



Original article

Visceral and subcutaneous adipose tissue association with metabolic syndrome and its components in a South African population

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SUMMARY

Background and aims: A number of studies concur that visceral abdominal tissue (VAT) is a metabolic organ that mostly contributes to the metabolic consequences of obesity, however reports regarding subcutaneous adipose tissue (SAT) are controversial. We aimed to investigate the association between computed tomography measured visceral and subcutaneous adipose tissue and metabolic syndrome as well as its individual components.

Methods: Computed tomography at level L4/L5 intervertebral disc space was performed in 401 mixed ancestry individuals from the Bellville South community of Cape Town. Data collections included OGTT, anthropometric, blood pressure, lipids, insulin cotinine, and alcohol consumption history.

Results: Both VAT and SAT were increased in subjects with metabolic syndrome ($p < 0.0001$). In logistic regression, adjusted for age, gender, BMI, smoking, alcohol use, hypertension, diabetes and dyslipidaemia treatment (for women also adjusted for menopausal age) increasing quartiles of VAT were associated with metabolic syndrome {odds ratio (95% confidence interval) ≥ 4.14 (1.92–8.93), $p < 0.001$ } and any type of hyperglycaemia (≥ 4.45 (1.89–10.47), $p \leq 0.001$) whilst decreasing quartiles of SAT were associated with metabolic syndrome, $p \leq 0.037$. In gender specific multivariate linear regression models, increased SAT levels were associated with 2-h plasma glucose, insulin levels and triglycerides in men, $\beta \geq 0.999$, $p \leq 0.01$.

Conclusions: Our study shows that increased VAT and decreased SAT are associated with metabolic syndrome in women, but in men increased SAT has deleterious effects to metabolic syndrome components. Therefore, in men increased SAT may like VAT increase the risk of diabetes development.

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1. Introduction

Metabolic syndrome (MetS) is a metabolic disorder used to identify high risk individuals for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [1]. Due to the global epidemic of

T2DM and CVD the need for optimal guidelines on the early diagnosis of MetS have been recognised by several which all recognise central obesity as a major component of MetS [2–5]. Central obesity is generally assessed by the measurement of the waist circumference (WaistC) due to convenience [6], however the abdomen contains both subcutaneous (SAT) and visceral (VAT) abdominal tissue and the VAT measurement is central to the pathogenesis of MetS [7,8].

Computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standards used to measure SAT and VAT and are endorsed by the International Diabetic Federation (IDF) [9,10]. The

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use of CT imaging is not always a preferential method due to the radiation exposure [9,11]. Consequently, several strategies aimed at reducing radiation dose to individuals are in place and include the use of CT single-slice measurements of SAT and VAT at the preferred anatomical level chosen [11,12]. Currently there is no consensus on the anatomical level for CT measurements, but it has been suggested that possibly all single-slice area-based CT measurements obtained at L1/2, L2/3, L3/4, the umbilicus, L4/5, L5/S1 are good indicators of SAT and VAT volume [12]. In this regard, a number of investigations have used the level of L4/L5 intervertebral disc space [12,13].

A number of studies concur that VAT is a metabolic organ that mostly contributes to the metabolic consequences of obesity [14,15], whilst reports regarding SAT are controversial [6,16–24]. Furthermore, in African Americans and black South Africans compared to Europeans from America and South Africa, the amount of VAT was found to be lower in the similar degrees of body mass index (BMI) [19–21]. These ethnic differences in the distribution of VAT and SAT may explain the observed differences between obesity and cardiometabolic risk factors [22–24]. Therefore, in this study we define the relationship between VAT, SAT, metabolic syndrome and its components in a mixed ancestry population from Africa.

2. Material and methods

2.1. Ethical approval

This investigation is based on the Cape Town Vascular and Metabolic Health (VMH) study, that has been approved by the Research Ethics Committees of the Cape Peninsula University of Technology (CPUT) and Stellenbosch University (respectively, NHREC: REC - 230 408–014 and N14/01/003). For this sub-study, ethical approval was also obtained from the CPUT Health and Wellness Sciences Research Ethics Committee (CPUT/HW-REC 2015/H18). The study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants signed written informed consent after all the procedures had been fully explained in the language of their choice.

