Cardiovascular risk markers in type II diabetes and hypertension at the Battor Catholic Hospital, Volta Region of Ghana

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Abstract

Background: Inflammation has been suggested to be associated with hypertension and type 2 diabetes; inflammation either precedes or is a consequence of the development of these diseases. This study sought to evaluate the role of inflammatory markers as cardiovascular risk factors and also determine their association with other potential risk factor variables among Ghanaian type 2 diabetes and hypertensive study participants undergoing medical care at the Battor Catholic Hospital in the Volta Region.

Methods: This hospital-based case-control study was conducted between December 2012 and February 2013, involving 125 participants with hypertension, type 2 diabetes or both. The control group consisted of 62 age-matched healthy individuals. Socio-demographic data was captured using a semi-structured questionnaire, anthropometric, haematological and biochemical variables were obtained using standard methods.

Results: The levels of inflammatory markers (hs-CRP, IL-6, ESR and WBC) with the exception of TNF-α were higher among the case participants compared to the controls. The case participants were more likely to cluster at higher quartiles of inflammatory biomarkers whilst the reverse was observed among the control group.

Conclusion: In this study among Ghanaians presenting with hypertension and type 2 diabetes, low-grade systemic inflammation in association with poor glycaemic control, haemodynamic dysregulation as well as disordered body fat distribution could be playing key roles in predisposing these individuals to future adverse cardiovascular outcomes.

Keywords: Type II diabetes, hypertension, Cardiovascular disease, Cardiovascular risk score, Inflammation, Inflammatory markers, Ghana

Introduction

Cardiovascular disease (CVD) and type 2 diabetes are among the leading causes of death globally (Roglic et al., 2005; Smith, 2012). CVD tends to affect people in their prime working years, thus the condition has socio-economic implications in developing countries (Gaziano, 2007). In Ghana, CVD and type 2 diabetes prevalence rates have recorded a steady increase over the years (de-Graft Aikins, 2007; Bosu, 2010). A burden of evidence suggests that inflammation is an essential risk factor in CVD and type 2 diabetes (Spranger et al., 2003; Hu et al., 2004; Nystrom, 2007; Lee & Liu, 2008). Inflammation may be characterized by acute phase reaction in which cytokines are released from adipocytes, creating a low-grade inflammatory environment (Haffner, 2006). Such systemic and subclinical inflammatory processes raise the levels of inflammatory cytokines including C-reactive protein (CRP) or high-sensitivity CRP (hs-CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) (Lee & Liu, 2008).

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Over the last few years, a good number of promising clinical markers have been suggested to link inflammation with atherosclerosis and type 2 diabetes (Lee & Liu, 2008; Nystrom, 2007). Increased Erythrocyte sedimentation rate (ESR) and White blood cell (WBC) levels serving as haematological markers of inflammation are reportedly associated with incident type 2 diabetes and atherosclerosis or cardiac death (De Rooij et al., 2009). Assaying serum inflammatory markers may be useful in providing information regarding a person’s risk of type 2 diabetes and CVD or contribute to the understanding of the pathophysiology of these morbidities (Kluft, 2004; Nystrom, 2007). This study therefore sought to evaluate markers of inflammation as cardiovascular risk factors and determine their associations with other potential risk factor variables among type 2 diabetes and hypertensive patients at the Battor Catholic Hospital in the North Tongu District of the Volta Region in Ghana.

Materials and methods

Study participants
This hospital-based case-control study was conducted between December 2012 and February 2013. A total of 187 study subjects were purposively recruited. They consisted of 125 cases who have been diagnosed of hypertension and/or types 2 diabetes and were on medication. The control group consisted of 62 age-matched healthy individuals in the study area without a history of diabetes, hypertension or any inflammatory indications. The cases were stratified into the following three groups: 43 known hypertensives, 42 known hypertensives and diabetics and 40 known diabetics only. The subjects comprised clients at the Out-Patient Department (OPD) of the hospital.

Socio-demographic data capture
Data was captured using self-reported semi-structured questionnaire. Socio-demographic variables included sex, educational background, period of work, dietary salt, sugar, fat as well as alcohol consumption, physical activity and family history of diabetes and cardiovascular diseases.

Blood pressure and anthropometric measurements
Mercury sphygmomanometer and stethoscope were used to measure the blood pressures after at least a 10 minute rest in accordance with the recommendation of the American Heart Association (Lemogoun et al., 2003). An appropriate-50 size blood pressure cuff was used to measure blood pressures of each patient by a single qualified nurse twice within an interval of 5 minutes and the average value taken.

