RESEARCH

Ethnic differences in regional adipose tissue oestrogen receptor gene expression

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Abstract

Studies have shown ethnic differences in body fat distribution, characterised by greater peripheral and less central fat accumulation in black compared to white South African (SA) women. As sex hormones play an important role in body fat distribution, our study aimed to determine whether differences in body fat distribution between black and white SA women were associated with subcutaneous adipose tissue (SAT) expression of oestrogen receptors (*ERA* and *ERB*) and aromatase (*CYP19A1*). Body fat distribution (DXA and CT) and *ERA*, *ERB* and *CYP19A1* expression in abdominal and gluteal SAT were measured in 26 black and 22 white SA women. Abdominal SAT *ERA* and *ERB* did not differ by ethnicity or BMI. Gluteal *ERA* was higher (1.08 ± 0.06 vs 0.99 ± 0.05, $P < 0.001$) and *ERB* was lower (0.99 ± 0.06 vs 1.10 ± 0.07, $P < 0.001$) in black vs white SA women. *CYP19A1* increased with obesity in all depots ($P < 0.001$). In both black and white SA women, gluteal *ERA* was associated with lower central fat mass (FM) and greater gynoid FM ($P < 0.05$), while the inverse association was shown for *CYP19A1* in all depots ($P < 0.01$). In conclusion, ethnic differences in gluteal *ERA* expression were associated with differences in body fat distribution previously reported between black and white SA women.

Key Words

- oestrogen receptor
- aromatase
- adipose tissue
- ethnicity
- gluteal fat
- abdominal fat

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Introduction

Sex hormones are important determinants of regional body fat distribution, as evidenced by gender differences in body fat distribution. Indeed, an increase in oestrogen levels are related to greater gynoid body fat deposition (1), whereas circulating oestrogen deficiency, experienced during the menopausal transition, is associated with an increase in central fat mass (FM), which is reduced with hormone replacement therapy (2, 3). Central or upper-body fat accumulation, which comprises both visceral (VAT) and subcutaneous adipose tissue (SAT), is commonly associated with increased cardiometabolic risk, whereas lower-body gluteo-femoral fat accumulation may be protective (4, 5).

Within adipose tissue, aromatase (*CYP19A1*) converts androstenedione to oestrone followed by the conversion to oestrogen (6). *CYP19A1* expression was shown to be greater in women with gynoid-type obesity compared to upper-body obesity (7). The effects of oestrogen in adipose tissue are mediated by oestrogen receptors (ERs), ERA and ERB, which are expressed in human adipose tissue (8, 9). It has been demonstrated that ERA and ERB have different actions, and ERB may even oppose the actions of ERA (10). Oestrogen receptor knockout (ERKO) mice present with high levels of VAT, insulin resistance and impaired glucose tolerance (11, 12, 13). Human studies have demonstrated regional differences in adipose tissue *ERA*, *ERB* and *CYP19A1* expression, which may be altered by sex and age (9, 14, 15, 16). Further, *ERA* expression is reduced in obese premenopausal women, and expression increases after weight reduction (17). In contrast,

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ERB, but not *ERA*, was significantly higher in adipose tissue of postmenopausal compared to premenopausal women (18).

Studies in the USA and South Africa (SA) have shown that at the same level of BMI, black African women have greater peripheral (gluteo-femoral) FM and abdominal superficial subcutaneous adipose tissue (SSAT), but less VAT than their white counterparts (19, 20, 21). We hypothesised that the ethnic difference in body fat distribution between black and white SA women may be associated with differences in the SAT gene expression of *ERA*, *ERB* and *CYP19A1*.

Accordingly, in a sample of black and white SA women, we aimed to (i) examine the differences in *ERA*, *ERB* and *CYP19A1* gene expression in abdominal and gluteal SAT depots and (ii) explore the ethnic-specific associations between gene expression and body fat distribution.