2.2. Study design and procedures

This was a prospective cross-sectional study involving participants from the ongoing Cape Town Vascular and Metabolic Health (VMH) study. VMH is an extension of the Cape Town Bellville South study, which has been described in detail previously [25,26]. The current study population consisted of 401 individuals ($n = 93$ men and $n = 308$ women) of mixed ancestry residing in Bellville-South, Cape Town, South Africa. Participants younger than 20 years, pregnant women, acutely ill individuals as well as individuals not eligible for CT scans (for example those with a pacemaker) were excluded from the study. All the participants were evaluated with respect to anthropometric, blood pressure measurements, CT assessments (SAT and VAT) and biochemical analyses {oral glucose tolerance test (OGTT), glycated haemoglobin (HbA1C), lipids, insulin and C-reactive protein (CRP)}. Body weight (to the nearest 0.1 kg) was measured with the subject in light clothing and without shoes, using an Omron body fat meter HBF-511 digital bathroom scale, which was calibrated and standardized using a weight of known mass. Waist circumference was measured using a non-elastic tape at the level of the narrowest part of the torso, as seen from the anterior view. The hip circumference was also measured using a non-elastic tape around the widest portion of the buttocks. All anthropometric measurements were performed three times and

their average used for analysis. Standard measures were used to measure height to the nearest centimetre using a stadiometer with subjects standing on a flat surface at a right angle to the vertical board of the stadiometer. The blood pressure was taken three times at 3-min intervals (World Health Organization, 2012) using a semi-automatic digital blood pressure monitor (Omron M6 comfort-preformed cuff BP Monitor) on the right arm in sitting position and at rest for at least 10 min. The lowest systolic blood pressure (SBP) and corresponding diastolic blood pressure (DBP) readings were used. The CT scan of the abdomen took place during the same week of the first examination and weight measurements were also repeated on the day of the scan. The CT examinations were conducted using a GE 16 slice Lightspeed CT scanner with a software program, Vitrea Core Version 6.4.4083.268 for abdominal imaging at level L4/L5 intervertebral disc space. Metabolic syndrome (MetS) classification was adapted from JIS criteria [2] which includes the presence of any three of the following conditions, with population- and country-specific definitions for WaistC recommended (Alberti et al., 2009): WaistC: ≥ 90 cm for both men and women [27], fasting blood glucose (FBG): ≥ 5.6 mmol/L, systolic blood pressure (SBP): ≥ 130 mmHg, diastolic blood pressure (DBP): ≥ 85 mmHg, high density lipoprotein cholesterol (HDL): men ≤ 1 mmol/L and women ≤ 1.3 mmol/L and Triglycerides: ≥ 1.7 mmol/L. Obesity was classified according to the BMI, using guidelines from the international classification of adult obesity (WHO, 2004, updated 2016) as follows: normal weight: 18.50–24.99 kg/m², overweight: ≥ 25.00 –29.99 kg/m² and obese: ≥ 30.00 kg/m². All participants underwent a 75 g OGTT and glucose tolerance status was defined as recommended by the WHO [5].

2.3. Sample size

The sample size was an important factor as the study used radiation to achieve one of its objectives. In order to obtain a representative sample, the following formula was used to calculate the sample size based on the prevalence of MetS (62%) previously reported in this population [25]:

$$n = \frac{z^2(pq)}{e^2} \rightarrow n = \frac{1.96^2(62 \times 38)}{5^2} \rightarrow n = 362 \text{ participants needed}$$

n = Sample size

z = Standard error association with chosen level of confidence

p = Estimated percentage in population affected

$q = 100 - p$

e = Acceptable sample error

2.4. Statistical analysis

Data was analysed using the software program Statistica (StatSoft, Southern Africa) and SPSS v.24 (IBM Corp, 2011). Distribution testing was done using the Shapiro–Wilk W test, based on the probability thresholds of $p > 0.1$. Skewed data was log transformed before analysis. General characteristics of the study participants are summarized as mean $\pm$ standard deviation (SD) for continuous variables and number (%) for categorical variables. The Pearson's partial correlation test was used for correlation analysis (R and P-values) between appropriate variables and a multivariable linear regression was used to assess the effects of VAT and SAT on the components of MetS. VAT and SAT was recategorised into quartiles with odds ratio (OR) being estimated for MetS, hypertension and hyperglycaemia using logistic regression, with the first quartile being used as the reference range. A P-value of less than 0.05 was considered to indicate statistical significance.

