Selective Contribution of Regional Adiposity, Skeletal Muscle, and Adipokines to Glucose Disposal in Older Adults

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OBJECTIVES: To study the relationships between muscle mass, regional adiposity, and adipokines and glucose disposal in an older population.

DESIGN: Cross-sectional analysis.

SETTING: Community-dwelling volunteers from the Baltimore Longitudinal Study of Aging.

PARTICIPANTS: Two hundred eighty men and 259 women with a mean age of 71.1 ± 0.4 (range 55–96) and complete data on fasting plasma adiponectin and leptin, oral glucose tolerance test (OGTT) (plasma glucose available at 0, 20, 40, 60, 80, 100, and 120 minutes), thigh computed tomography (CT), physical activity levels, and anthropometric measures.

MEASUREMENTS: Participants were classified into eight groups according to the presence of global adiposity (body mass index > 27 kg/m²), central adiposity (waist circumference > 88 cm for women and > 102 cm for men), and low muscle mass (CT thigh, lowest sex-specific tertile (93.8 cm² in women and 110.7 cm² in men) of adjusted thigh muscle area). Linear regression models were used to estimate the contribution of these eight groups to early glucose area under the curve (AUC) (t = 0–40 minutes), late glucose AUC (t = 60–120 minutes), and total glucose AUC (t = 0–120 minutes) from the OGTT.

RESULTS: Regardless of muscle mass, individuals with a combination of central and global adiposity were more likely to have delayed glucose disposal rates (P < .05). A strong negative association was also found between circulating adiponectin levels and glucose disposal rates (early AUC, β = −0.14; late AUC, β = −0.20; and total AUC, β = −0.20; P < .05 for all three AUCs) after adjusting for regional adiposity, muscle mass, circulating leptin levels, physical activity, age, and sex.


Key words: low muscle mass; regional adiposity; glucose disposal

Aging is associated with a progressive decline in glucose tolerance.1 It is still unclear whether aging per se causes this decline directly or whether it is caused indirectly because of the age-related changes in muscle mass and fat regional distribution. The lack of information on lean body or skeletal muscle mass limited previous studies that addressed this question,2,3 which may be problematic because changes in lean body mass and fat mass may not occur in parallel with aging. In some individuals, an accelerated decline in muscle mass with age accompanies a substantial increase in fat mass, leading to the syndrome of “sarcopenic obesity.”4 In others, changes in fat mass are more variable; fat mass appears to increase, remain stable, or even decline in different individuals and at different ages.5 Furthermore, fat tends to deposit preferentially in the visceral compartment in some individuals, whereas it assumes a more global and diffuse pattern in others.6 It is still not understood how these complex patterns of body composition affect glucose metabolism.

Adipose tissue and skeletal muscle may affect glucose homeostasis through different mechanisms. Adipocytes secrete adiponectin and leptin, which directly influence glucose homeostasis. Leptin stimulates energy expenditure and inhibits food intake, preventing excess adiposity.7 Adiponectin enhances insulin sensitivity, upregulates fatty acid oxidation and energy expenditure, and reduces hepatic gluconeogenesis.8 High leptin9 and low adiponectin10 levels are associated with obesity, insulin resistance, and type 2 diabetes mellitus. Skeletal muscle accounts for approximately 85% of postprandial insulin mediated glucose disposal,11 and changes in muscle mass may affect

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glucose disposal and insulin sensitivity. Insulin resistance has been associated with lower muscle strength in elderly adults even after controlling for adiposity, regardless of a diagnosis of diabetes mellitus, suggesting that age-related sarcopenia could contribute to glucose intolerance in elderly adults.

In spite of the potential contributions that age-related changes in body composition may have on glucose tolerance, there is no study, to the knowledge of the authors, that has considered the collective effects of muscle mass, regional adiposity, and adipokines on glucose tolerance in elderly adults. The hypothesis that adipokines, muscle mass, and different patterns of regional adiposity independently affect glucose disposal in older persons was tested using cross-sectional data from the Baltimore Longitudinal Study of Aging (BLSA).

