Adipose tissue distribution after weight restoration and weight maintenance in women with anorexia nervosa1–3

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ABSTRACT

Background: Body image distortions are a core feature of anorexia nervosa (AN). We, and others, previously reported abnormalities in adipose tissue distribution after acute weight restoration in adult women with AN compared with body mass index–matched healthy control women. Whether these abnormalities persist over time remains unknown.

Objectives: We aimed to 1) replicate previous findings that showed preferential central accumulation of adipose tissue in recently weight-restored AN women compared with control subjects, 2) describe the change within patients with longer-term (1-y) weight maintenance, and 3) compare adipose tissue distribution after 1-y maintenance with that of control subjects.

Design: Body composition and adipose tissue distribution were assessed by whole-body magnetic resonance imaging in women with AN shortly after weight normalization (n = 30) and again 1 y after hospital discharge (n = 16) and in 8 female control subjects at 2 time points.

Results: With acute weight restoration, AN patients had significantly greater visceral and intermuscular adipose tissue compared with control women [visceral: 0.75 ± 0.26 compared with 0.51 ± 0.26 kg in AN patients and controls, respectively (P = 0.02); intermuscular: 0.46 ± 0.17 compared with 0.29 ± 0.13 kg in AN patients and controls, respectively (P = 0.01)]. With maintenance of normal weight for ~1 y, visceral adipose tissue distribution in AN patients was not different from that in healthy control subjects.

Conclusions: In adult women with AN, normalization of weight in the short term is associated with a distribution of adipose tissue that is consistent with a central adiposity phenotype. This abnormal distribution appears to normalize within a 1-y period of weight maintenance. This research was registered at clinicaltrials.gov as NCT 00271921 and NCT 00368667.

INTRODUCTION

Anorexia nervosa (AN) is a psychiatric disorder characterized by an intense fear of weight gain and becoming fat, in the setting of severe underweight. Although patients’ perceptions of their bodies in the underweight state are greatly influenced by psychological distortion, the fear expressed about body fat distribution with weight regain may be based, in part, on a real occurrence. Specifically, patients often express concern that weight gain will result in a disproportionate and unacceptable increase in abdominal girth. We previously published findings from 29 patients with AN that showed abnormalities in body fat distribution with acute weight restoration, including increased visceral adipose tissue (VAT) (1), which is consistent with a growing body of evidence suggestive of a central adiposity phenotype in weight-restored women with AN (2–4). The aims of the current study were to replicate our previous findings, via the use of whole-body magnetic resonance imaging (MRI), of a central accumulation in regional adipose tissue after inpatient weight normalization in women with AN compared with control women and to extend measures to 1-y follow-up to determine whether these abnormalities persist or normalize in patients who maintain normal body weight.

SUBJECTS AND METHODS

Subjects

Participants were 30 women with AN and 10 healthy control women between the ages of 18 and 45 y. Patients with AN were receiving inpatient treatment on the Eating Disorders Service of the General Clinical Research Unit at the New York State Psychiatric Institute (NYSPI)/Columbia University Medical Center (CUMC) and, at admission, met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (5), criteria for AN, including amenorrhea, with the exception of one patient who, despite low weight, was still menstruating. Subjects were recruited from physician and mental health worker referrals or by contacting the clinic directly. Twenty-one of the 30 patients with AN were recruited specifically for this replication and

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2 Supported in part by the following grants: NIH DK66033, NIH DK02749, NIH DK42618, NCRR UL1 RR024156, and a CUMC Irving Scholars Award.

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extension study, and 9 of the 30 patients had participated in our previous study (1), which assessed body composition changes with weight restoration, and agreed to be followed for the year after hospital discharge; data regarding their end-of-inpatient-treatment body composition have been published previously (1) and are not included in the current analyses. One-year follow-up data for these participants, presented below, have not been published previously. Initial study recruitment began in April 2000.