Materials and methods

The study included 13 normal-weight and 13 obese black and 11 normal-weight and 11 obese white SA women who were recruited as described previously (22, 23). In summary, inclusion criteria were (i) age 18-45 years; (ii) no known diseases or taking any medication for metabolic disorders; (iii) not currently pregnant, lactating or postmenopausal and (iv) of self-reported Xhosa ancestry or white SA ancestry (both parents). This study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. Consent was obtained from each participant after full explanation of the purpose and nature of all procedures used.

Total body FM and android and gynoid regions of interest (ROI) were measured by dual-energy X-ray absorptiometry (DXA, Discovery-W, software version 12.7.3.7, Hologic, Bedford, MA, USA). Android and gynoid ROI were defined automatically using the Hologic software. The android ROI is defined as the area around the waist, with the upper demarcation a 5th of the distance from neck to waist cut-line and the lower demarcation at the top of the pelvis. The gynoid ROI is twice the height of the android ROI with the upper demarcation below the top of the iliac crest at a distance of 1.5 times the android height. Abdominal VAT, deep subcutaneous adipose tissue (DSAT) and SSAT were measured by CT (Toshiba X-press Helical Scanner, Toshiba). Fasting blood samples were drawn for the analysis of serum oestradiol (E2) concentrations using two-site sandwich immunoassay (Centaur, Siemens). Adipose biopsies were obtained from the DSAT, SSAT and gluteal SAT depots using a mini liposuction method (23). Total RNA was isolated using the QIAGEN RNeasy system (QIAGEN Ltd.), and RT-PCR performed using a StepOnePlus real-time PCR detection system (Applied Biosystems) and TaqMan gene expression assays (Applied Biosystems): *ERA* (Hs00174860_m1), *ERB* (Hs00230957_m1/Hs01100353_m1), *CYP19A1* (Hs00903413_m1/Hs00240671_m1), *18S* (Hs99999901_s1), *RPLPO* (Hs99999902_m1) and *Cyclophilin* (*PPIA*) (Hs04194521_s1). Transcript levels are presented as the ratio of abundance of the gene of interest to the mean of abundance of *18S*, *PPIA* and *RPLPO*.

Results were analysed using STATA 14 (StataCorp). Normality was tested using Shapiro–Wilk test and presented as mean±standard deviation for normally distributed data or median and interquartile range for VAT, which was skewed. Significance was set as $P<0.05$. Differences between ethnic and BMI groups were analysed using two-way ANOVA. Depot-specific differences in gene expression were assessed using repeated-measures mixed models, exploring the interaction with ethnicity and BMI. Pearson's correlation coefficients were used to explore bivariate associations between gene expression and body composition in black and white women separately.

Results

Participant characteristics

Participant characteristics have been described in detail previously (22, 23) and are presented in Table 1. White and black SA women did not differ by age, BMI, body fat or DXA-derived regional fat distribution. While abdominal VAT and SSAT did not differ by ethnicity in normal-weight women, obese black SA women had less VAT and more SSAT than their white counterparts. Obese women had less gynoid %FM (% of total FM) and greater android %FM and greater VAT and SAT than normal-weight women. Circulating E2 levels and hormonal contraceptive use (data not shown) did not differ by ethnicity or BMI.

SAT gene expression

Differences in abdominal DSAT, SSAT and GLUT expression of *ERA*, *ERB* and *CYP19A1* gene expression between ethnicity and BMI groups are shown in Fig. 1A. Within the abdominal DSAT and SSAT depots, *ERA* and *ERB* did not differ by ethnicity or BMI group. However, within the gluteal depot, *ERA* was higher ($P<0.001$) and *ERB* was lower ($P<0.001$) in black vs white SA women,

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Table 1 Characteristics of normal-weight and obese white and black SA women.