MATERIALS AND METHODS

Participants

The BLSA is an ongoing observational study of normative aging in community-dwelling volunteers conducted at and sponsored by the U.S. National Institute on Aging (NIA) since 1958. Participants undergo medical, physiological, and psychological examinations at regular intervals. The NIA Intramural Research Program and the Institutional Review Board of the MedStar Health Research Institute, Baltimore, Maryland, approved the BLSA protocol. All participants provided informed participation consent at each visit.

A cross-sectional analysis was performed on data from 539 BLSA participants aged 55 and older whose latest visit fell between January 2006 and October 2009 and who had information on fasting plasma adiponectin and leptin, oral glucose tolerance test (OGTT; with plasma glucose values available from 0, 20, 40, 60, 80, 100, and 120 minutes), computed tomography (CT) scan of the thigh, physical activity levels, and anthropometric measures. A 2-hour 75-g OGTT was performed in all participants after a 10-hour overnight fast; all participants taking insulin or corticosteroids within 3 months before the study visit were excluded.

Laboratory Measurements

Plasma glucose levels were measured using a glucose analyzer (Beckman Instruments, Brea, CA). Plasma leptin was measured using enzyme-linked immunosorbent assay with an interassay coefficient of variation (CV) of 2.6% to 6.2% and an intraassay CV of 2.6% to 4.6% (Millipore, Billerica, MA). Plasma total adiponectin was measured using radioimmunoassay with an interassay CV of 6.9% to 9.3% and an intraassay CV of 1.8% to 6.2% (Millipore).

Assessment of Glucose Disposal

Glucose disposal was assessed using the trapezoidal rule to determine the area under the curve (AUC) of plasma glucose values during OGTT. A high glucose AUC represents slow glucose disposal. Conversely, a low glucose AUC signifies more-rapid glucose disposal. In addition to total glucose disposal (total glucose AUC, 0–120 minutes), early-phase glucose disposal (early glucose AUC, 0–40 minutes) and late-phase glucose disposal (late glucose AUC, 60–120 minutes) were also evaluated. Plasma glucose response during the first 30 minutes of an OGTT has been associated with hepatic glucose uptake, and the decline in plasma glucose concentration 60 minutes after glucose ingestion primarily reflects glucose uptake by skeletal muscle.

Anthropometrics

Body mass index (BMI) was calculated as weight (kg)/height² (m²). Waist circumference (WC) was measured just below the rib cage, at the narrowest point where the waist tapers, and the average of three measurements was used in the analysis.

Determination of Global and Central Adiposity

Global adiposity was defined as a BMI greater than 27.0 kg/m² for men and women. Central adiposity, a surrogate for visceral obesity, was defined as a waist circumference greater than 102 cm for men and greater than 88 cm for women, the same thresholds used by the National Cholesterol Education Program Expert Panel to define metabolic syndrome.

Muscle Mass

A cross-sectional 10-mm CT image of the thigh was obtained from each participant at midfemur (midpoint between the medial edge of the greater trochanter and the intercondylar fossa in scout view image) using a Somatom Sensation 10 CT scanner (Siemens, Malvern, PA). The total mid-thigh cross-sectional area of nonadipose, nonbone tissue within the deep fascial plane was used as a proxy measure of muscle mass. Geanie software version 2.1 (BonAlyse Oy, Jyvaskyla, Finland) was used to quantify the cross-sectional area (cm²). This value was then divided by the participant’s weight and normalized by the mean weight of the study population.

Determination of Low Muscle Mass

Low muscle mass was defined as the lowest sex-specific tertile (93.8 cm² in women and 110.7 cm² in men) of adjusted thigh muscle area. Partitioning muscle mass into tertiles allows for the exploration of muscle mass across its entire spectrum and avoids focusing on single standard definitions of sarcopenia, an approach that has been widely criticized in the literature.