Of the original sample (n = 29) (1), 9 women were able to maintain weight within the normal range and agreed to have their body composition reassessed at the end of 1 y. Of the replication sample (n = 21), 7 patients were able to maintain weight and undergo repeat testing at the end of the year and 8 patients relapsed. One patient was diagnosed with a second psychiatric disorder that required specialized treatment and was dropped from study participation. One patient did not return phone calls from research staff and was lost to follow-up. Four patients, despite phone calls that confirmed appointments to come to the clinic for assessment, did not show up. Thus, we report body composition and adipose tissue distribution in 30 recently weight-restored women and in 16 women who were able to maintain normal weight during the year after hospital discharge.

Control subjects were healthy, weight-stable, regularly menstruating young women without histories of eating disorders or other significant psychiatric or medical history and with body mass indexes (BMI; in kg/m²) similar to those of weight-restored patients with AN (19.5–21.0), who were recruited from the Columbia University undergraduate and Medical Center campuses. Weight stability was defined as ±2 kg of current weight for the previous 6 mo by self-report. Two control subjects were lost to follow-up between baseline and 1-y assessments. All participants had been free from medications, including oral contraceptives but excluding acetaminophen and ibuprofen, for a minimum of 4 wk before initial testing. Seven of the 16 patients with AN assessed after 1 y were taking medications on follow-up assessment. Medications included selective serotonin reuptake inhibitors (n = 6), pantoprazole (n = 1), and lorazepam in addition to a selective serotonin reuptake inhibitor (n = 1). Control participants at the follow-up assessment reported taking oral contraceptives (n = 3), loratadine for seasonal allergies (n = 1), and levothyroxine sodium (n = 1).

All subjects gave written consent before participation in the study. This study was approved by the Institutional Review Boards of the NYSPI/Columbia University and St Luke’s-Roosevelt Hospital Center.

Protocol

All patients were admitted to the Eating Disorders Service of the General Clinical Research Unit at NYSPI/CUMC. Modest variations of the following treatment protocol have been in use for the past 20 y at NYSPI and are of established utility (6, 7). Treatment consisted of a structured behavioral program aimed at normalizing weight and eating patterns. Patients were prescribed 3 meals daily plus a snack with sufficient energy content to gain 1 kg/wk. Patients were weighed on a beam balance scale (Detecto, Webb City, MO) and were encouraged to consume energy in the form of food. If they were unable to gain weight with food alone, additional energy in the form of a liquid nutritional supplement was added (Ensure or Ensure Plus; Ross Nutritional, Columbus, OH). Exercise was not permitted on the unit at any time during weight gain. In addition to the behavioral protocol, patients were seen in individual therapy with supportive and cognitive-behavioral elements 3–5 times weekly and in group and family therapy. The weight-gain phase continued until the patient reached 90% ideal body weight (IBW) as per the 1959 Metropolitan Life Tables (8), approximately equivalent to a BMI of 19.5.

After patients reached 90% IBW, they remained as inpatients for a 2- to 6-wk period of weight maintenance, during which time they were encouraged to participate in off-unit activities such as day passes, with the aim of reintegration to an outpatient environment. During this time, patients participated in greater meal self-selection and limited group exercise of low intensity that included yoga and walking. Patients were discharged to outpatient care as arranged by the inpatient team. Research staff contacted participants monthly by phone, and in-person follow-up assessments were scheduled at 3, 6, 9, and 12 mo after hospital discharge to ascertain body weight, eating disorder symptoms, and general psychological status.

All patients underwent testing after normalization and maintenance of 90% IBW for 2–4 wk and again ~1 y after hospital discharge. Control participants underwent testing at 2 time points on a schedule similar to the patients, ~1 y apart. Menstruating patients and control subjects were tested during the first half of the cycle.

Body composition was assessed with the use of whole-body MRI. For the 9 study participants from our previous study, MRI was performed at St Luke’s-Roosevelt Hospital Center through the New York Obesity Research Center. For the remaining 21 patients and all control subjects, whole-body MRI was performed at the Program for Imaging in Cognitive Sciences of CUMC. In both centers, the MRI machines were 1.5 T GE Systems (General Electric, Milwaukee, WI). All MRI images were analyzed for body composition (see below) by the Image Analysis Laboratory, which is affiliated with the New York Obesity Research Center. To assess for the presence of increased fat accumulation in other depots often associated with increased VAT, magnetic resonance spectroscopy (MRS) was performed on the calf muscle and liver in a subset of 14 patients and in all control women through the Program for Imaging in Cognitive Sciences. Because of technical error, spectroscopy data were lost for one patient participant. Thus, data from 13 patients and 10 control subjects are available for analysis.

