Body movement and physical activity energy expenditure in children and adolescents: how to adjust for differences in body size and age¹–³

Ulf Ekelund, Agneta Yngve, Sören Brage, Klaas Westerterp, and Michael Sjöström

ABSTRACT

Background: Physical activity data in children and adolescents who differ in body size and age are influenced by whether physical activity is expressed in terms of body movement or energy expenditure.

Objective: We examined whether physical activity expressed as body movement (ie, accelerometer counts) differs from physical activity energy expenditure (PAEE) as a function of body size and age.

Design: This was a cross-sectional study in children \( n = 26; \bar{x} (±SD) \text{age: } 9.6 ± 0.3 \text{y} \) and adolescents \( n = 25; \text{age: } 17.6 ± 1.5 \text{y} \) in which body movement and total energy expenditure (TEE) were simultaneously measured with the use of accelerometry and the doubly labeled water method, respectively. PAEE was expressed as 1) unadjusted PAEE (TEE minus resting energy expenditure (REE); in MJ/d), 2) PAEE adjusted for body weight (BW) (PAEE · kg⁻¹ · d⁻¹), 3) PAEE adjusted for fat-free mass (FFM) (PAEE · kg FFM⁻¹ · d⁻¹), and 4) the physical activity level (PAL = TEE/REE).

Results: Body movement was significantly higher (\( P = 0.03 \)) in children than in adolescents. Similarly, when PAEE was normalized for differences in BW or FFM, it was significantly higher in children than in adolescents (\( P = 0.03 \)). In contrast, unadjusted PAEE and PAL were significantly higher in children (\( P < 0.01 \)).

Conclusions: PAEE should be normalized for BW or FFM for comparison of physical activity between children and adolescents who differ in body size and age. Adjusting PAEE for FFM removes the confounding effect of sex, and therefore FFM may be the most appropriate body-composition variable for normalization of PAEE. Unadjusted PAEE and PAL depend on body size. Am J Clin Nutr 2004;79:851–6.

KEY WORDS Accelerometry, doubly labeled water, physical activity energy expenditure, physical activity level

INTRODUCTION

Physical activity is a multidimensional human behavior. Because of its complex nature, physical activity is difficult to assess precisely under free-living conditions. As a result, no single method is available to quantify all dimensions of physical activity. Two methods of objectively assessing physical activity are the use of motion sensors, which are based on accelerometry, and the doubly labeled water (DLW) technique. Motion sensors measure the acceleration of the body, ie, body movement, in one or more directions and can quantify physical activity data in terms of time and intensity (1). Furthermore, in groups of free-living subjects similar in body size, physical activity assessed by accelerometry is significantly correlated both with physical activity energy expenditure (PAEE) normalized for body weight (BW) (2) and with physical activity level [PAL = total energy expenditure (TEE)/resting energy expenditure (REE)] assessed by using the DLW method (2, 3). PAEE is usually calculated by subtracting REE from TEE as measured by the DLW method. However, comparisons of PAEE between persons require correction for body size (4).

PAEE can be corrected for differences in body size either by dividing by BW or scaling by BW with the use of an exponent between 0.5 and 1 (4). The rationale for scaling PAEE by BW is that physical activity includes both weight-bearing and non-weight-bearing activities, and it has been suggested that there is no universal scaling exponent that is applicable to all types of physical activity (4). Thus, the use of multiple statistical approaches or the inclusion of time-motion measures (eg, accelerometry) is recommended for comparisons between groups having different body sizes (4). However, on the basis of energy expenditure measurements during light physical activities, in which energy expenditure through fidgeting is carefully controlled for, dividing PAEE by BW has also been suggested as an appropriate means of comparing the volume of physical activity (ie, time × intensity) between groups and persons who differ in body size (5).

Physical activity, as assessed by accelerometry, has also been shown to decrease by age (6, 7), whereas PAEE and PAL increase with age during childhood and adolescence (8). We previously showed that obese adolescents have lower physical activity, as assessed by accelerometry, but not PAEE than do their normal-weight peers (9). Thus, the interpretation of physical activity data in children and adolescents who differ in body size and age seems

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to be influenced by the assessment method used and by whether physical activity is expressed in terms of body movement or PAEE. Consequently, examination of potential differences between different expressions of physical activity is needed.