Definitions of Body Composition Patterns

To study the independent effects of muscle mass and regional adiposity on glucose metabolism, participants were cross-classified into eight groups according to global adiposity, central adiposity, and muscle mass:

- Lean with normal muscle mass: BMI ≤ 27; WC ≤ 88 cm for women and ≤ 102 cm for men;
thigh muscle area > 93.8 cm² for women and > 110.7 cm² for men (n = 203)
- Lean with low muscle mass: BMI ≤ 27; WC ≤ 88 cm for women and ≤ 102 cm for men; thigh muscle area ≤ 93.8 cm² for women and ≤ 110.7 cm² for men (n = 64)
- Central adiposity with normal muscle mass: BMI ≤ 27; WC > 88 cm for women and > 102 cm for men; thigh muscle area > 93.8 cm² for women and > 110.7 cm² for men (n = 21)
- Central adiposity with low muscle mass: BMI ≤ 27; WC > 88 cm for women and > 102 cm for men; thigh muscle area ≤ 93.8 cm² for women and ≤ 110.7 cm² for men (n = 23)
- Central and global adiposity with normal muscle mass: BMI > 27; WC > 88 cm for women and > 102 cm for men; thigh muscle area > 93.8 cm² for women and > 110.7 cm² for men (n = 93)
- Central and global adiposity with low muscle mass: BMI > 27; WC > 88 cm for women and > 102 cm for men; thigh muscle area ≤ 93.8 cm² for women and ≤ 110.7 cm² for men (n = 98)
- Global adiposity with normal muscle mass: BMI > 27; WC ≤ 88 cm for women and ≤ 102 cm for men; thigh muscle area > 93.8 cm² for women and > 110.7 cm² for men (n = 30)
- Global adiposity with low muscle mass: BMI > 27; WC ≤ 88 cm for women and ≤ 102 cm for men; thigh muscle area ≤ 93.8 cm² for women and ≤ 110.7 cm² for men (n = 7)

Physical Activity
Because physical activity levels may confound the association between body composition and glucose disposal, physical activity was included as a covariate in the analysis. Physical activity levels were assessed using the Leisure Time Physical Activity Questionnaire, a standardized, interviewer-administered instrument, supplemented with lower-intensity activities that older adults commonly perform.19 Total kilocalories expended in stair climbing, walking, and exercise activity per week (kcal/kg per hour) were used in this analysis.

Statistical Analysis
Distributions of plasma levels of adiponectin, leptin, and all markers of glucose disposal (early, late, and total glucose AUCs) were skewed and were log transformed for data analysis. Linear regression models were used to estimate early, late, and total glucose AUC, for the eight groups described above. Age, sex, and physical activity were added into regression models as covariates. Data with normal distributions were presented as means ± SDs, and data with nonnormal distributions were presented as median values (interquartile ranges). All analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL).

RESULTS
Baseline Characteristics
The mean age of the study population was 71.1 ± 0.4 (range 55–96). The mean and median BMI of the study population was 27.2 and 26.3 kg/m², respectively, therefore BMI greater than 27.0 kg/m² was set to define global adiposity. Of the 539 BLSA participants, 280 (51.9%) were men. Sixty of the 539 participants had diabetes mellitus based on OGTT. Thirty-nine of the 60 participants were taking medication for diabetes mellitus (19 metformin, 6 dipeptidyl peptidase-4 inhibitors, 8 sulfonylureas, and 6 thiazolidinediones).

The characteristics of the participants according to the eight different body composition groups are summarized in Table 1. Many participants (38%) were considered lean with normal muscle mass, followed closely by those with central and global adiposity (total 35.5%). Fewer than 10% of participants were considered to have central or global adiposity alone. Participants classified in groups with low muscle mass were significantly older (P < .05 for all groups) than those with normal muscle mass, so all statistical comparisons between groups were age adjusted. Within groups of regional adiposity, there were no differences in adiponectin associated with muscle mass. Within the groups with central and global adiposity and in men and women, low muscle mass was associated with higher leptin.