Body composition

Whole-body MRI was carried out to evaluate total body and regional adipose tissue and skeletal muscle (SM) mass (9). Cross-sectional images were analyzed for subcutaneous adipose tissue (SAT), VAT, intermuscular adipose tissue (IMAT), total adipose tissue (TAT), and SM by 3 trained observers with the use of VECT image analysis software (Slice-O-Matic, Montreal, Canada), and total volumes were calculated as reported by Shen (9). Initial volume results were reported in liters and converted to kilograms by multiplying volume of tissue by reference densities (SM: 1.04 g/L; adipose tissue: 0.92 g/L) (10). Intraclass correlation coefficients (and CIs) for agreement among multiple
readers were SM 0.99 (0.89–1.0), SAT 0.99 (0.81–1.0), and VAT 0.95 (0.58–0.99) (11). Percentage adipose tissue was measured as TAT/weight (kg).

Calf muscle MRS

Single-voxel MRS was used to assess intramyocellular lipid (IMCL) in the tibialis anterior muscle in the right calf of each subject with the use of a 1.5 T GE MRI scanner, with a quadrature lower extremity volume coil. Three-plane scout images were acquired to enable a 10 × 10 × 10 mm3 voxel to be prescribed within the tibialis anterior muscle and positioned to avoid vascular structures and gross adipose tissue depots. Spatially localized 1H spectra for this voxel were recorded with the use of the standard single-voxel, point-resolved spectroscopy sequence with echo time/repetition time 35/2000 ms, 2048 time-domain data points, a spectral width of 1000 Hz, and 128 excitations and then processed as described recently by Shen (12). IMCL concentrations were derived from the peak areas of the CH2 resonances or changes in the H2 resonance and were expressed as ratios relative to the unsuppressed water peak area in the same voxel. All MRS data were processed with the XsOsNMR software developed in-house by 2 of the investigators (XM, DCS).

Liver MRS

Standard axial, localizer MRI scans (repetition time/echo time, 466/minimum; field of view, 30 × 22 cm; matrix, 256 × 192; NEX: 1; thickness, 0.5 cm) were acquired to cover the whole liver. The single MRS voxel was prescribed on an axial localizer in the right lobe of the liver, free of visible blood vessel or biliary duct. MRS data were acquired with the standard point-resolved spectroscopy with echo time/repetition time of 35/3000 and voxel size of 2 × 2 × 2 cm (or 8 cm3) by using the body coil for radiofrequency transmission and a 5-in surface coil for signal detection. The intrahepatic lipid concentrations were also expressed as ratios relative to the unsuppressed liver water signal in the same voxel.

Statistical analyses

Clinical variables were compared between control subjects and patients at each time point with the use of Student’s t test. Paired t tests were used to compare clinical variables in each subject population at the 2 time points (for AN subjects: immediately after weight gain and after 1-y weight maintenance; for control subjects: at baseline and after 1 y). One-year change in VAT was also measured in patients and control subjects by subtraction of VAT at the second study from that measured at the first study. Analysis of covariance that covaried for the presence of medication was performed on patients and control subjects separately to determine whether medication was associated with differences or changes in BMI, percentage adipose tissue, SAT, VAT, IMAT, TAT, or SM. Analyses were performed with SPSS for Windows, version 16.0 (SPSS Inc, Chicago, IL). Means ± SDs are reported. The t tests were 2-tailed, and the significance level was set at 0.05.

RESULTS

Results from the cross-sectional assessment of body composition in acutely weight-restored women with AN compared with control subjects are shown in Table 1. Patients and control subjects were of similar ages, weights, and BMI. Patients reported average illness duration of 6 y (±4 y). Eight of the weight-restored patients had resumption of some menstrual activity before discharge from the inpatient program, and 13 remained amenorrheic. Data are presented for 21 patients with AN recruited specifically for this replication and extension study and for 9 patients who had participated in our previous study.

