

Adiposity and Exercise-Related Respiratory Exchange Ratio Response as Correlates of Cardiorespiratory Fitness in Women with Metabolic Syndrome According to Thyroid Status

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Research Article

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ARTICLE 1

Topic

Adiposity and Exercise-Related Respiratory Exchange Ratio Response as Correlates of Cardiorespiratory Fitness in Women with Metabolic Syndrome According to Thyroid Status

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Abstract

Background

Cardiorespiratory fitness in women with metabolic syndrome (MetS) may reflect the combined influence of adiposity, exercise-related substrate-use responses, and thyroid history. However, the relative associations of these factors with maximal oxygen uptake (VO_2max) remain insufficiently characterized, particularly in women with previously diagnosed and predominantly treated subclinical hypothyroidism (SCH).

Methods

This exploratory cross-sectional study analyzed baseline data from 24 women with MetS, including 16 with previously diagnosed SCH and 8 euthyroid women. Fifteen of the 16 women with SCH were receiving levothyroxine. Body composition was assessed by dual-energy X-ray absorptiometry (DXA), and cardiorespiratory fitness was assessed by cardiopulmonary exercise testing (CPET). The exercise-related respiratory exchange ratio response (ΔRER) was calculated as RER at maximal exercise minus resting RER. Associations with VO_2max were examined using correlation and prespecified exploratory multivariable linear regression. Basal metabolic rate was considered a secondary exploratory outcome.

Results

Analyses involving VO_2max included 23 participants. VO_2max did not differ significantly between the SCH and euthyroid groups (22.08 ± 3.48 vs. 24.28 ± 3.32 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Waist circumference ($r = -0.757$, $p < 0.001$) and body-fat percentage ($r = -0.675$, $p < 0.001$) were inversely correlated with VO_2max , whereas the bivariate association between ΔRER and VO_2max was not statistically significant ($r = 0.361$, p

= 0.091). In the primary multivariable model ($R^2 = 0.749$; adjusted $R^2 = 0.709$), greater waist circumference remained inversely associated with $VO_{2\max}$ ($B = -0.210$, 95% CI -0.279 to -0.142 ; $p < 0.001$), and greater ΔRER remained positively associated with $VO_{2\max}$ ($B = 17.709$, 95% CI 5.382 to 30.036 ; $p = 0.007$). Thyroid-status group was not statistically significant in this model ($B = -1.525$, 95% CI -3.276 to 0.225 ; $p = 0.084$). In a sensitivity model using body-fat percentage instead of waist circumference, adiposity and ΔRER remained significantly associated with $VO_{2\max}$, while previous SCH diagnosis also reached statistical significance, indicating sensitivity of the thyroid-status estimate to model specification.

Conclusions

In this small exploratory sample of women with MetS, adiposity and the exercise-related RER response showed consistent associations with $VO_{2\max}$ across multivariable models. Thyroid-status history was not significantly associated with $VO_{2\max}$ in the primary model, but its estimate varied in sensitivity analysis. These cross-sectional findings are hypothesis-generating and apply primarily to women with previously diagnosed, predominantly treated SCH.

Keywords: metabolic syndrome; cardiorespiratory fitness; $VO_{2\max}$; waist circumference; respiratory exchange ratio; subclinical hypothyroidism.

1. Introduction

Subclinical hypothyroidism (SCH) is characterized by elevated thyroid-stimulating hormone (TSH) concentrations in the presence of circulating thyroid hormone concentrations within the reference range and occurs predominantly in women [1–3]. Thyroid hormones participate in the regulation of carbohydrate and lipid metabolism, energy expenditure, and body-weight homeostasis, providing a physiological basis for the relationship between thyroid dysfunction and cardiometabolic alterations [3, 4]. SCH has also been associated with metabolic syndrome (MetS) and cardiovascular risk, conditions characterized by the coexistence of central adiposity and metabolic abnormalities such as dyslipidemia, elevated blood pressure, and impaired glucose regulation [5, 6].

Thyroid function may also be relevant to cardiorespiratory fitness because thyroid hormones contribute to energy metabolism, mitochondrial activity, and cardiovascular

responses during physical exertion. Nevertheless, exercise capacity in individuals with SCH remains incompletely characterized, particularly when SCH coexists with MetS [7]. Previous studies have reported altered functional or exercise-related responses in SCH, while the interaction between thyroid status, cardiometabolic characteristics, and maximal oxygen uptake (VO_2max) remains uncertain [8–10].

Adiposity represents another potentially important correlate of cardiorespiratory fitness in MetS, particularly when fat accumulation is centrally distributed. In parallel, the respiratory exchange ratio (RER) provides an indirect indication of relative carbohydrate and lipid oxidation, and the change in RER from rest to maximal exercise (ΔRER) can characterize the exercise-related shift in substrate utilization. Although this response is physiologically related to the broader concept of metabolic flexibility, ΔRER should not be considered a universally standardized direct measure of metabolic flexibility. Given the roles of adiposity, substrate utilization, and thyroid hormones in energy metabolism, examining these factors together may help characterize interindividual variability in VO_2max in women with MetS [11–13].

However, the relative associations of adiposity, the exercise-related RER response, and thyroid status with cardiorespiratory fitness remain insufficiently characterized in women with MetS, particularly in those with previously diagnosed and predominantly treated SCH. Therefore, this exploratory study aimed to investigate whether adiposity, the respiratory exchange ratio response to exercise (ΔRER), and thyroid status were associated with VO_2max in women with MetS, with basal metabolic rate (BMR) examined as a secondary exploratory outcome. Consistent with the hypothesis-generating nature of the study, we explored these associations rather than testing a confirmatory causal hypothesis.