3. Results

The clinical characteristics, categorised by gender and MetS status are summarized in Table 1. In a total of 401 participants, 93 (23.2%) were male and 308 (76.8%) were females. In the total group, 223 (55.6%) had MetS ($n =$ and 141 (41%) had hyperglycaemia (diabetes, or IFG and/or IGT). Age, SAT, VAT, blood pressure, anthropometric, glycaemic indices, triglycerides, were significantly increased ($p \leq 0.0174$) whilst HDL cholesterol was reduced ($p < 0.0001$) in subjects with MetS in both genders. In men, smoking was more prevalent in subjects without MetS ($p < 0.0001$). In age and BMI adjusted Pearson correlations, the hip circumference showed a negative correlation with VAT in men and women ($r \geq -0.162$, $p \leq 0.035$), but a positive correlation with SAT in women ($r = 0.394$, $p < 0.001$). In women, glycaemic indices (blood glucose, glycated haemoglobin, insulin levels) and triglycerides correlated positively with VAT ($r \geq 0.177$, $p \leq 0.002$), but in men, triglycerides, post 2-h glucose and post 2-h insulin correlated positively with SAT ($r \geq 0.267$, $p \leq 0.023$). On the other hand, post 2-h insulin showed a negative correlation with SAT ($r = -0.164$, $p = 0.012$) (Table 2).

In logistic regression, adjusted for age, gender, BMI, smoking, alcohol use, hypertension, diabetes and dyslipidaemia treatment (for women also adjusted for menopausal age) increasing quartiles of VAT were associated with MetS {OR (95% confidence interval) ≥ 4.14 (1.92–8.93), $p < 0.001$ } and any type of hyperglycaemia (≥ 4.45 (1.89–10.47), $p \leq 0.001$). Lower quartiles of SAT were associated with metabolic syndrome (≥ 2.66 (1.06–6.69), $p \leq 0.037$). Neither VAT nor SAT was associated with hypertension, all $p > 0.05$ (Table 3). In gender specific multivariate linear regression models, adjusted for age, BMI, smoking, alcohol use, hypertension, diabetes and dyslipidaemia treatment (for women also adjusted for menopausal age), fasting blood glucose levels, and triglycerides were associated with VAT in both genders, $p \leq 0.02$. However, in women only, post 2-h plasma glucose, insulin levels, glycated haemoglobin were also associated with VAT ($p \leq 0.02$), whilst the association was negative with high density lipoprotein cholesterol ($p = 0.013$). Contrasting, in men, post 2-h plasma glucose, insulin levels and triglycerides were associated with SAT as well ($p \leq 0.012$) (Table 4).

4. Discussion

In this community based study our principal findings are two-fold. First, higher VAT volume is associated with MetS and hyperglycaemia in men and women from this study. Second, we highlight the gender differences with regards to the relationship between SAT and metabolic syndrome in this population. In women for example, lower SAT was linked to increased MetS risk, whilst in men higher SAT was associated with individual components (post 2-h plasma glucose, insulin levels and triglycerides) of MetS.

Results from this study concur with a number of reports from different populations and ethnicities which have identified VAT as an important risk factor for the MetS, impaired glucose tolerance, dyslipidemia and hypertension [7,8,28,29]. The potential mechanisms implicated include the insulin resistance promoting effects of the proinflammatory molecules secreted by both VAT and SAT [30]. However, VAT and its adipose-tissue resident macrophages secrete larger amounts of these factors such as complement component 3 (C3) and tumor necrosis factor- α compared to SAT [31]. Our findings with regards to SAT add to the controversies surrounding the association between SAT and MetS. Previous studies have suggested that SAT may be a protective factor against some MetS components due to the observed lower fasting glucose levels in diabetic patients with higher SAT [28,32–34]. A study of South African women showed that SAT reduced the risk of impaired fasting glucose [32]. These findings have been further strengthened by a recent longitudinal study which linked higher SAT at baseline to a reduced risk of some MetS components, leading to the authors suggesting that SAT may be a possible ‘metabolic sink’ for metabolic abnormalities [28]. Although our study findings support this notion especially with regards to women, we observed significant associations between SAT and MetS components in men. These gender differences may partially be explained by a gender, body size and shape effect. In this study, women had lower waist to hip ratio compared to men indicating a comparatively more gynoid (pear) shaped which is associated with less metabolic complications and a lesser risk of MetS [34–36]. Furthermore, we also showed a positive correlation with SAT and weak negative correlation with VAT and hip circumference in women. Women are known to have more SAT than men, especially in the abdominal and gluteofemoral area and

Table 1
The baseline characteristics, categorised by both gender and MetS status.

