical setting or when more sophisticated methods of determining body composition (i.e., DXA or ADP) may not be available.

Peterson's equation, introduced in 2003 and originally designed for women over 18 years of age, has not been used before to determine percent BF in adolescents. It was therefore surprising that Peterson's equation proved to be the most precise estimator of percent BF in this analysis; indeed, it was superior even to three other equations designed specifically for adolescent females. Whether the precision of Peterson's equation in this comparative analysis was due to the choice of reference standard (ADP rather than DXA or UWW), our study's particular patient population, or the quality of the equation itself remains to be seen in future investigations.

In this study of female adolescents with PKU, Slaughter's equation arguably showed the poorest precision in determining percent BF, as it had the greatest mean percent error, the largest mean difference and standard deviation from the ADP values, and the weakest correlation to ADP results. Other studies have reported similar results for Slaughter's equation (Rodriguez et al. 2005; Loftin et al. 2007), though not consistently (Wong et al. 2000; Wells et al. 2008; Gonzalez-Aguero et al. 2011), and none others

Fig. 2 Percent error between skinfold equation percent BF results and ADP for all study participants

were PKU specific. The discrepancy between these studies and our own may be due to differences in the equations selected for comparison, as well as measuring techniques, reference standard (DXA or UWW rather than ADP), or patient population medical status and demographics.

The TAAG equation, despite showing poor agreement via the Bland-Altman analysis, does have a smaller mean percent error than either the Peterson or Durnin/Womersley equations, and a concordance correlation coefficient that matches Peterson's formula. In addition, the TAAG equation requires fewer anthropometric measures than Peterson's equation, making it an appropriate alternative to Peterson's equation, when measuring multiple skinfold sites would be impractical.

When using any skinfold equation, however, investigators and clinicians must consider the fact that the degree of error correlates strongly with body fat content and is greatest when body fat content is in the upper or lower extremes, as observed in both our study and others (Swan and McConnell 1999; Daniel et al. 2005).

Adiposity in PKU and Clinical Relevance

The mean percent BF of study participants with PKU was similar to the 33% BF mean value reported from NHANES 1999 to 2004 DXA results in females ages 8–19 years (Kelly et al. 2009; Flegal et al. 2010). Therefore, based on the cross-sectional sampling for this study, adolescent

females with PKU may not have higher body fat percentages than adolescent girls within the US background population. Whether this will remain the case in the future, given how the prevalence of overweight has been increasing steadily in US children, remains to be seen.

This does not mean that weight gain and body composition of patients with PKU is not worthy of attention. A 2010 article comparing twenty 6–16-year-old PKU children with age- and gender-matched healthy Dutch controls discovered that even though BMI was similar, there was a significantly higher BF percentage as measured by ADP in the children with PKU. Particularly in the subgroup of females ages 11–16 ($n = 8$), percent BF was 30% for females with PKU, but only 21.5% for age-matched healthy controls (Albersen et al. 2010). This, however, may not be contradictory to our result that percent BF is no higher in patients with PKU, since we are comparing our results to NHANES data gathered from over 4,300 US pediatric females from the general population (Kelly et al. 2009; Flegal et al. 2010), rather than against a healthy matched European control group. Also, when standardized by age, a higher proportion of PKU adolescent females within our study had a BMI-for-age status above the 85th percentile (44% of study subjects versus 33% of NHANES subjects) and percent BF values exceeding the 80th percentile (42% study subjects versus 20% NHANES) (Flegal et al. 2010). A study from Poland also showed that male and female adolescents with PKU whose serum Phe

levels were within recommended levels had greater lean body mass and bone mineral density than adolescents with serum Phe above recommended levels (Adamczyk et al. 2011). Therefore, the physiological impact of hyperphenylalaninemia, as well as the impact of dietary restriction, on weight gain, muscle mass, fat mass, and bone density are still research areas of clinical importance for disease management and patient care.

Of additional interest is the inverse trend we uncovered between birth cohort and percent BF in the adolescent females with PKU, which indicated that a girl with PKU who reached the age of 15 years in 2006 would likely have lower body fat than one who reached the same age in 1999. We speculate that continuing improvements in medical and nutrition management of patients with PKU have led to the overall decreases in percent BF. It will be interesting to observe if this trend continues given the emerging treatment options for patients with PKU, such as sapropterin dihydrochloride (BH4) and pegylated phenylalanine lyase (PEG PAL) therapies, which may affect body composition or weight status if they result in more liberalized diets. Accurate investigation of these changing factors on body composition, as well as routine clinical monitoring, requires anthropometric measurement techniques that are reliable and precise.

Conclusion

The comparative investigation of six skinfold equations to ADP indicated that Peterson's skinfold equation is an adequate substitute for ADP when determining body composition in female adolescents with PKU; therefore, the development of a new modified body composition formula was not necessary. Also shown was the superiority of Peterson's equation over five other skinfold equations tested, including three designed specifically for adolescent females, though the TAAG equation may be appropriate in circumstances when the measurement of more than one skinfold site is impractical.

In addition, mean percent body fat composition of female adolescents with PKU did not differ from an NHANES sampling representative of the US background female adolescent population. Even so, a larger proportion of the study group demonstrated adiposity beyond the healthy BMI and percent BF percentile criterion, though we did discover a trend toward decreasing percent BF associated with birth cohort.

This is the first study focused on determining the most accurate method of estimating body composition of individuals with PKU when using skinfold equations. Future studies should investigate the validity of these methods in other sizable demographic groups within the

PKU population, as well as longitudinal changes affected by various emerging therapies.

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Synopsis

When determining percent body fat in adolescent females with PKU, Peterson's anthropometric equation is closest to ADP in accuracy and reliability.

Contributions of Individual Authors

Teresa D. Douglas: Performed data cleaning, analysis of data, and writing all parts of manuscript.

Mary J. Kennedy: Project coordinator, writing and submission of IRB documents, obtained informed consent, organizing and coordinating of patients on the day of measurement, coordinating with staff and faculty at the Emory University Hospital Clinical Interaction Site.

Meghan E. Quirk: Made significant contributions in reviewing the article and in recommending large-scale revisions, additional analysis, and statistical approaches

Sarah H. Yi: Assisted with project coordination, obtaining informed consent, measuring of patients, and data entry and organization.

Rani H. Singh: Principal Investigator, developed initial project protocol, obtained essential funding every year; supervising of staff, volunteers, and graduate students involved in project coordination, data management, and data reporting.

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Competing Interest Statement

All the authors of this article have no competing interests to declare.

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Details of Ethics Approval

Research protocol, informed consent documents, and all procedures were submitted to Emory University Institutional Review Board (IRB), receiving approval. Project review and approval by IRB was conducted annually.

Patient Consent Statement

Written informed consent was received from participants 18+ years of age. For study participants who were 10–17 years old, written consent was received from the parents, and written or verbal assent (as age appropriate) from the participating minor. Consent/assent procedures were completed prior to any study measurements being performed. Consenting patients were at liberty to refuse anthropometric measures per their own discretion. Patients not providing informed consent were not involved in the research protocol.

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