	Normal weight		Obese	
	White	Black	White	Black
Age (years)	25 ± 4	23 ± 3	31 ± 8*	29 ± 8*
BMI (kg/m^2)	22.6 ± 1.5	23.0 ± 1.6	36.5 ± 6.3*	37.6 ± 3.7*
Fat (kg)	19.0 ± 5.1	17.7 ± 4.0	45.7 ± 12.3*	43.2 ± 6.7*
Fat (%)	29.2 ± 7.0	30.9 ± 5.8	45.7 ± 3.9*	47.3 ± 3.1*
Android (%FM)	6.0 ± 1.0	5.9 ± 0.7	8.9 ± 1.4*	9.0 ± 1.0*
Gynoid (%FM)	22.4 ± 2.9	21.2 ± 1.8	18.6 ± 2.3*	17.4 ± 2.1*
VAT (cm^2)	49 (41–77)	57 (46–117)	129 (91–203)*	94 (68–117)*,#
DSAT (cm^2)	79 ± 39	72 ± 25	270 ± 77*	258 ± 55*
SSAT (cm^2)	100 ± 34	102 ± 29	248 ± 49*	324 ± 85*,#
E2 (pg/mL)	249 ± 91	228 ± 125	174 ± 126	236 ± 76

Values are expressed as mean ± standard deviation or median and interquartile range. *P* values adjusted for age except for age.
*$P < 0.01$ for difference between obese vs normal-weight black or white women; #$P < 0.05$ for difference between obese black vs white women.
BMI, body mass index; DSAT, deep subcutaneous adipose tissue; E2, Oestradiol; FM, fat mass; SSAT, superficial subcutaneous adipose tissue; VAT, visceral adipose tissue.

irrespective of BMI. Moreover, *ERA* was lower in obese than normal-weight black and white SA women ($P=0.042$ and $P=0.012$, respectively). *CYP19A1* was higher in obese than normal-weight black and white SA women in all depots ($P<0.001$), and within the gluteal depot, *CYP19A1* was higher in black than white SA women ($P=0.030$).

Depot differences in *ERA* and *ERB* were not influenced by BMI category ($P>0.05$ for interaction) and hence normal-weight and obese women were combined to explore depot × ethnicity interactions in gene expression (Fig. 1B). Depot differences in gene expression were altered by ethnicity ($P<0.001$ for ethnicity × depot). In black SA women, *ERA* was highest in gluteal SAT, followed by DSAT ($P=0.048$) and then SSAT ($P<0.001$), whereas in white SA women, *ERA* was greater in DSAT than SSAT ($P=0.011$) and gluteal SAT ($P=0.025$). In contrast, in black SA women, *ERB* was the highest in DSAT, followed by gluteal SAT and then SSAT ($P<0.01$ for all depots), whereas in White SA women, *ERB* was the highest in the gluteal depot, followed by the DSAT and SSAT depots ($P<0.01$ for all depots). In both black and white SA women, *CYP19A1* was higher in gluteal SAT than SSAT ($P<0.001$) and DSAT ($P<0.001$).

Associations between gene expression and body fat and its distribution

Associations between body fat and its distribution and gluteal *ERA* and *CYP19A1* mRNA levels are shown in Fig. 2A and B, respectively. Gluteal *ERA* was associated with lower %FM in white SA women only. In both black and white SA women, gluteal *ERA* was associated with greater gynoid %FM, and lower android %FM, DSAT ($r=-0.45$, $P=0.032$ and $r=-0.51$, $P=0.021$) and SSAT, but not VAT (Fig. 2, Panel A). No associations between gluteal *ERB* or DSAT and SSAT *ERA* and *ERB* and body fat and its distribution were observed for black or white SA women (data not shown). For both black and white SA women, *CYP19A1* in all depots was similarly associated with increased total FM and central FM and reduced gynoid %FM (Fig. 2, Panel B).

Discussion

We show for the first time ethnic and regional differences in the expression of *ER* genes between black and white SA women that associated with body fat distribution. The novel and main finding of this study was the markedly elevated *ERA* and reduced *ERB* mRNA levels in the gluteal depot of black compared to white SA women, which accounted for the ethnic differences in regional gene expression. These differences were not explained by ethnic differences in E2 levels, which are known to regulate SAT expression of *ERA* and *ERB* similarly (9), as E2 levels did not differ between groups. Further, *CYP19A1* expression, responsible for local production of E2, was similar between ethnicities, albeit higher in the gluteal depot of black than white SA women.