2. Methods

This was an observational, cross-sectional, comparative analysis of 24 adult women diagnosed with metabolic syndrome, divided into two groups according to thyroid function: women with SCH (SCH group - $n = 16$) and euthyroid women (EU group - $n = 8$).

Participants were classified according to their previously established thyroid diagnosis. The SCH group comprised 16 women with a previous diagnosis of subclinical hypothyroidism, originally characterized by elevated serum thyroid-stimulating hormone (TSH) concentrations

with normal thyroxine (T4) levels. At the time of study assessment, 15 of the 16 women (93.8%) were receiving levothyroxine (LT4) replacement therapy and had TSH and T4 concentrations within the reference ranges reported by their respective laboratories. One participant had been recently diagnosed with SCH and was not receiving LT4 treatment. The euthyroid group comprised eight women without a previous diagnosis of thyroid dysfunction and with previous TSH and T4 results within laboratory reference ranges. Individual TSH and T4 values, the type of T4 assay (total or free), anti-thyroid peroxidase antibody (anti-TPO) concentrations, LT4 dose, duration of treatment, and time since SCH diagnosis were not systematically recorded and were therefore unavailable for analysis.

Metabolic syndrome was established during participant screening through a structured anamnesis combined with individual review of laboratory tests performed within the six months preceding study enrollment and available clinical and anthropometric information. Eligibility required the presence of at least three of five metabolic syndrome components, irrespective of the specific combination of criteria: increased waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-c), elevated blood pressure, and altered glucose metabolism. Antihypertensive treatment was considered as evidence of the blood-pressure component when applicable, as many participants were receiving pharmacological treatment for hypertension. Only women presenting at least three of these five components were included in the study. Body mass index, total cholesterol, and low-density lipoprotein cholesterol (LDL-c) were additionally assessed during screening as indicators of cardiometabolic status but were not counted as independent components toward the minimum of three criteria required for inclusion. Metabolic syndrome classification was determined before enrollment using the anamnesis and laboratory results obtained within the preceding six months.

BMR was assessed using an open-circuit spirometry system with direct analysis of expired gases in breath-by-breath collection mode (COSMED, Quark CPET model, Italy), under standardized resting and fasting conditions to minimize the influence of external factors on energy metabolism. During the procedure, participants remained at complete rest for 20 minutes in a quiet, temperature-controlled environment. BMR was calculated using the values obtained during the final 10 minutes of the assessment, a period in which greater stability of

respiratory variables is expected and, consequently, greater reliability in estimating resting energy expenditure.

Cardiorespiratory fitness was assessed by a maximal treadmill exercise test using the Modified Bruce protocol. Maximal oxygen uptake ($\text{VO}_{2\text{max}}$), as well as aerobic and anaerobic thresholds, was determined using an open-circuit spirometry system with direct analysis of expired gases in breath-by-breath collection mode (COSMED, Quark CPET model, Italy). The exercise-related RER response was quantified as the change in respiratory exchange ratio from resting conditions to maximal exercise (ΔRER), calculated as $\text{RER}_{\text{max}} - \text{RER}_{\text{rest}}$. Resting RER was obtained during the basal metabolic rate (BMR) assessment, whereas RER_{max} was obtained during the maximal cardiorespiratory test. ΔRER was used as an operational index of the change in substrate oxidation from resting conditions to maximal exercise and not as a direct or universally standardized measure of metabolic flexibility.

Body composition was assessed by dual-energy X-ray absorptiometry (DXA), allowing determination of fat mass, lean mass, body-fat percentage, and bone mineral density. In addition, anthropometric measurements were obtained to determine the waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR).

For assessment of maximal muscle strength, participants were instructed to perform the greatest possible number of repetitions with a given load. The 10RM load was defined as the load that allowed no more than 10 complete repetitions with appropriate technique. The load was progressively adjusted according to individual performance until the load corresponding to 10RM was determined. A recovery period of 3 to 5 minutes was provided between attempts to minimize fatigue and allow adequate performance in subsequent attempts. After determining the 10RM load, maximal strength equivalent to one repetition maximum (1RM) was estimated using the Lombardi correction, applying the correction factor corresponding to the number of repetitions performed. Tests were conducted under researcher supervision, with standardized range of motion, execution technique, and criteria for accepting repetitions. The estimated 1RM

leg press value was used as an indicator of lower-limb muscle strength, whereas the estimated bench press value was used as an indicator of upper-limb muscle strength.

Statistical analysis

Statistical analyses were performed using Jamovi. Continuous variables were initially inspected for distribution using histograms, Q-Q plots, boxplots, and the Shapiro–Wilk test. Continuous data are presented as mean $\pm$ standard deviation, and categorical variables as absolute and relative frequencies. Baseline differences between women with subclinical hypothyroidism and euthyroid women were examined using Welch’s independent-samples t-test for approximately normally distributed continuous variables. When the distribution was clearly non-normal or substantially influenced by outliers, the Mann–Whitney U test was used. All tests were two-tailed, with statistical significance set at $p < 0.05$.

Pearson correlation coefficients were calculated to examine the linear associations between VO_2max and prespecified anthropometric, body-composition, metabolic, and strength variables. Given the substantial overlap among adiposity measures, waist circumference and body-fat percentage were prioritized for interpretation as the principal indicators of central and total adiposity, respectively. Correlations involving BMI, body mass, hip circumference, waist-to-hip ratio, waist-to-height ratio, and fat mass were retained as exploratory analyses to characterize the consistency of the adiposity pattern rather than as independent findings. The correlation analyses were considered exploratory, and the Benjamini–Hochberg false discovery rate procedure was additionally applied as a sensitivity analysis to account for multiple comparisons.