The anthropometric measurements were made using the methods described by Bannerman et al. (2002). Measurements of height (to the nearest 0.1 cm) without shoes and in upright position were made using a stadiometer (height meter) and body weight (to the nearest 0.1 kg) in light clothing using a portable weighing scale. Then body mass index (BMI) was calculated using the formula: BMI = weight (kg)/height² (m)². The waist circumference was measured at the point yielding the smallest circumference between the lower rib margin and the iliac crest. Hip circumference was recorded at the point yielding the maximum circumference over the buttocks. The waist-to-hip ratio (WHR) was then calculated dividing the waist circumference (cm) by the hip circumference (cm).

Blood sample collection and preparation
About 7ml of fasting venous blood was drawn from each subject fasting overnight (12-14 hours) using standard procedures. Two ml of whole blood was taken into Potassium Ethylenediaminetetraacetic acid EDTA.K3 sterile vacuum tube. Another 2 ml was dispensed into BD vacutainer® serum separator tubes for the estimation of different biochemical parameters. About 0.8 ml of the blood was dispensed into a prefilled vial (0.2 ml of 3.8% sodium citrate used as diluents making a 4:1 dilution). Two millilitres of the rest was then dispensed into sodium fluoride tube. Blood samples in anti-coagulated tubes were mixed adequately. The
samples were immediately transported to the clinical biochemistry and haematology laboratories of Battor Catholic Hospital, where clotted blood was centrifuged at 3,000 g for 5 minutes to obtain serum stored at -20°C until analysis. Biochemical indices such as hs-CRP were measured using i-CHROMA™ reader system (Boditech Med Inc. Chuncheon, Korea). Serum for IL-6 and TNF-a were measured on Tecan Absorbance Microplate Reader (Sunrise) system (Tecan Trading AG, Switzerland). EDTA.K3 blood for total white blood cell count was done using Sysmex KX-21N automated haematology analyser (Sysmex Corporation, Japan). Sample for fasting blood glucose was estimated using a semi-auto biochemistry analyser (Maysun Company Limited, China) and the citrated whole blood sample was used for the estimation of ESR using Westergren ESR Kits (Guest Scientific Swaziland).

Plasma sample was used to estimate fasting blood glucose using ELITech reagents from Vital Scientific Co Ltd. Stored frozen serum was thawed adequately at room temperature. Parameters measured were hs-CRP using kits from Boditech Med Inc. Chuncheon (Korea), IL-6 and TNF-a levels, MABTECH AB Sweden (2012 and 2013) reagents, total WBC counts using cell pack reagents and stromatolysers from Sysmex Corporation, Japan and ESR levels obtained using Westergren ESR kits (Guest Scientific Swaziland). The methods used in analysing specimens were predetermined by reagent manufacturers.

Data analysis
Categorical data was presented as figure and percentage. Parametric data was presented as means and 95% confidence intervals. Nonparametric data was expressed as geometric mean (95% CI of geometric mean). Where appropriate, continuous data were compared using unpaired t-test and Mann-Whitney and one-way ANOVA with a Bonferroni posthoc test or Kruskal-Wallis with Dunn’s post-test. Associations were evaluated using Pearson Correlation Coefficient. A p-Value < 0.05 was taken as significant. Graph Pad Prism version 6.00 for windows (Graph pad software, San Diego California, USA, www.graphpad.com) and IBM Statistical Package for the Social Sciences (SPSS Inc, Chicago, USA; www.spss.com) version 20.00 were used for data analysis where appropriate.

Ethical considerations
The participation of the respondents was voluntary and informed consent was obtained from each of them after thorough explanation of what the study entailed. This study was approved by the School of Medical Sciences and Komfo Anokye Teaching Hospital Committee on Human Research Publications and Ethics (CHRPE/RC/119/12).

Results
Out of the study population of 187, participants classified as control were 62 (33.2%) and the rest as case presenting with diabetes, hypertension or both (66.8%). Majority of the participants were females (130/187; 69.5%). In general significantly higher levels of education were reported among the controls, the inverse was however observed among the case group. Majority of the respondents worked within one (1) to eight (8) hours a day, though longer working hours was recorded among the case group in comparison to the control (p = 0.04). Dietary salt, sugar and fat intake as well as alcohol intake was predominantly moderate among the study group with consumption significantly higher among the controls. Casual participation in exercise was recorded among respondents; with significant majority (54.0%; n=67) of the case group not engaged at all in exercise (Table 1).