	Men		P-value	Women		P-value
	MetS/No, n = 46	MetS/Yes, n = 47		MetS/No, n = 132	MetS/Yes, n = 176	
Age (years)	51.8 $\pm$ 15.5	58.7 $\pm$ 13.4	0.0243	49.9 $\pm$ 16.0	56.0 $\pm$ 11.7	0.0001
Total fat (cm ²)	164.7 $\pm$ 158.9	376.8 $\pm$ 164.5	<0.0001	385.7 $\pm$ 173.8	576.1 $\pm$ 175.5	<0.0001
VAT (cm ²)	56.8 $\pm$ 75.4	132.2 $\pm$ 71.9	<0.0001	71.3 $\pm$ 43.4	131.7 $\pm$ 57.8	<0.0001
SAT (cm ²)	108.6 $\pm$ 103.3	244.6 $\pm$ 124.0	<0.0001	314.1 $\pm$ 145.8	441.1 $\pm$ 153.3	<0.0001
VAT to SAT ratio	0.91 $\pm$ 1.09	0.61 $\pm$ 0.37	0.0775	0.24 $\pm$ 0.14	0.34 $\pm$ 0.26	0.0002
BMI (kg/m ²)	23.5 $\pm$ 7.7	29.3 $\pm$ 5.8	0.0001	28.2 $\pm$ 7.1	35.2 $\pm$ 7.1	<0.0001
Waist circumference (cm)	85.6 $\pm$ 16.7	102.5 $\pm$ 13.2	<0.0001	90.4 $\pm$ 14.9	106.4 $\pm$ 12.8	<0.0001
Hip circumference (cm)	97.1 $\pm$ 14.2	104.7 $\pm$ 10.3	0.0040	106.9 $\pm$ 13.2	117.9 $\pm$ 14.9	<0.0001
Systolic blood pressure (mmHg)	125.6 $\pm$ 25.8	146.3 $\pm$ 23.2	0.0001	116.8 $\pm$ 18.7	136.0 $\pm$ 20.2	<0.0001
Diastolic blood pressure (mmHg)	80.0 $\pm$ 14.2	90.9 $\pm$ 12.6	0.0002	76.0 $\pm$ 9.5	87.3 $\pm$ 11.3	<0.0001
Fasting blood glucose (mmol/L)	5.15 $\pm$ 1.88	6.28 $\pm$ 2.38	0.0124	5.06 $\pm$ 1.57	7.02 $\pm$ 3.69	<0.001
Post 2-h glucose (mmol/L)	5.63 $\pm$ 2.25	7.85 $\pm$ 4.27	0.0050	6.51 $\pm$ 2.51	8.23 $\pm$ 3.40	<0.001
HbA1c (%)	5.94 $\pm$ 1.24	6.41 $\pm$ 1.32	0.0798	5.81 $\pm$ 1.04	6.98 $\pm$ 1.91	<0.001
Fasting insulin (mIU/L)	7.2 $\pm$ 11.5	10.5 $\pm$ 6.4	0.0963	7.1 $\pm$ 4.51	12.7 $\pm$ 9.4	<0.001
Post 2-h insulin (mIU/L)	36.0 $\pm$ 49.8	70.7 $\pm$ 59.2	0.0067	52.7 $\pm$ 39.5	85.6 $\pm$ 63.8	<0.001
Hyperglycaemia, N (%)	12 (26.1)	24 (51.1)	0.0134	28 (21.2)	101 (57.4)	<0.0001
HDL-cholesterol (mmol/L)	1.32 $\pm$ 0.31	1.09 $\pm$ 0.30	0.0009	1.45 $\pm$ 0.37	1.22 $\pm$ 0.25	<0.0001
LDL-cholesterol (mmol/L)	3.12 $\pm$ 0.94	3.43 $\pm$ 1.11	0.1593	3.22 $\pm$ 1.03	3.50 $\pm$ 0.93	0.0111
Cholesterol (mmol/L)	5.07 $\pm$ 1.04	5.34 $\pm$ 1.27	0.2773	5.29 $\pm$ 1.17	5.48 $\pm$ 1.08	0.1375
Smokers, N (%)	25 (54.3)	15 (31.9)	<0.0001	48 (36.9)	51 (29.1)	0.3074
Drinkers, N (%)	18 (39.1)	15 (31.9)	0.2063	26 (19.8)	18 (10.2)	0.0405