Acutely weight-normalized patients did not differ significantly from control subjects in percentage adipose tissue, SM mass, or mean TAT. Adipose tissue distribution differed significantly: VAT and IMAT were significantly higher in AN patients than in control subjects (P = 0.023 and P = 0.012, respectively; Table 1), although SAT mass did not differ between the groups (P = 0.51). There were no significant differences in body composition or adipose tissue distribution between the cycling and amenorrheic patients (data not shown).

Among the subset of subjects who participated in spectroscopy assessments, no significant differences were shown between patients and control subjects. IMCL concentrations normalized for water concentrations (IMCL/water peak area) were 0.07 ± 0.01 in acutely weight-restored patients (n = 13) compared with 0.05 ± 0.03 in control subjects (n = 10, P = 0.15). Intrahepatic lipid normalized for tissue water concentrations was 0.065 ± 0.078 in patients (n = 13) and 0.084 ± 0.075 in control subjects (n = 10) (P = 0.56).

Results from the longitudinal assessment of body composition over 1 y are presented in Table 2. Of the 30 patients who provided body composition data at 90% IBW, 16 were able to maintain normal weight and participate in longitudinal follow-up. Of note, pretreatment BMI (ie, on admission to the inpatient unit) for those 16 patients was not significantly different from the BMI of those who did not maintain weight or were lost to follow-up in the year after hospitalization (n = 14; BMI: 16.11 ± 1.28 compared with 15.43 ± 1.70; P = 0.246). Mean duration of follow-up testing was ~10 mo and was not significantly different between the groups. Patients and control subjects were of

TABLE 1

Clinical characteristics and body composition in acutely weight-restored patients and healthy control subjects at initial assessment

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 21)</th>
<th>Control subjects (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>25 ± 4</td>
<td>26 ± 3</td>
<td>0.34</td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>6 ± 4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.72 ± 4.12</td>
<td>55.37 ± 4.67</td>
<td>0.326</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 ± 0.05</td>
<td>1.66 ± 0.07</td>
<td>0.303</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>20.16 ± 0.45</td>
<td>20.11 ± 0.74</td>
<td>0.859</td>
</tr>
<tr>
<td>Percentage body fat</td>
<td>24 ± 4</td>
<td>24 ± 4</td>
<td>0.751</td>
</tr>
<tr>
<td>SM (kg)</td>
<td>17.73 ± 1.72</td>
<td>18.85 ± 2.04</td>
<td>0.119</td>
</tr>
<tr>
<td>VAT (kg)</td>
<td>12.96 ± 2.29</td>
<td>13.08 ± 2.31</td>
<td>0.893</td>
</tr>
<tr>
<td>SAT (kg)</td>
<td>11.75 ± 2.03</td>
<td>12.27 ± 1.97</td>
<td>0.506</td>
</tr>
<tr>
<td>IMAT (kg)</td>
<td>0.75 ± 0.26</td>
<td>0.51 ± 0.26</td>
<td>0.025</td>
</tr>
<tr>
<td>Percentage VAT (VAT/TAT)</td>
<td>0.46 ± 0.17</td>
<td>0.29 ± 0.13</td>
<td>0.012</td>
</tr>
<tr>
<td>Percentage SAT (SAT/TAT)</td>
<td>6 ± 2</td>
<td>4 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>Percentage IMAT (IMAT/TAT)</td>
<td>91 ± 2</td>
<td>94 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage IMAT (IMAT/TAT)</td>
<td>3 ± 1</td>
<td>2 ± 1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1 All values are means ± SDs. NA, not applicable. SM, skeletal mass; TAT, total adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; IMAT, intermuscular adipose tissue.
similar age, BMI, and percentage adipose tissue, both at baseline and at 1-y follow-up assessment.

Of the 16 AN patients who underwent follow-up assessment, 9 were from the previous study and 7 were from the current investigation. One-year, weight-maintained patients showed a redistribution of adipose tissue compartments: as a percentage of TAT, SAT and IMAT were significantly greater, and VAT showed a trend toward a decrease. There was also a trend toward a decrease in total VAT. Control participants, on the other hand, showed a nearly significant increase in overall TAT (P = 0.06) and significantly higher IMAT. There was also a trend toward increased SAT and VAT. Expressed as a percentage of TAT, IMAT was increased significantly and SAT was diminished (trend).