The exercise-related RER response was operationalized as ΔRER , calculated as $\text{RER}_{\text{max}} - \text{RER}_{\text{rest}}$. ΔRER was interpreted as an index of the change in substrate oxidation pattern from rest to maximal exercise rather than as a direct or universally standardized measure of metabolic flexibility.

Multiple linear regression was used to explore variables associated with VO_2max after covariate adjustment. Because of the limited sample size, models were specified a priori based on physiological relevance and the observed bivariate associations rather than by automated stepwise variable selection. The primary model included waist circumference, ΔRER , and thyroid-status group as predictors. A sensitivity model replaced waist circumference with

body-fat percentage to evaluate the robustness of the observed association between adiposity and VO_2max . Multicollinearity was assessed using variance inflation factors (VIF), and residual assumptions were evaluated using Q-Q plots, residual-versus-fitted plots, the Shapiro–Wilk test, and inspection of influential observations using Cook’s distance. Given the limited sample size and the number of parameters included in the multivariable models, all regression analyses were considered exploratory and hypothesis-generating. Regression coefficients, confidence intervals, and model-fit statistics were therefore interpreted as estimates of association within the present sample rather than as confirmatory evidence.

BMR was treated as a secondary exploratory outcome. Between-group differences and bivariate associations were examined using the same procedures described above. A secondary exploratory multiple linear regression model including bone mineral density, ΔRER , and thyroid-status group was additionally evaluated because these variables showed the strongest associations with BMR in the present sample. Given the limited sample size and the secondary nature of this analysis, the model was considered hypothesis-generating rather than confirmatory, and its estimates were interpreted cautiously.

For analyses involving VO_2max , BMR, and cardiopulmonary exercise variables, the participant who had these variables recorded as zero because of incomplete testing was treated as having missing data for those specific analyses rather than as having physiological values of zero. Available valid baseline anthropometric data from this participant were retained for the corresponding analyses. Complete-case analysis was used for each regression model.

Ethics approval and consent to participate. The larger research protocol from which the present baseline analysis was derived was approved by the Research Ethics Committee of the Federal University of Rio Grande do Sul (CEP/UFRGS), Brazil (CAAE 89714825.7.0000.5347; approval no. 7.895.574). All participants provided written informed consent before participation. The protocol was approved in accordance with applicable Brazilian ethical regulations for research involving human participants.

3. Results

The study included 24 women with metabolic syndrome, of whom 16 were classified as having subclinical hypothyroidism and 8 as euthyroid. One participant did not have valid cardiopulmonary exercise and basal metabolic rate measurements; therefore, analyses involving VO_2max , basal metabolic rate, and related exercise variables included 23 participants

(15 with subclinical hypothyroidism and eight euthyroid women). Baseline anthropometric data from this participant were retained for the corresponding analyses. Participant characteristics and clinical/thyroid status are presented in Table 1, including age, body mass, height, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), previous SCH diagnosis, and medication use. In the SCH group, mean age was 50.07 ± 13.20 years, height was 161.03 ± 8.80 cm, body mass was 85.15 ± 16.71 kg, and BMI was 33.17 ± 7.84 kg/m². In the EU group, these values were 40.25 ± 13.24 years, 158.69 ± 6.08 cm, 83.31 ± 20.93 kg, and 32.74 ± 6.06 kg/m², respectively. Resting SBP was 139.53 ± 16.91 mmHg in the SCH group and 142.50 ± 27.50 mmHg in the EU group, whereas resting DBP was 89.60 ± 12.35 and 93.75 ± 13.60 mmHg, respectively. No statistically significant differences between groups were identified for the anthropometric or blood-pressure variables evaluated.

Regarding clinical characteristics and medication use, 15 of 16 participants in the SCH group (93.8%) were receiving levothyroxine (LT4), whereas none of the participants in the EU group used this medication. Lipid-profile-modifying medications were used by 43.8% of participants with SCH and 13% of euthyroid participants. Glucose-regulating medications were used by 50% of participants with SCH and were not reported in the euthyroid group. Antihypertensive medication use was observed in 50% of participants with SCH and 25% of euthyroid participants. Anxiolytics and/or antidepressants were used by 56.3% of participants with SCH and 50% of euthyroid participants. A history of cardiovascular disease was observed in 38% and 25% of participants in the SCH and euthyroid groups, respectively, mainly including arrhythmias and elevated blood pressure. These clinical and treatment characteristics are summarized in Table 1.

Table 1. Participant characteristics and clinical/thyroid status

	SCH	EU
Age (years)	50.07 ± 13.2	40.250 ± 13.24
Height (cm)	161.03 ± 8.8	158.69 ± 6.08
Body mass (kg)	85.15 ± 16.71	83.31 ± 20.93
BMI (kg/m ²)	33.17 ± 7.84	32.74 ± 6.06
SBP (mmHg)	139.53 ± 16.91	142.50 ± 27.50
DBP (mmHg)	89.60 ± 12.35	93.75 ± 13.60

Clinical and thyroid-related characteristics

Previous SCH diagnosis, n (%)	16 (100)	0 (0)
Levothyroxine use, n (%)	15 (93.8)	0 (0)
Lipid-lowering medication, n (%)	7 (43.8)	1 (13.0)
Glucose-regulating medication, n (%)	8 (50.0)	0 (0)
Antihypertensive medication, n (%)	8 (50.0)	2 (25.0)
Anxiolytic and/or antidepressant use, n (%)	9 (56.3)	4 (50.0)
History of cardiovascular disease, n (%)	6 (38.0)	2 (25.0)

Groups: SCH, previously diagnosed subclinical hypothyroidism; EU, euthyroid. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Medication and clinical-history variables are presented as n (%).