Table 1: General socio-demographic characteristics of respondents by disease status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total, n (%)</th>
<th>Control, n (%)</th>
<th>Case, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>130(69.5)</td>
<td>43(69.4)</td>
<td>87(69.6)</td>
</tr>
</tbody>
</table>
The average age of the respondents in this study was 48.2 (SD±14.2) years. In general the anthropometric parameters of the case group was significantly higher compared to the controls, the exception though was found in the height of participants where though not statistically significant the controls were averagely 0.1 meter taller than the cases. Significantly higher systolic and diastolic blood pressures values were observed among the cases compared to the controls. The average WBC and ESR levels serving as proxy markers for nonspecific inflammations were significantly higher among the case group. Among the biochemical markers assayed, higher glycaemic levels were observed among the cases. The log Hs-CRP concentration was also higher in the case group (Table 2).

Table 2: General anthropometric, haemodynamic, haematological and biochemical characteristics of study population by disease status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Control</th>
<th>Case</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age± SD (years)</td>
<td>48.2(14.2)</td>
<td>47.3(15.0)</td>
<td>50.4(13.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Anthropometric parameters</td>
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<tr>
<td>Weight (kg)</td>
<td>71.6(16.4)</td>
<td>69.2(15.7)</td>
<td>73(17.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.6(0.01)</td>
<td>1.7(0.01)</td>
<td>1.6(0.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9(5.5)</td>
<td>25.6(5.5)</td>
<td>27.7(6.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>87.7(14.1)</td>
<td>79.2(11.8)</td>
<td>92.5(12.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HC (cm)</td>
<td>102.5(15.5)</td>
<td>98.1(11.8)</td>
<td>104.9(16.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHR</td>
<td>0.86(0.01)</td>
<td>0.81(0.01)</td>
<td>0.89(0.01)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hemodynamic Parameter</td>
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<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>131(26.0)</td>
<td>113.9(12.6)</td>
<td>140.7(26.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80.9(13.7)</td>
<td>73.7(8.7)</td>
<td>85(13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematological Assays</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Hb(g/dl)</td>
<td>12.5(0.1)</td>
<td>12.9(0.2)</td>
<td>12.3(0.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>WBC(10^9/L)</td>
<td>5.5(1.4)</td>
<td>4.9(1.5)</td>
<td>5.8(1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR(mmfall/hr)</td>
<td>47.3(15.3)</td>
<td>40.9(10.5)</td>
<td>51(20.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Biochemical Assays</td>
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<tr>
<td>FBG(mmol/l)</td>
<td>8.1(0.4)</td>
<td>5.3(0.1)</td>
<td>9.7(0.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Among the female population, the control groups exhibited a significantly different quartile trend of high sensitive C-reactive protein levels compared to the case group. Thus majority of the controls (83.7%, n=36) clustered at the first quartile for high sensitive C-reactive protein concentration with the remaining 26 (16.3%) in the second. However the population cluster among the cases increased from the first through to the fourth quartile for high sensitive C-reactive protein concentration (11.3%, 27.5%, 30.0% and 31.2%, respectively) (Figure 1A).

The trend clusters of female study population for Interleukin 6 levels showed a steady increase in frequency from the first through to the fourth quartile among the case but a 39.5% initial number cluster below the 25th percentile cut-off reduced to 25.6% beyond the 50th percentile cut-off of Interleukin 6. (Figure 1B). No significant distinguishable trends were observed among the case and the control groups when study participants were grouped with the levels of tumour necrotic factor alpha (p = 0.46) (Figure 1C). Though not statistically significant a continuous increasing number of participants among the case group was found with an increasing fall in erythrocytes whiles the opposite was generally observed among the control group. (Figure 1D).

The trends of population cluster in general recorded significant increasing numbers of patients (case group) from the first to the fourth quartile whilst the inverse was observed among the control group (Figure 2). Out of a total of 19 male participants in the control group 16 representing 84.2% had hs-CRP levels lower than the second quartile cut-off, whiles 20 out of the total male case population of 38 patients had hs-CRP levels over the cut-off of the second quartile (Figure 2A). With IL-6 the percentage cluster trend was (6.7%, 13.3%, 30.0%, and 50.0% for first to fourth quartile respectively) for the case group and 21.1%, 42.1%, 21.1% and 15.7% for first to fourth quartile respectively for the control group. That of TNF-α was for case (16.7%, 26.7%, 23.3% and 33.3% for first to fourth quartile, respectively) and control (42.1%, 26.3%, 15.8% and 15.8% for first to fourth quartile, respectively). The ESR percentage cluster trend for the case group was (16.7%, 26.7%, 23.3% and 33.3% for first to fourth quartile, respectively) and (47.4%, 21.1%, 21.1% and 10.4% for first to fourth quartile respectively) for the control group.