To our knowledge, Gavin *et al.* (15) is the only other study that has described ethnic differences in regional protein expression of ERs in a small sample of Caucasian ($n=7$) and African American ($n=8$) women. They showed that ERA protein expression was higher in abdominal compared to gluteal depot, and this was largely driven by the Caucasian women, with no differences in African American women. In contrast, ERB expression was higher in the gluteal depot and not different between ethnicities.

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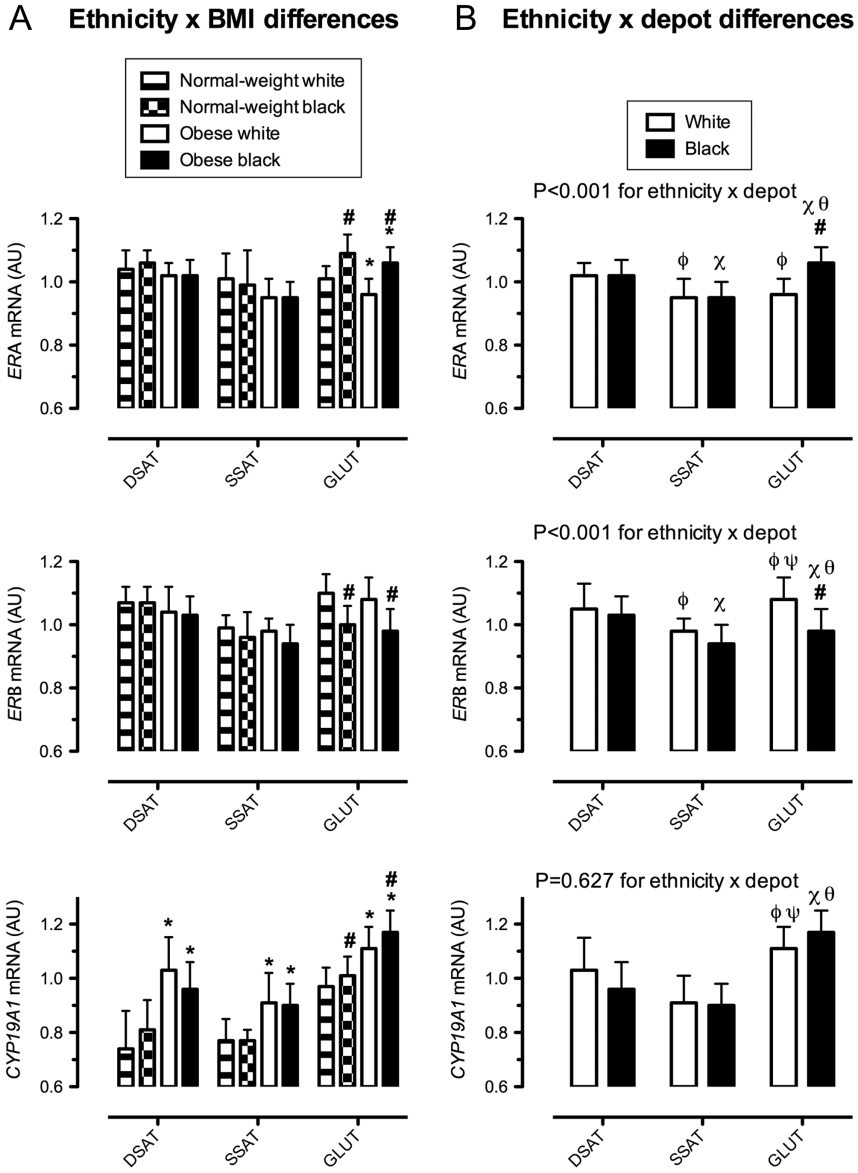

Figure 1
Expression of genes in abdominal deep subcutaneous adipose tissue (DSAT), superficial subcutaneous adipose tissue (SSAT) and gluteal (GLUT) depots of normal-weight and obese, white and black SA women. Panel A: Ethnic and BMI differences in gene expression within each depot. Bars represent mean ± standard deviation. $^{*}P < 0.05$, obese vs normal-weight; $^{\#}P < 0.05$, black vs white SA women. Panel B: Depot and ethnic (combining normal-weight and obese groups) differences in gene expression. Bars represent mean ± standard deviation. $^{\#}P < 0.05$, black vs white SA women; $^{\phi}P < 0.05$ for differences to DSAT in White SA women; $^{\varphi}P < 0.05$ for differences to SSAT in White SA women; $^{\chi}P < 0.05$ for differences to DSAT in black SA women; $^{\theta}P < 0.05$ for differences to SSAT in black SA women. CYP19A, aromatase; ERA, oestrogen receptor alpha; ERB, oestrogen receptor beta.