Table 2 presents the anthropometric and body-composition indicators assessed by DXA, as well as waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) measurements.

Table 2. Body composition and anthropometric characteristics

	SCH	EU
WC (cm)	93.77 ± 11.71	91.43 ± 14.15
WHR	0.82 ± 0.06	0.80 ± 0.07
WHtR	0.58 ± 0.09	0.57 ± 0.08
BMD (g/cm ²)	1.193 ± 0.12	1.177 ± 0.11
%FM	45.77 ± 6.72	47.31 ± 4.29
FM (kg)	38.85 ± 11.99	39.04 ± 13.05
FFM (kg)	44.41 ± 6.7	42.15 ± 7.80

Groups (SCH: subclinical hypothyroidism; EU: euthyroid) for normally distributed variables. WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BMD: bone mineral density; %FM: fat mass percentage; FM: fat mass; FFM: fat-free mass.

As shown in Table 2, WC was 93.77±11.71 cm in the SCH group and 91.43±14.15 cm in the euthyroid group. WHR values were 0.82±0.06 and 0.80±0.07, whereas WHtR values were 0.58±0.09 and 0.57±0.08 in the SCH and euthyroid groups, respectively.

BMD was 1.193±0.12 g/cm² in the SCH group and 1.177±0.11 g/cm² in the euthyroid group. %FM was 45.77±6.72% and 47.31±4.29%, respectively. FM values were 38.85±11.99 kg in the SCH group and 39.04±13.05 kg in the euthyroid group, whereas FFM was 44.41±6.70 kg and 42.15±7.80 kg, respectively.

Between-group comparisons presented in Table 2 identified no statistically significant differences in the anthropometric or body-composition indicators evaluated.

Metabolic, cardiorespiratory, and physical-fitness parameters are presented in Table 3. At rest, basal metabolic rate (BMR) was 1930.47±355.09 kcal/day in the SCH group and 1993.24±338.19 kcal/day in the euthyroid group. Resting VO₂ values were 3.50±0.88 and 3.52±0.64, respectively, whereas resting RER was 0.82±0.06 and 0.84±0.04.

During the treadmill exercise test using the Modified Bruce protocol, at the aerobic-threshold stage, VO₂-AT was 15.03±3.35 mL·kg⁻¹·min⁻¹ in the SCH group and 17.08±2.53 mL·kg⁻¹·min⁻¹ in the EU group. Heart rate at the aerobic threshold (HR-AT) was 95.73±26.51 and 109.75±19.35 bpm, respectively, whereas RER-AT values were 0.86±0.08 and 0.87±0.03.

At the anaerobic-threshold stage, $\text{VO}_2\text{-AnT}$ was $21.85 \pm 3.68 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the SCH group and $23.29 \pm 2.78 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the euthyroid group. Heart rate at the anaerobic threshold (HR-AnT) was significantly lower in the SCH group than in the euthyroid group (120.07 ± 27.82 vs. 145.12 ± 22.31 bpm; $p < 0.05$). RER-AnT values were 1.05 ± 0.09 and 1.05 ± 0.05 , respectively.

At the stage corresponding to VO_2max attainment, values were $22.08 \pm 3.48 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the SCH group and $24.28 \pm 3.32 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the EU group. Maximal heart rate was 126.00 ± 27.75 and 149.50 ± 24.24 bpm, respectively, whereas RERmax was 1.08 ± 0.07 and 1.14 ± 0.17 .

For the exercise-related RER response, ΔRER values of 0.25 ± 0.07 were observed in the SCH group and 0.27 ± 0.07 in the euthyroid group. Lower-limb muscle strength, assessed by the one-repetition maximum (1RM) test, was 182.56 ± 78.00 kg in the SCH group and 245.09 ± 82.19 kg in the euthyroid group. For the upper limbs, values were 32.43 ± 6.88 kg and 39.95 ± 5.91 kg, respectively.

Except for heart rate at the anaerobic threshold, no statistically significant differences between groups were identified for the metabolic, cardiorespiratory, or physical-fitness parameters evaluated.

Table 3. Cardiopulmonary and metabolic responses

	SCH	EU
Baseline resting analyses		
BMR (kcal/day)	1930.47 ± 355.09	1993.24 ± 338.19
Resting VO_2	3.50 ± 0.88	3.52 ± 0.64
Resting RER	0.82 ± 0.06	0.84 ± 0.04
Cardiorespiratory and metabolic profile during exercise		
Aerobic-threshold analyses		
$\text{VO}_2\text{-AT}$ ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	15.03 ± 3.35	17.08 ± 2.53

HR-AT	95.73 ± 26.51	109.75 ± 19.35
RER-AT	0.86 ± 0.08	0.87 ± 0.03
Anaerobic-threshold analyses		
VO ₂ -AnT (mL·kg ⁻¹ ·min ⁻¹)	21.85 ± 3.68	23.29 ± 2.78
HR-AnT	120.07 ± 27.82	145.12 ± 22.31*
RER-AnT	1.05 ± 0.09	1.05 ± 0.05
Maximum-value analyses		
VO ₂ max (mL·kg ⁻¹ ·min ⁻¹)	22.08 ± 3.48	24.28 ± 3.32
HRmax	126.00 ± 27.75	149.50 ± 24.24
RERmax	1.08 ± 0.07	1.14 ± 0.17
Exercise-related RER response and strength		
ΔRER	0.25 ± 0.07	0.27 ± 0.07
1RM-LL	182.56 ± 78	245.09 ± 82.19
1RM-UL	32.43 ± 6.88	39.95 ± 5.91