In the control group the study revealed no significant correlation among the anthropometric variable with the haematological, as well as glycaemic indices. An observed increase in waist circumference corresponded to an increase in both the systolic and diastolic blood pressure. Increased BMI resulted in a significant increase in hs-CRP and decreased in TNF-α levels among the control group. Among the case group an increase in any of the anthropometric indices (BMI, WC, HC, WHR) was associated with a corresponding increase in the haemodynamic parameters measured for this study (SBP and DBP). Positive correlation was observed among WC as well as WHR and WBC. An increase in any of the anthropometric variables showed a corresponding increase in hsCRP among the case group. The haemodynamic parameters of the case group were found to be positively associated with glycaemia and most strongly with hs-CRP. WBC and ESR significantly correlated positively with hs-CRP among the control group but this relation was not significant in the case group. For the control participants significant association was recorded between glycaemic levels and IL-6. In the patients the relation was between glycaemic levels and hs-CRP (Table 3).
Figure 1: Trends of female quartile cluster distributions of respondents by inflammation biomarkers stratified by case and control
Key: Q1-First quartile, Q2-Second quartile, Q3-Third quartile, Q4-Fourth quartile; HsCRP-High sensitive; C-reactive protein; IL-6-Interleukin 6; TNF-α-Tumour Necrotic Factor Alpha; ESR-Erythrocyte sedimentation rate.

Figure 1: Trends of male quartile cluster distributions of respondents by inflammation biomarkers stratified by case and control
Key: Q1-First quartile, Q2-Second quartile, Q3-Third quartile, Q4-Fourth quartile; HsCRP-High sensitive; C-reactive protein; IL-6-Interleukin 6; TNF-α-Tumour Necrotic Factor Alpha; ESR-Erythrocyte sedimentation rate.
These observations corroborate findings of several existing studies from various populations (Hue et al., 2004; Pitsavos et al., 2007; Sesso et al., 2007; Magen et al., 2008; Babio et al., 2013; Nadeem et al., 2013; Twig et al., 2013).

The association of subclinical inflammation with states of haemodynamic and glycaemic dysregulations were more apparent in the present study. The trends of population cluster in general recorded increasing numbers of patients from first to the fourth quartiles of inflammatory markers whilst the reverse was observed among the control group. Our finding is similar to that of the CoLaus study, where apart from TNF-α, diabetic subjects significantly exhibited an incremental linear trend of inflammatory biomarkers from the lowest to the highest quartiles (Marques-Vidal et al., 2012). In the Women Health Study, the higher quartiles of plasma CRP levels retained a significant increased risk of hypertension (Sesso et al., 2007), a finding agreeing with the results of our study.

Among the case group hs-CRP levels positively correlated with systolic and diastolic blood pressure. Consistent with our results, a study which examined hs-CRP as a potential marker of inflammation in

### Table 3: Pearson’s correlation coefficients of Anthropometric variables, haemodynamic, haematologic, atherogenic and inflammation indices for control group (upper right-hand side) and case group (lower left-hand side)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMI</th>
<th>WC</th>
<th>HC</th>
<th>WHR</th>
<th>SBP</th>
<th>DBP</th>
<th>HB</th>
<th>WBC</th>
<th>ESR</th>
<th>FBG</th>
<th>hsCRP</th>
<th>IL6</th>
<th>TNF-α</th>
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<tbody>
<tr>
<td>BMI</td>
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<tr>
<td>WC</td>
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</tr>
</tbody>
</table>

**Hb**: Haemoglobin, **WBC**: White Blood Cell, **ESR**: Erythrocyte Sedimentation Rate, **VLDL-C**: Very Low Density Lipoprotein-Cholesterol, **LDL-C**: Low BMI: Body Mass Index, **WC**: Waist Circumference, **HC**: Hip Circumference, **WHR**: Waist-to-Hip Ratio, **SBP**: Systolic Blood Pressure, **DBP**: Diastolic Blood Pressure, **FBG**: Fasting Blood Glucose, **hsCRP**: High sensitive C-reactive protein, **IL**: Interleukin 6, **TNF-α**: Tumour Necrotic Factor Alpha.