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

Table 2

Pearson's partial correlation adjusted for age and BMI.

	VAT (cm ²)				SAT(cm ²)			
	Male		Female		Male		Female	
	R	P-value	R	P-value	R	P-value	R	P-value
Waist circumference (cm)	0.381	<0.001	0.33	<0.001	0.283	0.007	0.179	0.002
Hip circumference (cm)	−0.224	0.035	−0.162	0.005	0.088	0.414	0.394	<0.001
Systolic blood pressure (mmHg)	−0.125	0.244	0.092	0.116	0.113	0.292	−0.073	0.213
Diastolic blood pressure (mmHg)	−0.177	0.096	0.067	0.254	0.147	0.169	0.03	0.61
Fasting blood glucose (mmol/L)	−0.088	0.412	0.132	0.024	0.142	0.183	−0.020	0.729
Post 2-h glucose (mmol/L)	0.010	0.931	0.266	<0.001	0.267	0.023	−0.078	0.225
HbA1c (%)	0.15	0.16	0.183	0.002	0.041	0.701	−0.04	0.494
Fasting insulin (mIU/L)	0.071	0.515	0.233	<0.001	0.179	0.098	−0.056	0.337
Post 2-h insulin (mIU/L)	0.080	0.500	0.300	<0.001	0.412	<0.001	−0.164	0.012
LDL-cholesterol (mmol/L)	−0.09	0.406	0.021	0.724	0.104	0.336	−0.015	0.796
HDL-cholesterol (mmol/L)	−0.068	0.529	−0.112	0.057	−0.128	0.238	−0.06	0.308
Cholesterol (mmol/L)	−0.144	0.182	0.032	0.58	0.091	0.4	−0.026	0.657
Triglycerides ^a	−0.0928	0.6170	0.327	<0.001	0.281	0.008	−0.075	0.203

^a Log transformed.**Table 3**

Logistic regression, adjusted for age, gender, BMI, smoking, alcohol use, hypertension treatment, diabetes treatment and dyslipidemia treatment.

	Odds Ratio (95% confidence interval)	P-value
MetS ^a		
VAT (cm ²) Q1	1.00	
VAT (cm ²) Q2	4.14 (1.92–8.93)	<0.001
VAT (cm ²) Q3	5.34 (2.31–12.34)	<0.001
VAT (cm ²) Q4	24.85 (8.05–76.75)	<0.001
SAT (cm ²) Q1	1.00	
SAT (cm ²) Q2	2.77 (1.34–5.75)	0.006
SAT (cm ²) Q3	2.66 (1.06–6.69)	0.037
SAT (cm ²) Q4	2.64 (0.76–9.13)	0.125
Hypertension ^b		
VAT (cm ²) Q1	1.00	
VAT (cm ²) Q2	1.76 (0.84–3.68)	0.131
VAT (cm ²) Q3	1.06 (0.47–2.37)	0.887
VAT (cm ²) Q4	1.33 (0.47–3.71)	0.590
SAT (cm ²) Q1	1.00	
SAT (cm ²) Q2	1.02 (0.49–2.11)	0.957
SAT (cm ²) Q3	1.08 (0.42–2.78)	0.875
SAT (cm ²) Q4	0.93 (0.25–3.44)	0.916
Hyper-glycaemia ^c		
VAT (cm ²) Q1	1.00	
VAT (cm ²) Q2	2.15 (0.96–4.82)	0.064
VAT (cm ²) Q3	4.45 (1.89–10.47)	0.001
VAT (cm ²) Q4	7.20 (2.57–20.13)	0.0001
SAT (cm ²) Q1	1.00	
SAT (cm ²) Q2	2.07 (1.00–4.29)	0.051
SAT (cm ²) Q3	1.70 (0.72–4.01)	0.230
SAT (cm ²) Q4	0.63 (0.20–2.00)	0.433

{odds ratio (95% confidence interval) ≥ 4.14 (1.92–8.93), p < 0.001}.