* $p < 0.05$ for between-group comparison of normally distributed variables. BMR: basal metabolic rate; resting VO₂: oxygen uptake at rest; resting RER: respiratory exchange ratio at rest; VO₂-AT: oxygen uptake during the aerobic-threshold stage of the exercise test; HR-AT: heart rate during the aerobic-threshold stage of the exercise test; RER-AT: respiratory exchange ratio during the aerobic-threshold stage of the exercise test; VO₂-AnT: oxygen uptake during the anaerobic-threshold stage of the exercise test; HR-AnT: heart rate during the anaerobic-threshold stage of the exercise test; RER-AnT: respiratory exchange ratio during the anaerobic-threshold stage of the exercise test; VO₂max: maximal oxygen uptake during the exercise test; HRmax: maximal heart rate during the exercise test; RERmax: maximal respiratory exchange ratio during the exercise test; ΔRER: change in respiratory exchange ratio from rest to maximal exercise; 1RM-LL: one-repetition maximum test for the lower limbs; 1RM-UL: one-repetition maximum test for the upper limbs.

In the correlation analysis, waist circumference and body-fat percentage were prioritized as the primary adiposity indicators for interpretation and were both

strongly and inversely associated with VO_2max (waist circumference: $r = -0.757$, $p < 0.001$; body-fat percentage: $r = -0.675$, $p < 0.001$). Additional anthropometric and adiposity indicators were examined as exploratory correlates and showed concordant inverse associations, including BMI ($r = -0.597$, $p = 0.003$), waist-to-height ratio ($r = -0.771$, $p < 0.001$), and fat mass ($r = -0.600$, $p = 0.003$). ΔRER was positively, but not significantly, correlated with VO_2max in the bivariate analysis ($r = 0.361$, $p = 0.091$). The complete set of primary and exploratory correlations is presented in Table 4. This inverse relationship is illustrated in Figure 1.

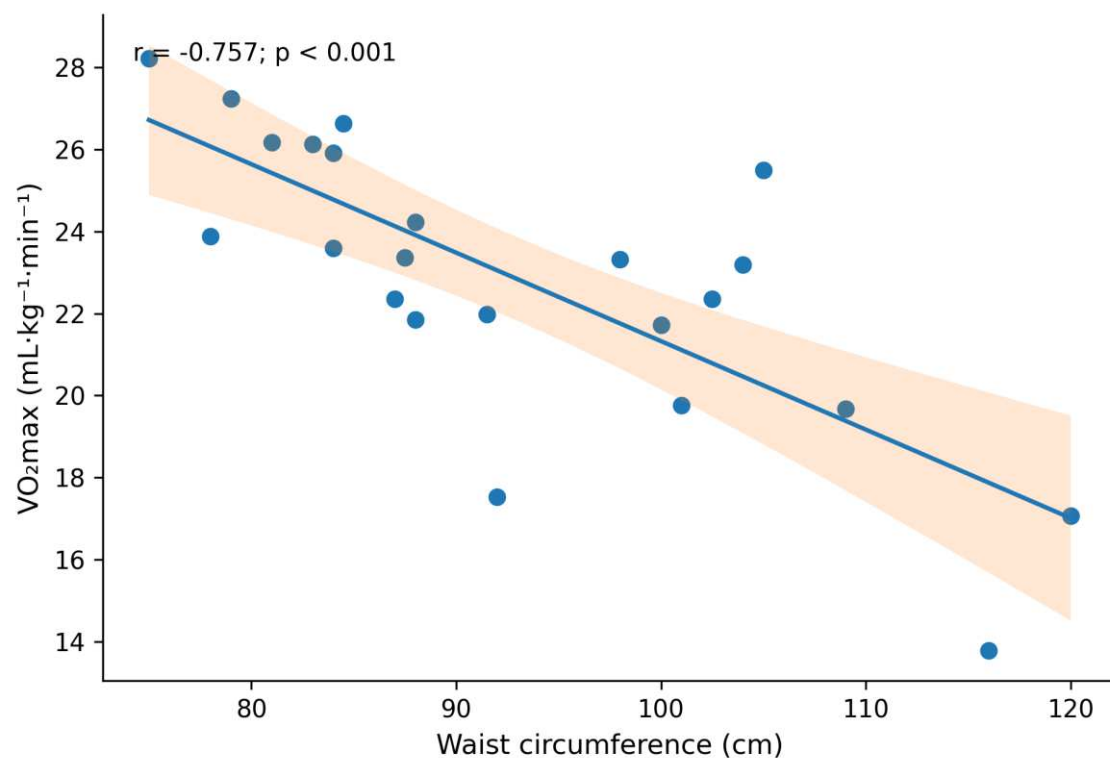


Figure 1. Association between waist circumference and VO_2max . Individual observations ($n = 23$) are shown with the fitted linear regression line and 95% confidence interval. Waist circumference was inversely correlated with VO_2max ($r = -0.757$, $p < 0.001$).