The purpose of the present study was to examine differences in physical activity, which was expressed as body movement measured by accelerometry and as energy expenditure (PAEE and PAL) measured simultaneously by using the DLW method, between children and adolescents who differed in body size and age. We hypothesized that body movement would be higher in children than in adolescents and that, because of the effect of body size, PAEE and PAL would be higher in adolescents than in children.

SUBJECTS AND METHODS

Study design and subjects

We included data from our own database of results in a cohort of children and adolescents in whom TEE was measured by using the DLW method and body movement was simultaneously measured by accelerometry. This cohort has been described in detail previously (2, 9). Because obese persons typically expend a high absolute amount of energy through physical activity but are characterized by low levels of physical activity expressed as body movement (9), obese subjects with an age-adjusted body mass index (in kg/m²) > 30 (10) and athletes in training were excluded from the analyses to obtain a more homogeneous study population. The present study included 26 children (15 boys and 11 girls) and 25 adolescents (15 males and 10 females). The subjects and their parents (for subjects aged <18 y) provided written informed consent, and the study protocol was approved by the Ethics Committee of the Örebro County Council and by the Ethics Committee of Vejle and Funen counties.

Body composition

While the subjects were in the fasting state, their BW was measured with a standard laboratory scale to the nearest 0.1 kg, and their height was measured with a stadiometer to the nearest 0.5 cm. Total body water was measured by deuterium dilution as described by Westerterp et al (11). The deuterium dilution space was divided by 1.04 to derive total body water. Fat mass and fat-free mass (FFM) were calculated from total body water by assuming a hydration factor for FFM of 76.6% and 74.9% for boys and girls, respectively (12). In the adolescent males and females, a hydration factor of 73.2% was assumed (13). The mean (±SD) ratios of deuterium dilution space to oxygen dilution space in the children and the adolescents were 1.048 ± 0.013 and 1.039 ± 0.004, respectively.

Resting energy expenditure

After the adolescent males and females had fasted overnight, their REE was measured in the morning by indirect calorimetry as previously described (9, 14). REE was also calculated on the basis of sex, age, BW, and height according to published equations (15). A significant correlation was observed between measured and predicted REE ($r = 0.93$, $P < 0.001$). There was no significant difference between measured and predicted REE, and the mean (±SD) difference between measured and predicted REE was $-0.20 ± 0.65$ MJ/d ($P = 0.08$). Because of practical limitations (ie, data were collected in schools during normal teaching hours), no attempt was made to measure REE in children, and, instead, published equations were used to predict REE (15).

Total energy expenditure

TEE was measured over 10–14 d by using the DLW method previously described (2, 9, 14). The dose, sampling protocol, sample analysis, and calculation procedure have been described previously (11). Briefly, a weighted dose of water with a measured enrichment of $\sim$5 atom% $^2$H and 10 atom% $^{18}$O was ingested by the study subjects. This dose increases baseline concentrations of $^2$H and $^{18}$O by 150 and 300 ppm, respectively. Baseline urine samples were collected before dosing on day 0, from the second and last voidings on day 1, on the midpoint day, and on the last day of the measurement period. Samples were analyzed in duplicate with an isotope-ratio mass spectrometer (Aqua Sira; VG Isogas, Middlewich, United Kingdom). Carbon dioxide production was calculated from the elimination rates of the isotopes, as calculated from the slope of the elimination curve, with correction for changes in body water from the first to the last day, which were assumed to be proportional to changes in body mass. Carbon dioxide production was converted to TEE by using an energy equivalent based on the individual food quotient calculated from the macronutrient composition of the diet as described by Black et al (16), with the assumption that the respiratory quotient was equal to the food quotient. In all the children, a 4-d weighed dietary record was used for calculation of energy intake. In the adolescents, a 7-d weighed dietary record and a precoded food record were used.