Multivariable Analysis
Table 2 summarizes the multiple linear regression models estimating the independent contribution of the eight different body composition groups, leptin, and adiponectin to different phases of glucose disposal (early, late, and total glucose AUC) with the lean with normal muscle mass group serving as the reference group. All analyses were adjusted for age, sex, and physical activity.

The results showed no significant association between low muscle mass and glucose disposal in the lean group. Central adiposity by itself was also not associated with early, late, or total glucose AUC, regardless of presence of low muscle mass. Participants with central and global adiposity had higher early, late, and total glucose AUCs, and of them, those with low muscle mass had the highest effect on the three phases of glucose disposal (glucose AUCs: early: b = 0.13, P = .02; late: b = 0.17, P = .002; total: b = 0.17, P = .002). Participants with global adiposity and normal muscle mass also had significantly higher early, late, and total glucose AUCs.

Within each respective model, adiponectin had a significant inverse relationship with and was one of the strongest predictors of early (b = −0.14, P = .003), late (b = −0.20, P < .001), and total (b = −0.20, P < .001) glucose AUCs. Age was also a strong predictor of late (b = 0.18, P < .001) and total (b = 0.14, P = .003) glucose AUCs. Leptin was not a significant predictor of glucose disposal rate. To determine whether adiposity confounded this lack of association between leptin and glucose disposal, a separate backward regression analysis was run (data not shown). A significant direct interaction was found between leptin and glucose disposal rates, which was attenuated when the two groups with central and global adiposity remained in the model. Physical activity had a significant inverse relationship with early glucose AUC (b = −0.10, P = .03) but not with late or total glucose AUC.
Table 1. Baseline Characteristics of the Study Population According to the Eight Different Body Composition Groups (N = 539)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lean (Normal MM)</th>
<th>Lean (Low MM)</th>
<th>Central Adiposity Only (Normal MM)</th>
<th>Central Adiposity Only (Low MM)</th>
<th>Central and Global Adiposity Only (Normal MM)</th>
<th>Central and Global Adiposity Only (Low MM)</th>
<th>Global Adiposity Only (Normal MM)</th>
<th>Global Adiposity Only (Low MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n/n</td>
<td>107/96</td>
<td>39/25</td>
<td>5/16</td>
<td>8/15</td>
<td>51/42</td>
<td>46/52</td>
<td>20/10</td>
<td>4/3</td>
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<tr>
<td>Proportion of total population,%</td>
<td>37.7</td>
<td>11.9</td>
<td>3.9</td>
<td>4.3</td>
<td>17.3</td>
<td>18.2</td>
<td>5.6</td>
<td>1.3</td>
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<tr>
<td>Age, mean (SE)</td>
<td>70.1 (0.7)</td>
<td>80.1 (1.2)</td>
<td>68.9 (1.8)</td>
<td>75.6 (1.7)</td>
<td>67.1 (0.8)</td>
<td>71.7 (0.9)</td>
<td>66.1 (1.6)</td>
<td>75.7 (2.1)</td>
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<tr>
<td>Body mass index, kg/m², mean (SE)</td>
<td>23.6 (0.2)</td>
<td>24.1 (0.2)</td>
<td>25.7 (0.2)</td>
<td>25.3 (0.2)</td>
<td>31.2 (0.3)</td>
<td>32.9 (0.4)</td>
<td>28.8 (0.3)</td>
<td>28.0 (0.4)</td>
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<td>Weight, kg, mean (SE)</td>
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<td>Height, cm, mean (SE)</td>
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<td>Waist circumference, cm, mean (SE)</td>
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<td>Muscle mass, cm², mean (SE)</td>
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<td>Adiponectin, µg/mL, median (IQR)</td>
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<td>Leptin, ng/mL, median (IQR)</td>
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<td>Fasting glucose, mg/dL, median (IQR)</td>
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<td>Glucose area under the curve, mg × h/dL, median (IQR)</td>
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<td>Physical activity, kcal/wk, median (IQR)</td>
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</table>

All variables have age-adjusted means and medians.