At 1-y follow-up assessments, no significant differences were found between patients and control subjects with respect to weight, BMI, percentage adipose tissue, SM mass, TAT, SAT, or VAT; a trend was observed only for higher IMAT in patients compared with control subjects (P = 0.089). Change in VAT over the 1-y period differed significantly in patients compared with control subjects (P = 0.065, and no difference was found between patients and control subjects at follow-up (P = 0.803). This difference was statistically significant (P = 0.04). No effect of medication on adipose tissue redistribution (VAT) was found in patients or in control subjects (F = 0.065, P = 0.803), and no differences were found between groups taking and not taking medication.
medications at follow-up on any of the variables tested: BMI ($F = 3.00, P = 0.11$), percentage AT ($F = 0.52, P = 0.48$), SM ($F = 4.01, P = 0.07$), TAT ($F = 1.50, P = 0.24$), SAT ($F = 1.83, P = 0.20$), and IMAT ($F = 0.18, P = 0.90$).

**DISCUSSION**

The present data replicate our previous finding that adipose tissue distribution differs significantly between acutely weight-recovered AN patients and healthy control women. Furthermore, our results suggest that weight-recovered women with AN who are able to maintain a normal body weight show redistribution of adipose tissue back toward the distribution seen in matched control subjects over 1 y of follow-up. To our knowledge, this is the first report of redistribution of adipose tissue in weight-maintained AN patients.

**Concordance with previous studies**

Findings of adipose distribution abnormalities and increased relative central adiposity on weight restoration in adult AN patients have been reported previously by us (1) and others (2–4, 13–15). Advantages of our methodology include our use of MRI technology, which has greater specificity than the dual-energy X-ray absorptiometry and single-slice computed tomography used in other investigations, to characterize distinct compartments of adipose tissue, and our inclusion of a comparison population of weight-matched healthy control women. Furthermore, we were able to conduct our assessments after patients had achieved full, as opposed to partial, weight normalization. These factors, in addition to our examination of an adult population, may account for differences in our findings as compared with some previous investigations.

Recent findings by Misra et al (16) as well as by de Alvaro et al (17), for example, suggest that in adolescent women with AN, weight recovery results in a tendency toward normalization of adipose tissue mass and not of increased central adiposity. It is possible, as has been suggested elsewhere (16), that hypercortisolism observed in adult women with AN, which is not observed as prominently among adolescents with this disorder, contributes to differential adipose tissue distribution with weight gain. Discrepancies in findings across studies may also be attributable to different rates of weight gain and variability in dietary composition and/or physical activity levels (18) in patients undergoing different treatment protocols, the effects of which on body composition changes in AN patients warrant further investigation.

**Potential clinical implications**

AN is characterized by the fear of fatness, and the fear of abdominal fat in particular, which contributes to patients’ difficulty in gaining and maintaining weight. The current study adds to a growing body of literature that suggests that patients’ concerns regarding increased abdominal adiposity with acute weight gain are based, at least in part, on an accurate perception of a disproportionate gain in VAT. It is unknown whether patients would benefit from therapeutic measures that address psychological reactions specifically linked to increased abdominal adiposity on weight gain. However, our finding that increased VAT appears to redistribute among patients who maintain normal weight for a year supports clinicians reassuring patients that this phenomenon is only temporary and in the setting of maintenance of normal weight. In addition, the finding of adipose redistribution over time highlights previous research and clinical observations that recovery in AN does not end with acute normalization of body weight. In the year after weight normalization, recovery continues in cognitive and behavioral domains; our current data indicate that physiologic recovery continues as well. The precise time course of adipose tissue redistribution, and individual factors that predict or influence it, are important areas that may warrant further study, as does the relation of these processes to resumption of menstrual activity. Confirmation of these findings with a larger sample size would increase confidence in these results and would provide increased power to detect more subtle differences in areas such as SM and IMCL between acutely weight-restored AN patients and control subjects.