Physical activity energy expenditure

PAEE was calculated as $0.9 \times$ TEE minus REE, and 10% diet-induced thermogenesis was assumed (17). PAEE was adjusted for differences in body size by dividing PAEE by BW. PAL was calculated as the ratio of TEE to REE. For consistency, predicted REE (15) was used in both groups in these calculations.

Body movement measured by accelerometry

Physical activity was assessed with an MTI uniaxial accelerometer (formerly known as the CSA activity monitor) (model WAM 6471; Manufacturing Technology, Inc, Fort Walton Beach, FL) simultaneously with measurements of TEE by the DLW technique. Activity data from the accelerometer were sampled on a minute-by-minute basis. The accelerometer was secured directly to the skin on the lower part of the back, which was defined as the region around the fourth and fifth lumbar vertebrae, by using an elastic belt. The subjects wore the accelerometer during the daytime except during water-based activities. Body movement data were processed and cleaned by using a macro written in Microsoft EXCEL (Microsoft Inc, Redmond, WA). Missing data, which were defined as sequences of $\geq$10 consecutive zero counts, were automatically deleted before analysis. All activity data were averaged over the 10–14-d period. Only days with $\geq$600 min of registered data were included in analyses. The mean (±SD) recorded times in the children and the adolescents were 803 ± 37 and 847 ± 65 min/d, respectively. All subjects wore the accelerometer for $\geq$8 d. The total volume of physical activity was expressed as total counts divided by number of days registered (counts/d).
TABLE 1
Descriptive characteristics, resting energy expenditure (REE), and total energy expenditure (TEE) of study participants

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
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<th>Adolescents</th>
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<td></td>
<td>Boys</td>
<td>Girls</td>
<td>Males</td>
<td>Females</td>
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<tr>
<td>Age (y)</td>
<td>9.7 ± 0.3</td>
<td>9.6 ± 0.3</td>
<td>18.1 ± 1.1</td>
<td>17.3 ± 1.9</td>
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<tr>
<td>Weight (kg)</td>
<td>33.0 ± 5.0</td>
<td>37.0 ± 5.7</td>
<td>71.4 ± 7.8</td>
<td>62.3 ± 9.3</td>
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<tr>
<td>Height (m)</td>
<td>1.40 ± 0.06</td>
<td>1.39 ± 0.05</td>
<td>1.79 ± 0.04</td>
<td>1.66 ± 0.06</td>
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<tr>
<td>FFM (kg)</td>
<td>26.2 ± 3.0</td>
<td>26.9 ± 2.7</td>
<td>60.9 ± 5.9</td>
<td>43.4 ± 4.9</td>
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<tr>
<td>FM (kg)</td>
<td>6.7 ± 3.0</td>
<td>10.1 ± 3.2</td>
<td>10.4 ± 4.1</td>
<td>18.9 ± 6.0</td>
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<tr>
<td>Body fat (%)</td>
<td>19.6 ± 5.6</td>
<td>26.7 ± 5.8</td>
<td>14.4 ± 4.4</td>
<td>29.9 ± 5.8</td>
</tr>
<tr>
<td>REE (MJ/d)</td>
<td>5.2 ± 0.5</td>
<td>5.1 ± 0.4</td>
<td>8.0 ± 0.5</td>
<td>6.2 ± 0.4</td>
</tr>
<tr>
<td>TEE (MJ/d)</td>
<td>8.9 ± 1.1</td>
<td>8.2 ± 0.8</td>
<td>14.4 ± 2.3</td>
<td>10.4 ± 0.8</td>
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All values are ± SD. FFM, fat-free mass; FM, fat mass. There were significant (P < 0.001, two-way ANOVA) effects of age group for age, weight, height, FFM, REE, and TEE. There were significant (P < 0.001, two-way ANOVA) effects of sex for height, FFM, FM, body fat, REE, and TEE. There were significant interactions between age and sex for height, FFM, REE, and TEE (P < 0.001 for all, two-way ANOVA); for weight and body fat (P < 0.01 for both, two-way ANOVA); and for FM (P < 0.05, two-way ANOVA).

