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Sex differences in the ventilatory responses to exercise in mild to moderate obesity

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Abstract

Obesity is associated with altered ventilatory responses, which may be exacerbated in females due to the functional consequences of sex-related morphological differences in the respiratory system. This study examined sex differences in ventilatory responses during exercise in adults with obesity. Healthy adults with obesity ($n = 73$; 48 females) underwent pulmonary function testing, underwater weighing, magnetic resonance imaging (MRI), a graded exercise test to exhaustion, and two constant work rate exercise tests; one at a fixed work rate (60 W for females and 105 W for males) and one at a relative intensity (50% of peak oxygen uptake, $\dot{V}_{O_2peak}$). Metabolic, respiratory and perceptual responses were assessed during exercise. Compared with males, females used a smaller proportion of their ventilatory capacity at peak exercise (69.13 ± 14.49 vs. 77.41 ± 17.06% maximum voluntary ventilation, $P = 0.0374$). Females also utilized a smaller proportion of their forced vital capacity (FVC) at peak exercise (tidal volume: 48.51 ± 9.29 vs. 54.12 ± 10.43%FVC, $P = 0.0218$). End-expiratory lung volumes were 2–4% higher in females compared with males during exercise ($P < 0.05$), while end-inspiratory lung volumes were similar. Since the males were initiating inspiration from a lower lung volume, they experienced greater expiratory flow limitation during exercise. Ratings of perceived breathlessness during exercise were similar between females and males at comparable levels of ventilation. In summary, sex differences in the manifestations of obesity-related mechanical ventilatory constraints were observed. Since dyspnoea on exertion is a common complaint in patients with obesity, particularly in females, exercise prescriptions should be tailored with the goal of minimizing unpleasant respiratory sensations.

KEYWORDS

breathing limitations, dynamic hyperinflation, dyspnoea, expiratory flow limitation, operating lung volumes

1 | INTRODUCTION

A growing body of evidence suggests that there are important sex differences in the anatomy and physiology of the respiratory system. Studies have reported that females have smaller lungs for a given age and stature (Goldman & Becklake, 1959; Thurlbeck, 1982) and smaller large conducting airways that are the main sites of airway resistance (Christou et al., 2021; Dominelli et al., 2018). Furthermore, their rib cage geometry (i.e., more declined ribs and higher positioning of the sternum) makes them rely more on intercostal muscles (vs. the diaphragm) for inspiration (Garcia-Martinez et al., 2016; Torres-Tamayo et al., 2018) and they have relatively less respiratory musculature (Aslan et al., 2019; Black & Hyatt, 1969).

Obesity imposes a mechanical load on the respiratory system, reducing functional residual capacity (FRC) and altering breathing mechanics during exercise (Babb, 2013b; Salome et al., 2010). The pathophysiological changes imposed by obesity on the respiratory system could be amplified in females, who already exhibit morphological differences in the respiratory system compared with males (Archiza et al., 2021; Molgat-Seon et al., 2018). The distribution of fat deposits also differs by sex, with females having relatively more subcutaneous and less visceral fat in the abdomen and a gynoid obesity pattern (Karastergiou et al., 2012). Morphological sex differences combined with obesity-related changes in respiratory function could affect ventilatory responses during exercise. For example, smaller lung volumes could lead females with obesity to adopt a rapid and shallow breathing pattern and experience ventilatory constraints; smaller airways in females could predispose to expiratory flow limitation (EFL) and dynamic hyperinflation; and differences in rib cage geometry and respiratory musculature could induce respiratory muscle fatigue or increase the oxygen cost of breathing (Archiza et al., 2021; McClaran et al., 1998). Alternatively, the android obesity pattern (i.e., more abdominal, especially visceral, fat) in males could push up against the diaphragm altering breathing mechanics and provoking EFL, but their relatively larger airways could also defend against some of these changes. Studying sex differences in respiratory physiology among individuals with obesity is critical because: (1) there are significant reports of high rates of dyspnoea on exertion in obese individuals (Bowden et al., 2011; Sin et al., 2002) and (2) females report dyspnoea on exertion more than males (Bowden et al., 2011; Currow et al., 2009; Ofir et al., 2008; Schaeffer et al., 2014).

Little is known about the implications of morphological sex differences on ventilatory responses to exercise in the context of obesity. Therefore, the purpose of this study was to examine sex differences in ventilatory responses to exercise in adults with obesity. We hypothesized that ventilatory constraints during exercise including EFL and dynamic hyperinflation would be greater in females when compared with males with obesity.