Whether variability among patients in VAT accumulation during weight restoration affects clinical outcome is unknown. It is conceivable that patients who gain the most abdominal fat and VAT are also the most distressed about their body shape and thus more prone to relapse. On the other hand, it is possible that patients who have the greatest increase in abdominal fat also solicit more therapy and psychological support to address their distress about weight gain. Our group recently reported a protective effect of absolute percentage body fat on outcome among patients followed over the course of a year through a treatment study (19); however, specific components of adipose tissue were not assessed. The relatively high rate of attrition that includes relapse in our present investigation, one limitation of this study, reflects, at least in part, the recidivism of this disorder, in which =35–50% of hospitalized patients are found to relapse within a year of hospital discharge (20, 21). Whether failure to redistribute increased VAT is associated with heightened risk of relapse is a question that warrants investigation in future studies.

Previous studies that showed increased VAT among weight-recovered women with AN promoted speculation that this abnormality might reflect a premorbid tendency that predisposes patients with AN to excessive dieting behavior. The present study findings do not support this hypothesis. Although an underlying central adiposity phenotype may promote dieting among some individuals, our finding that it resolves in weight-maintained AN patients suggests that central adiposity does not represent a vulnerability factor for most women with AN. On the contrary, it appears that it is the process of acute weight gain among underweight adults with AN that promotes a preferential deposit of adipose tissue around the viscera. This pattern has been described previously in human populations subjected to starvation (22, 23), and rats that are refed after a period of deprivation also show overcompensation in fat regain, regardless of whether they are refed with a high-fat or high-carbohydrate diet (24). Whether this pattern is observable in individuals who gain significant weight under other conditions is not certain.

**Study limitations**

Several factors limit our results. First, we assessed women with AN undergoing inpatient weight restoration at a fairly rapid pace, with a nutritionally balanced, largely solid-food diet and without opportunity for vigorous activity during the weight-gain phase.
It is unknown whether our findings can be generalized to populations undergoing more gradual weight gain or weight restoration under different dietary and/or activity protocols. In addition, some data suggest that adolescent women with AN, an important population given the typical age at onset of this disorder, experience a different distribution of adipose tissue with weight normalization (16). Additional limitations include the variability of outpatient treatment, high (although, for AN, not unexpectedly high) rates of patient attrition between study assessment points, and our relatively small sample size. The apparent persistent difference between patients and control subjects at follow-up in percentage SAT and percentage IMAT further supports the impression that adipose tissue may be continuing to redistribute; however, given the small sample size, it is also possible that TAT would differ in a larger population as well.

Conclusions

AN is a disorder of self-starvation and fear of fatness, with high morbidity and mortality. Treatment of AN hinges on weight gain, which characteristically provokes psychological distress among patients. The current study confirms previous findings that adipose tissue is not distributed normally during weight recovery; it is disproportionately deposited around the waist and in the abdominal cavity in women with AN. Importantly, however, this study also provides evidence that for patients who maintain normal body weight over a 1-y period, adipose tissue distribution normalizes. This information may be useful to clinicians who seek to provide reassurance to AN patients embarking on weight-gain therapy.

We thank the patients and staff of the General Clinical Research Unit at NYSPI/CUMC without whose participation and support this project could not have been conducted. We also thank the staff at the Body Composition Unit at St Luke’s-Roosevelt Hospital Center and Steve Dashnaw and the staff of the Program for Imaging in Cognitive Sciences. We thank Richard N Pierson Jr, Michael J Devlin, Sarah Fischer Etn, Annie Haynos, and Danila Musante for their advice, assistance, and guidance.

The authors’ responsibilities were as follows—LESM, BTW, HNG, SBH, and DG: study concept and design; LESM, EB, and JW: acquisition of data; and DG: analysis and interpretation of data; LESM, XM, MP, WS, DCS, and BTW: study concept and design; LESM, EB, and JW: acquisition of data; and DG: analysis and interpretation of data; LESM, DAK, DG, HNG, SBH, BH, WS, DCS, BTW, and JW: drafting of manuscript; and LESM, DG, HNG, SBH, BH, and JW: study supervision. No conflicts of interest were reported.

REFERENCES