These findings are largely supported by the mRNA results from the white SA women in our study, as well as by other small studies of premenopausal women (8, 9). Differences in the findings between the African American and the black SA women may merely be due to a sample size effect ($n=7$ vs $n=26$, respectively), but may also be confounded by the fact that the African American women had greater centralisation of body fat (android FM) than their white counterparts. Alternatively, differences in genetics, lifestyle (diet and physical activity) and environmental factors may have also played a role.

Notably, in both black and white SA women, greater expression of *ERA* (and not *ERB*) in gluteal, and not abdominal SAT, was associated with less central SAT and greater peripheral FM. In contrast to our findings, Gavin *et al.* (15) found that ERA protein expression in the abdominal and gluteal regions was not associated with any anthropometric measure of body fat distribution, but lower gluteal ERB protein expression and a higher ERA/ERB were associated with higher WHR. The findings of Gavin *et al.* (15) are surprising given that studies of global *ERA*-knockout (ERKO) mice models have shown that ERKA mice have increased FM, and specifically greater VAT compared to WT mice (11). In contrast, body composition does not differ between *ERB*-knockout (ERKO) mice and WT mice (13), suggesting that *ERB* has a limited impact on body composition. Although the mechanisms are not entirely clear, Nilsson *et al.* (24) showed an inverse correlation between abdominal *ERA* expression and basal lipolysis and adrenoceptor responsiveness in

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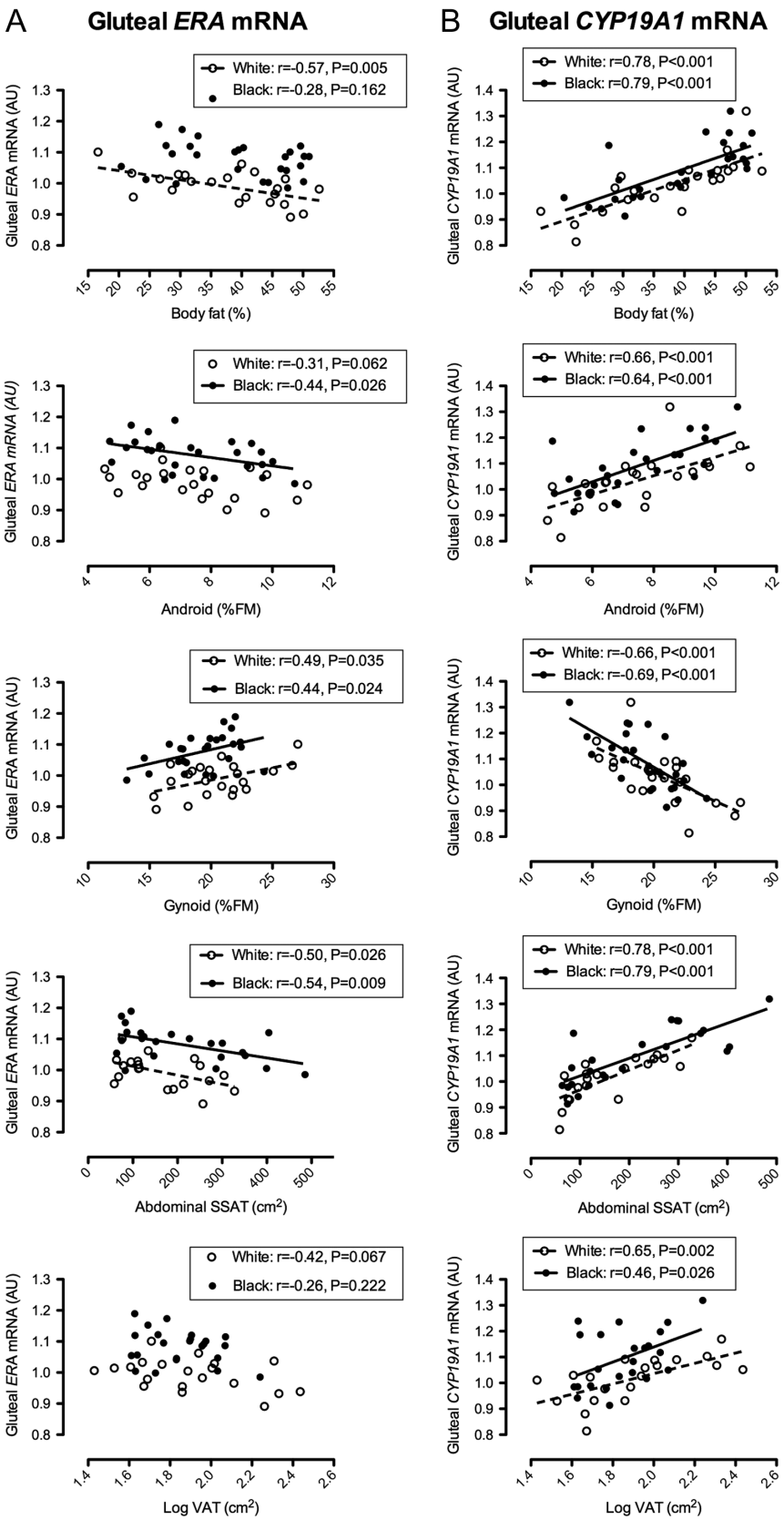