Table 4. Correlations of primary adiposity indicators, ΔRER , and exploratory variables with VO_2max

Variable	r	p
Age	-0.241	0.268

Body mass	-0.477	0.021
BMI	-0.597	0.003
Waist circumference	-0.757	<0.001
Hip circumference	-0.459	0.028
Waist-to-hip ratio	-0.541	0.008
Waist-to-height ratio	-0.771	<0.001
Body fat	-0.675	<0.001
Fat mass	-0.600	0.003
Lean/muscle mass	-0.110	0.618
BMD	-0.196	0.371
Basal metabolic rate	0.022	0.921
RER at rest	0.196	0.371
Δ RER	0.361	0.091
1RM bench press	0.268	0.215
1RM leg press	0.066	0.772

r: correlation coefficient; BMI: body mass index; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BMD: bone mineral density; BMR: basal metabolic rate; RER: respiratory exchange ratio; Δ RER: change in respiratory exchange ratio; 1RM: one-repetition maximum. Values in bold indicate statistical significance ($p < 0.05$).

A multiple linear regression model including waist circumference, ΔRER , and thyroid-status group was statistically significant ($R^2 = 0.749$, adjusted $R^2 = 0.709$, $p < 0.001$; Table 5). Greater waist circumference remained inversely associated with VO_2max after adjustment for ΔRER and thyroid status ($B = -0.210$, 95% CI -0.279 to -0.142 , $p < 0.001$), whereas a greater ΔRER remained positively associated with VO_2max after adjustment for waist circumference and thyroid status ($B = 17.709$, 95% CI 5.382 to 30.036 , $p = 0.007$). Thyroid-status group was not statistically significant after adjustment for these variables ($B = -1.525$, 95% CI -3.276 to 0.225 , $p = 0.084$). The model showed no evidence of problematic multicollinearity, with VIF values close to 1.0, and the residuals were approximately normally distributed (Shapiro–Wilk $p = 0.111$). Figure 2 displays the corresponding unadjusted relationship between ΔRER and VO_2max .

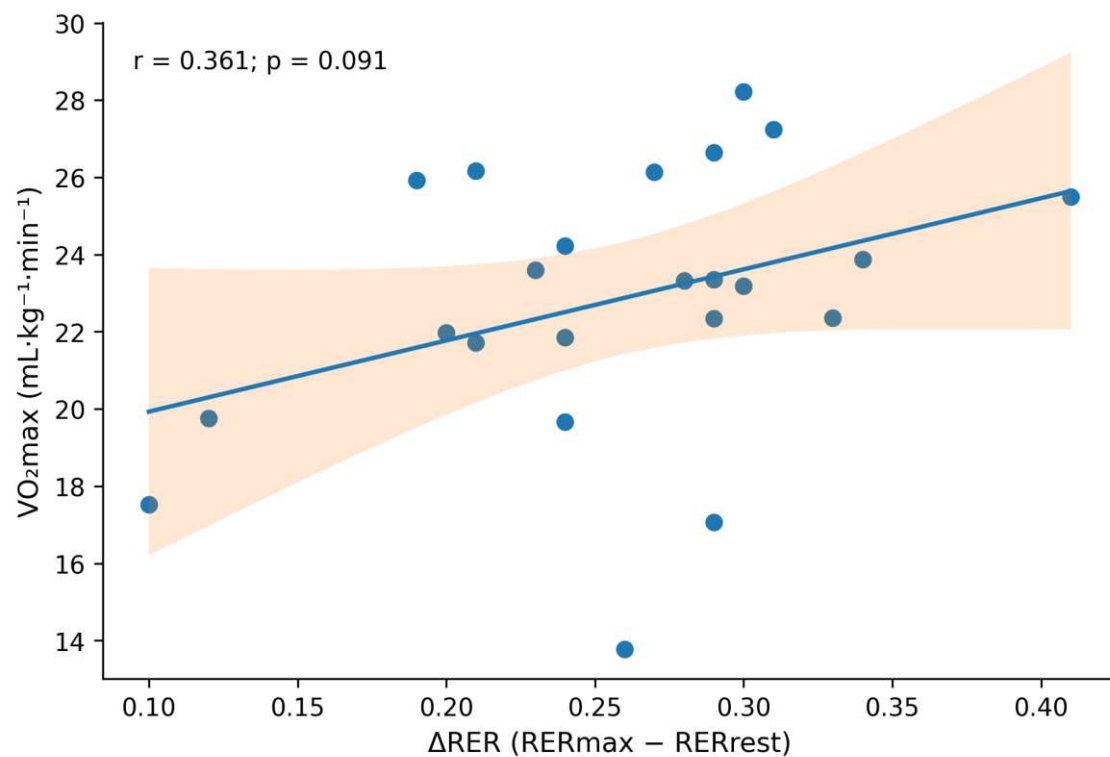


Figure 2. Unadjusted association between ΔRER and VO_2max . Individual observations ($n = 23$) are shown with the fitted linear regression line and 95% confidence interval. The bivariate association did not reach statistical significance ($r = 0.361$, $p = 0.091$); however, ΔRER remained significantly associated with VO_2max after adjustment for waist circumference and thyroid status in the primary multivariable model ($B = 17.709$, $p = 0.007$). ΔRER : change in respiratory exchange ratio from rest to maximal exercise.

Table 5. Multivariable linear regression for VO₂max

Predictor	B	SE	Standardized β	p	95% CI
Waist circumference, cm	-0.210	0.033	-0.738	<0.001	-0.279 to -0.142
Δ RER	17.709	5.889	0.347	0.007	5.382 to 30.036
Previous SCH diagnosis vs. euthyroid	-1.525	0.836	-0.211	0.084	-3.276 to 0.225

B: unstandardized regression coefficient; SE: standard error; β : standardized regression coefficient; 95% CI: 95% confidence interval; RER: respiratory exchange ratio; Δ RER: change in respiratory exchange ratio from rest to maximal exercise. The euthyroid group was used as the reference category for thyroid status. Values of $p < 0.05$ indicate statistical significance.