Statistics
An analysis of variance design was used to test for the effect of sex and age group (children compared with adolescents) and the interaction between sex and age group. All data assumptions for analysis of variance were fulfilled. Correlations and partial correlations were calculated to assess the linear relation between variables. Data presented are means ± SDs unless otherwise stated. All analyses were performed by using SPSS (version 10.0 for WINDOWS; SPSS Inc, Chicago), and P values < 0.05 were considered significant.

RESULTS
Descriptive characteristics and energy expenditure estimates of the study participants are shown in Table 1. Significant sex-by-group interactions were observed for all body-composition variables (BW, height, FFM, fat mass, and percentage of body fat). Similarly, significant sex-by-group interactions were observed for the energy expenditure estimates, which indicates that age or body composition and sex influence the estimation of energy expenditure.

Physical activity assessed by accelerometry and PAEE and PAL assessed by using the DLW method are shown in Table 2. The total amount of physical activity expressed as body movement (counts/d) and as body movement adjusted for time wearing the activity monitor (counts · min⁻¹ · d⁻¹) was significantly higher in the children than in the adolescents (P = 0.006 and 0.028, respectively). Similarly, PAEE divided by BW (kJ · kg⁻¹ · d⁻¹) or by FFM (kJ · kg FFM⁻¹ · d⁻¹) was significantly higher in the children than in the adolescents (P = 0.03 and 0.015, respectively). In contrast, unadjusted PAEE and PAL were significantly higher in the adolescents than in the children (P < 0.001 and P = 0.02, respectively). Significant differences between sexes were observed for PAEE (P < 0.001) and PAEE adjusted for BW (P < 0.01). The between-sex difference for PAL was also nearly significant (P = 0.052). However, when PAEE was adjusted for FFM, there was no significant difference between the sexes (P = 0.09).

The linear relations between body movement data (counts · min⁻¹ · d⁻¹) and PAEE and PAL are shown in Figures 1-4. Body movement was significantly associated with PAEE and PAL in the children (r = 0.47–0.57, P < 0.02) and the adolescents (r = 0.45–0.69, P < 0.03). No significant interactions between age group and body movement were observed for any of the relations between body movement and energy expenditure, which indicates that the slopes of the regression lines did not differ between the children and the adolescents. Age group was a significant cofactor of the relations of body movement (counts · min⁻¹ · d⁻¹) with unadjusted PAEE (P < 0.0001), PAL (P < 0.01), and PAEE adjusted for FFM (P = 0.047) but not with PAL adjusted for BW (P = 0.21).

DISCUSSION
In the present study, we compared body movement measured by accelerometry and energy expenditure measured simultaneously by using the DLW method between children and adolescents who differed in body size. Physical activity expressed as

TABLE 2
Total amount of physical activity (expressed as activity counts), physical activity energy expenditure (PAEE), and physical activity level (PAL) in children and adolescents