^a Not adjusted for hypertension treatment, diabetes treatment and dyslipidaemia treatment.^b Not adjusted for hypertension treatment.^c Not adjusted for diabetes treatment.

this promotes the storage of meal derived triglyceride-fatty acids in SAT than in men [36,37]. The storage of fat following a meal necessitates the inhibition of lipolysis and an increase in circulating insulin, consequently an increase insulin sensitivity in women compared to men [38].

The strength of this study lies in the use of CT scan which can differentiate SAT and VAT and the use of oral glucose tolerance test to assess glycaemic status. This was a population-based cohort of mixed ancestry South Africans, however similar findings have also been reported in other South African population groups [19–24,36]. Another limitation includes the cross-sectional nature of the study which precludes drawing inferences on the direction of

Table 4

Gender specific multivariate linear regression models, adjusted for age, BMI, smoking, alcohol use, hypertension, diabetes and dyslipidemia treatment (for women also adjusted for menopausal age).

	Men		Women	
	β	P-value	β	P-value
Systolic blood pressure (mmHg)				
VAT	−0.019	0.739	0.048	0.096
SAT	0.036	0.270	−0.018	0.258
Diastolic blood pressure (mmHg)				
VAT	−0.041	0.238	0.026	0.130
SAT	0.029	0.152	0.005	0.582
Fasting blood glucose (mmol/L)				
VAT	−0.013	0.003	0.004	0.152
SAT	0.004	0.093	0.002	0.379
Post 2-h glucose (mmol/L) ^a				
VAT	−0.006	0.515	0.023	<0.001
SAT	0.012	0.012	−0.003	0.187
HbA1c (%)				
VAT	−0.002	0.371	0.004	0.020
SAT	0.001	0.480	<0.001	0.618
Fasting insulin (mIU/L)				
VAT	0.004	0.854	0.041	<0.001
SAT	0.017	0.133	−0.005	0.431
Post 2-h insulin (mIU/L) ^a				
VAT	0.100	0.496	0.449	<0.001
SAT	0.283	<0.001	−0.130	0.006
Triglycerides (mmol/L) ^b				
VAT	0.999	0.010	1.002	<0.001
SAT	1.001	0.010	1.001	0.358
HDL-cholesterol (mmol/L)				
VAT	<0.001	0.898	−0.001	0.013
SAT	−0.001	0.225	<0.001	0.459
LDL-cholesterol (mmol/L)				
VAT	−0.001	0.619	0.001	0.44
SAT	0.001	0.607	<0.001	0.557
Cholesterol (mmol/L)				
VAT	−0.002	0.385	0.0011	0.468
SAT	0.001	0.657	−0.001	0.542

^a Not adjusted for diabetes treatment.^b Exponential value.

the associations. Although correlations in this study were significant, they were weak. Thus, findings of this study should be treated with caution and need to be validated in a larger cohort. In conclusion, our study shows that increased VAT and decreased SAT are associated with metabolic syndrome, but in men increased SAT has deleterious effects to metabolic syndrome components, particularly blood glucose levels and insulin. Therefore, in men increased SAT may like VAT increase the risk of diabetes

development. The findings of this study should be treated with caution because the correlation.

Statement of authorship

TEM: conception and design of the study, acquisition of data, drafting of the article, final approval of the version to be published; responsible for ensuring that all authors have agreed 1) to be authors and to be listed in the order specified by the submitting author; 2) to the manuscript's content; and 3) to its submission to the journal. **SI:** acquisition of data, analysis and interpretation of data; and final approval of the version to be published. **AS:** revising it for important content; final approval of the version to be published. **GMH:** acquisition of data, analysis and interpretation of data; revising it for important content; final approval of the version to be published. **SD:** analysis and interpretation of data; revising it for important content; final approval of the version to be published. **RTE:** conception and design of the study revising it for important content; final approval of the version to be published. **APK:** conception and design of the study analysis and interpretation of data; revising it for important content; final approval of the version to be published.

Conflict of interest statement

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clnesp.2019.04.010>.

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