The sensitivity analysis in which waist circumference was replaced by body-fat percentage remained statistically significant ($R^2 = 0.712$, adjusted $R^2 = 0.666$, $p < 0.001$). Body-fat percentage was inversely associated with VO₂max ($B = -0.424$, $p < 0.001$), and a greater Δ RER remained positively associated with higher VO₂max ($B = 16.323$, $p = 0.018$). In contrast to the primary model, previous SCH diagnosis was also statistically significant in this sensitivity model ($B = -2.685$, $p = 0.008$). Thus, the inverse association between adiposity and VO₂max and the positive association with Δ RER were observed with both adiposity indicators, whereas the estimate for thyroid-status group was sensitive to model specification. Given the small sample size, this difference between models should be interpreted cautiously and as hypothesis-generating rather than confirmatory (Table 6).

Table 6. Sensitivity analysis using body-fat percentage

Predictor	B	Standardized β	p
Body fat, %	-0.424	approximately -0.69	<0.001
Δ RER	16.323	approximately 0.31	0.018

Previous SCH diagnosis vs. euthyroid	-2.685	approximately -0.37	0.008
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B: unstandardized regression coefficient; β : standardized regression coefficient; Δ RER: change in respiratory exchange ratio from rest to maximal exercise. The euthyroid group was used as the reference category for thyroid status. Values of $p < 0.05$ indicate statistical significance. β values are approximate.

In secondary exploratory analyses of basal metabolic rate, bivariate associations were observed with bone mineral density ($r = 0.510$, $p = 0.013$), Δ RER ($r = 0.471$, $p = 0.023$), and 1RM leg press ($r = 0.488$, $p = 0.021$), whereas no significant association was observed with muscle mass ($r = 0.286$, $p = 0.186$). The secondary exploratory regression model including bone mineral density, Δ RER, and thyroid-status group accounted for 49.5% of the observed variance in BMR ($R^2 = 0.495$, adjusted $R^2 = 0.415$, $p = 0.004$). Within this model, bone mineral density ($B = 1581.21$, $p = 0.005$) and a greater Δ RER ($B = 2337.50$, $p = 0.010$) were positively associated with BMR, whereas thyroid-status group was not statistically significant ($p = 0.582$). Given the limited sample size, these estimates should be regarded as hypothesis-generating. Full coefficients for this secondary model are provided in Table 7.

Table 7. Exploratory multivariable analysis of basal metabolic rate

Predictor	B	SE	Standardized β	p	95% CI
BMD, g/cm ²	1581.21	496.39	approximately 0.57	0.005	542.25–2620.17
Δ RER	2337.50	814.02	approximately 0.51	0.010	633.73–4041.27
Previous SCH diagnosis vs. euthyroid	-64.62	115.40	-0.09	0.582	-306.1–176.90

B: unstandardized regression coefficient; SE: standard error; β : standardized regression coefficient; 95% CI: 95% confidence interval; BMD: bone mineral density; Δ RER: change in respiratory exchange ratio from rest to maximal exercise. The euthyroid group was used as the reference category for thyroid status. Values of $p < 0.05$ indicate statistical significance. β values indicated as approximate were estimated.

4. Discussion

4.1 Principal findings

The main finding of this exploratory study was that, among women with metabolic syndrome (MetS), VO_2max was consistently associated with adiposity and the exercise-related respiratory exchange ratio response (ΔRER), whereas the association with thyroid status was less robust. In the primary prespecified model, greater waist circumference was associated with lower VO_2max and greater ΔRER was associated with higher VO_2max after mutual adjustment and adjustment for thyroid status. Previous subclinical hypothyroidism (SCH) diagnosis was not statistically significant in this model. The model accounted for 74.9% of the observed variance in VO_2max (adjusted $R^2 = 0.709$), although this estimate requires cautious interpretation given the small sample. In the sensitivity model using body-fat percentage instead of waist circumference, adiposity and ΔRER remained significantly associated with VO_2max , while previous SCH diagnosis also reached statistical significance, indicating that the thyroid-status estimate was sensitive to model specification. Between-group comparisons showed no significant differences in VO_2max , basal metabolic rate (BMR), ΔRER , or body-composition indicators; heart rate at the anaerobic threshold was the only cardiorespiratory variable that differed significantly between groups.

4.2 Thyroid status and exercise capacity

Interpretation of the thyroid-related findings requires consideration of treatment status. Fifteen of the 16 women with previous SCH diagnosis (93.8%) were receiving levothyroxine and had TSH and T4 concentrations within their respective laboratory reference ranges at assessment. Thus, the study primarily compared euthyroid women with women with a history of SCH who were predominantly treated and biochemically controlled, rather than untreated active SCH. Although VO_2 values at the aerobic threshold, anaerobic threshold, and maximal exercise were numerically lower in the SCH group, these differences were not statistically significant. Werneck et al. [14] reported functional impairment in women with SCH despite similar age, body mass, and BMI, whereas Lankhaar et al. [15] described exercise intolerance in SCH as a multifactorial phenomenon involving cardiovascular, cardiopulmonary, musculoskeletal, neuromuscular, and cellular-metabolic factors. Almas et al. [16] also described alterations in chronotropic responses to exercise in SCH. These observations provide physiological context for the lower heart rate at the anaerobic threshold observed in the present study, but the lack of a group effect after age adjustment and the predominantly treated SCH sample argue against attributing this finding to thyroid status alone. Evidence from treated hypothyroid populations likewise suggests that modest variation in thyroid function does not

necessarily translate into consistent differences in energy expenditure or body composition [17].