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), ***Correlation is significant at the 0.001 level (2-tailed)

### Discussion

Low-grade systemic inflammation has been found to be an important pathogenesis factor in cardiovascular morbidity and in type 2 diabetes (Haffner, 2006). The inflammatory markers assayed in the current study were hs-CRP, IL-6, TNF-α, total WBC and ESR. Hs-CRP, IL-6, TNF-α, are markers of low-grade systemic inflammation (Lee & Liu, 2008; Magen et al., 2008) whiles WBC and ESR measurements serve as proxy markers for nonspecific inflammation (Twig et al., 2013). With the exception of TNF-α levels, the case participants recorded higher levels of inflammatory markers when compared with their control counterparts. Among the case group, significant intra group differences were observed with respect to the levels of hs-CRP, increasing from participants with hypertension through those with both hypertension and type 2 diabetes to type 2 diabetic individuals compared with controls. These observations corroborate findings of several existing studies from various populations (Hue et al., 2004; Pitsavos et al., 2007; Sesso et al., 2007; Magen et al., 2008; Babio et al., 2013; Nadeem et al., 2013; Twig et al., 2013).
hypertension among the Kashmiri population in India revealed an association although graded, between blood pressure variables and serum hs-CRP levels while individuals with pre-hypertension were more likely to have significantly elevated hs-CRP levels compared to normotensive control subjects (Dar et al., 2010). Similarly, in the prospective nested case-control Women’s Health Initiative-Observational Study (WHI-OS), before adjustment for measures of adiposity, Wang et al., (2011) recorded positive associations between plasma concentrations of hs-CRP and risk of hypertension among a cohort of postmenopausal white and black women. Though an area which is not fully elucidated, the mechanism explaining inflammation in hypertension has implicated endothelial dysfunction (Watson et al., 2008). CRP may stimulate endothelial dysfunction by decreasing the expression and activity of nitric oxide synthase, facilitating the release of endothelin-1, reducing the endothelial progenitor cell survival and differentiation; impairing endothelium-dependent vasorelaxation, compromising vascular tone, ultimately leading to increases in blood pressure (Wang et al., 2011).

Control participants recorded a significant association between glycaemic levels and IL-6 whiles among the patients the association was between glycaemic levels with hs-CRP. Previous studies have shown differing results regarding the association between glycaemia and hs-CRP with Hotamisligil (2006) and Pickup (2004) recording positive association whiles Rytter et al. (2009) found no association between glycaemic levels and inflammation among type 2 diabetic subjects. Mechanisms by which cytokines could contribute to the development of insulin resistant states and type 2 diabetes are diverse (Pickup, 2004). Cytokines can directly inhibit insulin receptor signalling by activating the enzyme, c-Jun amino-terminal kinase, an inhibitor of nuclear factor kappa-beta kinase, which could lead to the serine phosphorylation of insulin receptor substrate (Hotamisligil, 2006). In addition, these cytokines could influence hepatic fatty acid syntheses, provoking the liver to produce more acute-phase proteins, as well as recruit more inflammatory cells to adipose tissue and pancreatic beta-cells (Butler et al., 2003). Inflammatory cytokines do not only affect insulin resistance but may also contribute to pancreatic cell destruction, ultimately leading to type 2 diabetes (Lee & Liu, 2008).

Overweight and obesity are key determinants of health which could lead to adverse metabolic imbalances (Deshmukh et al., 2006). Obesity plays a pivotal role in the development of low-grade inflammation (Teng et al., 2014). In the present study, an increase in any of the anthropometric variables saw a corresponding increase in hs-CRP levels among the case group. Some studies have shown that abdominal adiposity is associated with elevation of CRP levels (Lemieux et al., 2001; Rodríguez-Hernández et al., 2013). Other studies have demonstrated significant correlation between CRP levels with parameters of the metabolic syndrome, including measures of adiposity (Yudkin et al., 1999; Festa et al., 2000). The mechanism linking obesity to inflammation is still an area of intense scrutiny. However, a plausible explanation is that obesity is characterized by a greater number of adipose tissue (hyperplasia) and an increase in the size of adipocytes (hypertrophy) (Jo et al., 2009; Maury & Brichard, 2010). These conditions may lead to oxygen depletion in adipose tissue thus causing adipocyte cell death (Teng et al., 2014). In addition, the excess storage of triacylglycerols from dietary intake results in an excessive influx of free fatty acids into blood circulation (Teng et al., 2014) leading to low-grade inflammation characterized by the over production of pro-inflammatory adipocytokines (Anghel & Wahl, 2007).

In conclusion, in this study adverse cardiovascular risks were associated with Ghanaians presenting with hypertension and type 2 diabetes at the Battor Catholic Hospital. This could be mediated by subclinical inflammation in association with poor glycaemic control, haemodynamic dysregulation as well as disordered body fat distribution.

**Competing Interests**

Authors have declared that no competing interests exist.
Authors Contributions

WKBAO, JOY, CO, MTA-F and SA conceptualized and designed the study. JOY and SYL recruited the study participants. JOY, SYL, CO and SA generated the data. JOY, SYL and WKBAO analysed the data and drafted the manuscript. All authors reviewed the manuscript for intellectual content and each author approved the final manuscript.

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