Figure 2
Associations between gluteal *ERA* mRNA (A) and *CYP19A1* (B) expression and measures of body fat and its distribution in black and white South African women. Values are Pearson correlation coefficients. FM, fat mass, SSAT, superficial subcutaneous adipose tissue; VAT, visceral adipose tissue.

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obese women, possibly explaining the greater peripheral and lower central fat patterning in black compared to white SA women in this study. More recently, adipose-specific *ERA*-knockdown studies in mice have shown that decreased adipose tissue *ERA* results in larger, fibrotic and inflamed adipocytes (25). We propose that the higher *ERA* expression in the gluteal depot of black SA women may protect these depots from adipocyte hypertrophy, fibrosis and inflammation, providing a favourable site for storage of excess fatty acids and protecting against central accumulation of fatty acids (26, 27).

Studies in humans have shown reduced abdominal SAT *ERA* gene expression in obese compared to normal-weight premenopausal women and increased expression in response to weight loss (17). Although we showed no BMI effects on *ERA* expression in the abdominal depots, *ERA* expression was lower in the gluteal depot of obese vs normal-weight white SA women and to a lesser extent, in black SA women. Furthermore, obese women had less gluteal %FM and more android %FM than their normal-weight counterparts, supporting the associations between *ERA* expression and body fat distribution observed in black and white SA women.

Due to the cross-sectional nature of this study, it is not known if the associations reported are a cause or a consequence of obesity and the ethnic differences in body fat distribution. Larger studies including the functional assessment of oestrogen action are required to gain a greater understanding of these observations. Another limitation of the study is the absence of protein expression. However, it has been consistently shown that ERA and ERB protein expression corresponds to the mRNA levels, showing similar between-depot and gender differences (8, 9).

In conclusion, black SA women had greater gluteal *ERA* expression than white SA women. This study provides preliminary evidence that ethnic differences in gluteal *ERA* gene expression may explain the differences in body fat distribution previously reported between black and white SA women. Future studies including a larger, more representative sample of black and white SA women and incorporating more mechanistic aspects of oestrogen action are required to verify these findings.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

J H G and D K were involved in the study design, data collection and analysis, writing and approving the final manuscript for submission. M T was involved in data collection, analysis and writing of the manuscript.

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