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<td>Males</td>
<td>Females</td>
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<td>Physical activity</td>
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<tr>
<td>Total counts (counts/d × 10³)</td>
<td>505 ± 89</td>
<td>550 ± 131</td>
<td>428 ± 164</td>
<td>405 ± 135</td>
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<tr>
<td>Adjusted counts (counts · min⁻¹ · d⁻¹)</td>
<td>626 ± 98</td>
<td>689 ± 174</td>
<td>560 ± 200</td>
<td>539 ± 176</td>
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<td>PAEE</td>
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<tr>
<td>(kJ · kg⁻¹ · d⁻¹)</td>
<td>3.7 ± 0.9</td>
<td>3.1 ± 0.9</td>
<td>6.5 ± 1.8</td>
<td>4.4 ± 0.8</td>
</tr>
<tr>
<td>(kJ · kg FFM⁻¹ · d⁻¹)</td>
<td>113 ± 30</td>
<td>86 ± 29</td>
<td>93 ± 28</td>
<td>71 ± 14</td>
</tr>
<tr>
<td>PAL (TEE/REE)</td>
<td>1.71 ± 0.17</td>
<td>1.61 ± 0.19</td>
<td>1.87 ± 0.25</td>
<td>1.73 ± 0.16</td>
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All values are ± SD. TEE, total energy expenditure; REE, resting energy expenditure. There were significant effects of age group for PAEE in MJ/d (P < 0.001, two-way ANOVA), total physical activity counts (P < 0.01, two-way ANOVA), and adjusted physical activity counts, PAEE in kJ · kg⁻¹ · d⁻¹ and kJ · kg FFM⁻¹ · d⁻¹, and PAL (P < 0.05 for all, two-way ANOVA). There were significant effects of sex for PAEE in MJ/d (P < 0.001, two-way ANOVA) and kJ · kg⁻¹ · d⁻¹ (P < 0.01, two-way ANOVA). There was a significant interaction between age group and sex for PAEE in MJ/d (P < 0.05, two-way ANOVA).
body movement was significantly higher in the children than in the adolescents. In agreement with this observation, PAEE adjusted for BW was significantly higher in the children, but adjusted PAEE was also significantly higher in the males than in the females. In contrast, unadjusted PAEE was significantly higher in the adolescents and in the males, and PAL was significantly higher in the adolescents. PAEE adjusted for FFM was significantly higher in the children than in the adolescents, but the effect of sex, which was significant in previous models, was no longer significant when FFM was included as a cofactor.

The present study was limited to nonobese subjects. However, we previously showed that obese and normal-weight adolescents who differed in body weight by >40 kg did not differ in activity counts obtained during the performance of a standard exercise task, ie, walking at 4 km/h on a treadmill, but that PAEE during this standardized exercise was significantly higher in the obese group (9). In addition, physical activity assessed by accelerometry was significantly lower in the obese group, whereas there was no difference between the obese and normal-weight adolescents in unadjusted PAEE under free-living conditions (9). Thus, when comparing the total amount of physical activity between persons who differ in body size, PAEE needs to be corrected for this difference.

Nonetheless, normalization of PAEE data is controversial (4, 5). In the present study, we were able to directly compare PAEE normalized for BW or FFM with body movement measured by accelerometry, which takes into account the intensity and duration of physical activity, in comparisons between the 2 age groups. When PAEE was divided by BW or FFM, the differences between the groups, ie, the higher values in the children than in the adolescents, agreed with the differences observed between these 2 groups in body movement measured by accelerometry. On the basis of the unadjusted PAEE values and PAL values in

the present study, physical activity is higher in adolescents than in children; however, on the basis of the values for PAEE adjusted for BW or FFM and of the values for physical activity expressed as body movement, children are more physically active (Table 2). The slope of the regression lines for the relations of body movement with PAEE and PAL did not differ significantly between the 2 age groups (Figures 1–4). However, age group significantly influenced the relations of body movement with unadjusted PAEE (Figure 1) and PAL (Figure 4). Thus, for a given value of body movement (ie, activity counts), the corresponding energy expenditure estimate was higher in the adolescents than in the children. In contrast, when PAEE was adjusted for FFM (Figure 3), a given value of body movement corresponded to a slightly higher energy expenditure estimate in the children than in the adolescents. Finally, when PAEE was adjusted for BW (Figure 2), age group was no longer a significant cofactor, which indicates that for a given value of body movement, the corresponding PAEE value did not differ as a function of age group and body size. Thus, the present data suggest that PAEE normalized for differences in body composition (ie, BW or FFM) is an energy estimate that is similar to body movement measured by accelerometry in groups who differ in age and body size. Therefore, PAEE needs to be adjusted when the total volume of physical activity is expressed by energy expenditure estimates. However, future studies are needed to determine whether other scaling coefficients (ie, <1) for normalizing differences in body size are more appropriate for assessment of free-living PAEE in children and adolescents.