*P < .05, †P < .001, ‡P = .001 for comparisons between normal and low MM.

MM = muscle mass; SE = standard error; IQR = interquartile range.
OGTT.21 Physical activity was a significant negative age-dependent increase in 2-hour glucose values during This is in agreement with previous findings that showed an rates after adjusting for body composition and adipokines. AUCs revealed that these body composition traits, as define in the Materials and Methods Section, correlate with fasting adiponectin and glucose disposal rates, with no predilection for a specific glucose disposal phase. Age is a significant inverse relationship with glucose disposal across the spectrum, with no predilection for fasting adiponectin and glucose disposal. A recent study found that insulin sensitivity measured in euglycemic clamp studies strongly correlated with fasting adiponectin and leptin, but only adiponectin remained significant after adjusting for age, sex, BMI, and waist circumference.24 Although a strong association between low muscle mass and glucose disposal was not found in the current study, the analysis was strengthened by further classifying adiposity into central and global adiposity to examine differences based on regional fat deposits. These findings using early, late, and total glucose AUCs revealed that these body composition traits, as defined in the Materials and Methods Section, correlate with glucose disposal across the spectrum, with no predilection for a specific glucose disposal phase. Age is a significant positive predictor of late and total glucose disposal rates after adjusting for body composition and adipokines. This is in agreement with previous findings that showed an age-dependent increase in 2-hour glucose values during OGTT.21 Physical activity was a significant negative predictor of early glucose AUC but not of late or total glucose AUC.

Leptin levels were found to be significantly higher in the group with central and global adiposity and low muscle mass after controlling for age (Table 1). Although a higher leptin level is expected with obesity, the added insult of low muscle mass appears to contribute to higher circulating leptin levels. This is consistent with two recent studies that reported a correlation with high leptin levels and low muscle mass in healthy elderly people after adjusting for adiposity.22,23 A significant inverse relationship between adiponectin and glucose disposal rates was found after controlling for age, sex, leptin, muscle mass, physical activity, and adiposity. An unexpected finding was the lack of an association between leptin levels and glucose disposal rates after controlling for the same covariates, which suggests that leptin may depend on a combination of factors in its relationship with glucose disposal. A previous study found that insulin sensitivity measured in euglycemic clamp studies strongly correlated with fasting adiponectin and leptin, but only adiponectin remained significant after adjusting for age, sex, BMI, and waist circumference.24

There are clinical implications from these findings. It was possible to identify a sizable number of elderly participants who did not necessarily have both central and global adiposity. Forty-four of the 272 participants (16.2%) were categorized as having only global adiposity, 37 (13.6%) were categorized as having only central adiposity, and 37 (13.6%) were categorized as having both central and global adiposity. Previous studies have shown that visceral fat is more predictive of insulin resistance, type 2 diabetes mellitus25 and cardiovascular disease.26 Participants with a combination of central and global adiposity had significantly slower glucose disposal than lean individuals. Therefore, by using a single measure of BMI or waist circumference, there is a possibility of ignoring risks associated with specific regional fat distributions. Thus, in elderly adults, a comprehensive assessment may require the use of more than one measurement to determine regional adiposity and stratify metabolic risk.