4.3 Adiposity and VO₂max

The strongest and most consistent pattern in the present study involved adiposity and cardiorespiratory fitness. Waist circumference and body-fat percentage were prioritized as the principal indicators of central and total adiposity, respectively, and both were inversely associated with VO₂max. BMI, waist-to-height ratio, fat mass, body mass, hip circumference, and waist-to-hip ratio showed concordant exploratory associations and should be interpreted as related manifestations of adiposity rather than as independent discoveries. In the primary model, greater waist circumference remained associated with lower VO₂max after adjustment for Δ RER and thyroid status; in the sensitivity model, body-fat percentage showed a similar inverse association. This pattern is consistent with Adams-Campbell et al. [18], who reported lower cardiorespiratory fitness among women with greater adiposity and an inverse association between waist circumference and VO₂peak. Central adiposity is also closely linked to the metabolic abnormalities that characterize MetS [19]. The absence of significant between-group differences in anthropometric and DXA-derived measures is compatible with previous reports showing no consistent excess adiposity attributable to SCH itself, particularly among treated individuals [20, 17]. Therefore, within this sample, VO₂max was more strongly associated with adiposity than with thyroid-status classification in the primary model, without implying a causal direction.

4.4 Δ RER and metabolic physiology

Δ RER was used as an operational index of the change in respiratory exchange ratio from rest to maximal exercise and should not be interpreted as a comprehensive or universally standardized measure of metabolic flexibility. No significant between-group difference in Δ RER was observed. However, although its bivariate correlation with VO₂max did not reach statistical significance ($r = 0.361$, $p = 0.091$), Δ RER remained significantly associated with VO₂max after adjustment for waist circumference and thyroid status ($B = 17.709$, $p = 0.007$). This difference between unadjusted and adjusted estimates suggests that the association between the exercise-related RER response and VO₂max may depend on the covariate structure of the model, particularly adiposity, and may be compatible with confounding, statistical suppression, or another conditional relationship. The present sample is too small to establish which statistical mechanism underlies this pattern. Physiologically, alterations in substrate

switching are frequently described in obesity, insulin resistance, and MetS [21], and experimental work suggests that substrate-use adaptations may involve mechanisms beyond thyroid-hormone concentrations [12]. These studies provide context for the observed Δ RER association but should not be interpreted as validating Δ RER as a direct measure of metabolic flexibility.

4.5 Clinical implications and limitations

From a clinical perspective, the findings support considering central adiposity and exercise-related metabolic responses alongside thyroid history when evaluating cardiorespiratory fitness in women with MetS. They do not establish that reducing adiposity or modifying Δ RER would cause an improvement in VO_2max , and the thyroid-status findings should not be generalized to untreated or biochemically active SCH. BMR was examined as a secondary exploratory outcome; the associations observed with bone mineral density and Δ RER are hypothesis-generating and require confirmation in larger samples.

Limitations

This study has several limitations. First, the small sample size and unequal group distribution, particularly the small euthyroid group ($n = 8$), limit statistical power, precision, and generalizability; analyses involving VO_2max and BMR included 23 participants, which also increases the possibility of instability in multivariable models. Second, the cross-sectional design precludes determination of temporal sequence or causal inference. Third, 15 of the 16 women with previous SCH diagnosis were receiving levothyroxine and were biochemically controlled at assessment, which may have attenuated between-group differences and limits extrapolation to untreated SCH. Detailed information on anti-TPO antibodies, levothyroxine dose, treatment duration, time since diagnosis, and individual thyroid-hormone values was not systematically recorded. Fourth, Δ RER was an operational index of the change in RER from rest to maximal exercise and should not be interpreted as a comprehensive measure of metabolic flexibility. Fifth, residual confounding related to medication use and other metabolic or behavioral factors cannot be excluded. Dietary intake and habitual physical activity were not quantified using dedicated standardized measures, limiting assessment of their potential contribution to VO_2max , substrate utilization, and BMR. Finally, several adiposity indicators were correlated with VO_2max and are biologically and statistically redundant; accordingly, the additional correlation analyses should be considered exploratory. These limitations reinforce

the hypothesis-generating nature of the findings and the need for larger, prospectively designed studies with detailed treatment, dietary, and physical-activity characterization.

5. Conclusion

In women with MetS, central adiposity and the exercise-related change in RER remained significantly associated with VO_2max in the primary exploratory model after covariate adjustment. Greater waist circumference was associated with lower VO_2max , whereas a greater ΔRER was associated with higher VO_2max . Previous SCH diagnosis was not statistically significant in the primary model; however, it reached statistical significance in the sensitivity model using body-fat percentage instead of waist circumference, indicating that the thyroid-status estimate was sensitive to model specification. Because 15 of the 16 women in the SCH group were receiving LT4 and were biochemically controlled at assessment, these findings apply primarily to women with previously diagnosed, predominantly treated SCH and should not be extrapolated to untreated or biochemically active SCH. Overall, adiposity and ΔRER showed consistent associations with VO_2max across the exploratory models, whereas the association with thyroid-disease history was less robust and varied according to model specification. Because of the small sample and cross-sectional design, these findings are hypothesis-generating and do not establish temporal or causal relationships. Further studies with larger samples, detailed thyroid-treatment characterization, and longitudinal designs are needed to confirm these associations.

Declarations

Ethics approval and consent to participate

The larger research protocol from which the present baseline analysis was derived was approved by the Research Ethics Committee of the Federal University of Rio Grande do Sul (CEP/UFRGS), Brazil (CAAE 89714825.7.0000.5347; approval no. 7.895.574). All participants provided written informed consent before participation.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

[Complete with each author's initials and contributions before submission.]

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Competing interests

The authors declare that they have no competing interests.

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