When expressed in absolute values (MJ/d) or when adjusted for BW (kJ · kg⁻¹ · d⁻¹), PAEE was consistently higher in the males than in the females. This is in contrast with the data derived from accelerometry, in which no difference between the sexes was observed. A plausible explanation for this difference is that
the males engaged in non-weight-bearing physical activities such as bicycling and upper body movements to a greater extent than did the females. Such non-weight-bearing activities would elevate PAEE without having any effect on movement registration by the accelerometer. However, differences in body composition are more likely to explain the difference in energy expenditure between the males and the females. The relatively higher FFM observed in the males than in the females in both age groups could have resulted in an elevated TEE, and thereby an elevated PAEE. Differences between the sexes in FFM are unlikely to be fully accounted for when PAEE is divided by BW. Our data support this notion because we did not observe any significant effect of sex when PAEE was adjusted for FFM. Thus, normalizing PAEE for FFM appeared to remove the confounding effect of sex. The difference between the groups in PAEE adjusted for FFM was similar to the difference in body movement, and adjustment for FFM may therefore be the most appropriate means of normalizing PAEE, given that the total volume of physical activity is of interest.

Our observations are supported by previous cross-sectional studies showing a decline in physical activity with age both in studies in which physical activity was assessed by accelerometry (6, 7) and in longitudinal studies using self-report instruments (18, 19). Furthermore, a recent meta-analysis describing PAEE and PAL values in children aged 3–16 y showed that these measures increase with age in both sexes during growth (8). However, whether an increase in PAEE and PAL during growth could be interpreted as an increase in the total amount of physical activity per se is doubtful. As we have already highlighted, PAEE is weight dependent and PAL is the ratio of TEE to REE. The present data indicate that the denominator (i.e., REE) does not fully remove the confounding effect of body size on the numerator (i.e., TEE), at least not when compared with physical activity assessed by accelerometry. Thus, an increase in PAEE and PAL during growth may not necessarily equate to a higher level of physical activity expressed as body movement. An increase in PAEE and PAL is more likely due to an increase in body size or body weight, and therefore these estimates may not be the best indicators of the total amount of physical activity in comparisons between groups who differ in body size or in longitudinal assessments during growth.

The data from the present study should be interpreted with several limitations in mind. First, accelerometers do not record all types of movement: energy expenditure during bicycling and upper-body movement, for example, is underestimated by accelerometry. Previous studies have shown that energy expenditure during different household tasks is underestimated by 30–60% when it is assessed by accelerometry (20). This may make it difficult to accurately compare body movement measured by accelerometry with PAEE measured by using the DLW method, although it is assumed that most daily activities involve a weight-bearing component. Second, differences in total activity counts may be due to differences in the length of time during which the accelerometer was worn. The adolescents in the present study may have spent less time sleeping than did the children, which would have increased the adolescents’ activity level and consequently their PAEE and PAL. However, we expressed body movement both as total counts averaged per day and as total counts adjusted for differences in the amount of time that the subjects wore the monitor (i.e., counts · min⁻¹ · d⁻¹) and showed that with both approaches, body movement was significantly higher in the children than in the adolescents. Finally, predicted
rather than measured REE was used in the calculation of PAEE and PAL because of the limitations imposed by the school-based environment in which the data were collected from the children. However, the results did not change markedly when directly measured REE was used (in the adolescent group only). Furthermore, predicted and measured REE did not differ significantly in the adolescent group, and values obtained with the predictive equations used (15) have previously been shown to agree well with measured REE values in children and adolescents (21). Thus, the use of predicted REE in our calculations is unlikely to have biased our results.

In conclusion, the total volume of physical activity expressed as body movement seems to be similar to PAEE normalized for BW or FFM in comparisons of physical activity between children and adolescents who differ in body size and age. Adjusting PAEE for FFM removes the confounding effect of sex, and therefore FFM may be the most appropriate body-composition variable for normalization of PAEE. Unadjusted PAEE and PAL depend on body size.

We are grateful to the participants and their families for contributing their time to the study. We thank the staff at the Clinical Physiology Department, Örebro University Hospital, for assistance during the study.

UE, MS, AY, and KW initiated the study and were responsible for data collection and organization of the data. UE and SB analyzed the data. All authors contributed to the interpretation and discussion of the results. UE drafted the manuscript, and all authors critically revised it. None of the authors had any conflicts of interest with regard to this study.

REFERENCES