This study has limitations. First, it might have been underpowered to examine the contributions of the groups with central or global adiposity alone because of the small sample size. Second, a single slice of CT mid-thigh image might not be representative of the muscle mass of the whole body. Similarly, the use of waist circumference as a measure of central adiposity can be questioned because of its inability to differentiate subcutaneous from visceral fat. In addition, the OGTT is used as a measure of glucose

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Early Glucose AUC</th>
<th></th>
<th>Late Glucose AUC</th>
<th></th>
<th>Total Glucose AUC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean + low muscle mass (n = 64)</td>
<td>-0.05</td>
<td>.26</td>
<td>0.02</td>
<td>.77</td>
<td>-0.002</td>
<td>.96</td>
</tr>
<tr>
<td>Central adiposity + normal muscle mass (n = 21)</td>
<td>-0.01</td>
<td>.70</td>
<td>0.02</td>
<td>.79</td>
<td>0.01</td>
<td>.83</td>
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<tr>
<td>Central adiposity + low muscle mass (n = 23)</td>
<td>0.04</td>
<td>.40</td>
<td>0.04</td>
<td>.38</td>
<td>0.04</td>
<td>.33</td>
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<tr>
<td>Central + global adiposity + normal muscle mass (n = 93)</td>
<td>0.11</td>
<td>.03</td>
<td>0.13</td>
<td>.01</td>
<td>0.14</td>
<td>.01</td>
</tr>
<tr>
<td>Central + global adiposity + low muscle mass (n = 98)</td>
<td>0.13</td>
<td>.02</td>
<td>0.17</td>
<td>.002</td>
<td>0.17</td>
<td>.002</td>
</tr>
<tr>
<td>Global adiposity + normal muscle mass (n = 30)</td>
<td>0.09</td>
<td>.04</td>
<td>0.12</td>
<td>.01</td>
<td>0.12</td>
<td>.01</td>
</tr>
<tr>
<td>Global adiposity + low muscle mass (n = 7)</td>
<td>0.03</td>
<td>.54</td>
<td>-0.05</td>
<td>.27</td>
<td>-0.03</td>
<td>.47</td>
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<tr>
<td>Adiponectin</td>
<td>-0.14</td>
<td>.003</td>
<td>-0.20</td>
<td>&lt; .001</td>
<td>-0.20</td>
<td>&lt; .001</td>
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<tr>
<td>Leptin</td>
<td>0.07</td>
<td>.23</td>
<td>0.04</td>
<td>.52</td>
<td>0.04</td>
<td>.46</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>.32</td>
<td>0.18</td>
<td>&lt; .001</td>
<td>0.14</td>
<td>.003</td>
</tr>
<tr>
<td>Sex (female = 0)</td>
<td>0.16</td>
<td>.002</td>
<td>0.08</td>
<td>.13</td>
<td>0.11</td>
<td>.04</td>
</tr>
<tr>
<td>Physical activity</td>
<td>-0.10</td>
<td>.03</td>
<td>-0.07</td>
<td>.09</td>
<td>-0.08</td>
<td>.07</td>
</tr>
<tr>
<td>Adjusted coefficient of determination</td>
<td>0.09</td>
<td>.11</td>
<td>0.11</td>
<td>.11</td>
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</tr>
</tbody>
</table>

Body composition group coefficients are in comparison with the lean and normal muscle mass group. Glucose area under the curve (AUC) variables, leptin, and adiponectin were log transformed for analyses.

β = standardized coefficient.
disposal without taking into account insulin levels, so no inference regarding insulin resistance can be made. Finally, the cross-sectional nature of the study does not allow for assessment of cause-and-effect relationships.

In conclusion, the study results indicated that elderly adults with a combination of central and global adiposity were more likely to have worse glucose tolerance, and the presence of low muscle mass did not profoundly magnify this relationship. With the projected increases in lifespan and incidence of obesity in older adults, it may help to identify measures aimed at quantifying specific regional adiposity patterns as potential risk factors of age-related glucose impairment.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: RR: Study concept and design, analysis and interpretation of data, preparation of manuscript. KSG: Study concept and design, analysis and interpretation of data. EJM: Study concept and design, acquisition of participants and data, analysis and interpretation of data. JME: Acquisition of participants and data and preparation of manuscript. CWC and LF: Study concept and design, acquisition of participants and data, analysis and interpretation of data, preparation of manuscript.

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