New Findings

- **What is the central question of the study?**
  What are the sex differences in ventilatory responses during exercise in adults with obesity?
- **What is the main finding and its importance?**
  Tidal volume and expiratory flows are lower in females when compared with males at higher levels of ventilation despite small increases in end-expiratory lung volumes. Since dyspnoea on exertion is a frequent complaint, particularly in females with obesity, careful attention should be paid to unpleasant respiratory symptoms and mechanical ventilatory constraints while prescribing exercise.

2 | METHODS

2.1 | Ethical approval

The UT Southwestern IRB approved this study (no. 122010-108) and all individuals provided written informed consent. The studies conformed to the standards set by the latest revision of the *Declaration of Helsinki*, except for registration in a database.

2.2 | Participants

Participants were 20- to 45-year-old non-smokers with a body mass index (BMI) between 30 and 50 kg/m^2. Participants were excluded if they had a history of asthma, cardiovascular disease, musculoskeletal abnormalities or engaged in a vigorous physical activity routine (i.e., exercised more than twice per week with a specific training goal) in the past 6 months. Given that hormonal changes during the menstrual cycle appear to have no effect on submaximal exercise $\dot{V}_E$ or the ventilatory response to exercise (Macnutt et al., 2012), we did not limit testing to a particular phase of the menstrual cycle.

The data in this article were collected as part of a larger study examining the effects of weight loss and exercise training on dyspnoea on exertion in adults with obesity. Baseline and post-intervention body composition, pulmonary and exercise test data separated by absence or presence of significant dyspnoea on exertion (ratings of perceived breathlessness ≤2 vs. ≥4 at 60 W and 105 W in females and males, respectively) were previously reported for 22 females who completed 12 weeks of exercise training and 18 males who completed a 12-week weight loss programme (Bernhardt et al., 2016, 2019).

Baseline data from 74 obese females who completed a multidimensional dyspnoea profile during constant work rate exercise at 60 W were reported in a paper that investigated the relationship between the intensity of dyspnoea and the unpleasantness and negative emotions associated with dyspnoea (Marines-Price et al., 2019). Our current article combines baseline data from males and females for sex comparisons and we repeat only the methods essential to the findings presented here.

2.3 | Protocol

Participants reported to the laboratory on four occasions. Measures of height, weight, body circumferences, percent body fat (underwater weighing) and pulmonary function were collected during the first visit. The constant work rate exercise test and the graded exercise test were performed on the second visit. The 50% $\dot{V}_{O_2 max}$ constant work rate exercise test were performed during the third visit. Magnetic resonance imaging (MRI) for quantifying fat distribution was performed on the fourth visit.

2.4 | Pulmonary function

All participants had spirometry, lung volumes, diffusing capacity and maximal voluntary ventilation determinations in a body plethysmograph (model V62W, Vyaire Medical, Yorba Linda, CA, USA) according to ATS/ERS guidelines (Macintyre et al., 2005; Miller et al., 2005; Wanger et al., 2005). Published reference equations were used to calculate predicted values (Burrows et al., 1961; Goldman & Becklake, 1959; Hankinson et al., 1999). Bronchodilator responsiveness was assessed in response to 360 μg of albuterol sulfate.

2.5 | Constant work rate exercise tests

Participants completed two 6-min constant work rate exercise tests on two separate visits. Resting measurements were collected with participants seated on a cycle ergometer (Lode Corival, Groningen, The Netherlands). For the first test, females and males cycled at a constant work rate of 60 W and 105 W, respectively, and were requested to keep cadence between 60 and 70 rpm. These work rates reflected the ventilatory threshold from our previous studies (Babb et al., 2002; DeLorey et al., 2005) and were selected to standardize the work for measurements of perceived breathlessness before and after the weight loss or exercise training intervention (primary aim of the larger study). Any participants who rated their perceived breathlessness as moderate (i.e., a rating of 3) during this test were excluded as per the larger study protocol (Bernhardt & Babb, 2014; Bernhardt et al., 2019; Bhammar et al., 2016; Marines-Price et al., 2019). For the second test, participants cycled at a work rate selected to elicit a relative exercise intensity of 50% $\dot{V}_{O_2 peak}$ based on the individuals' peak exercise test. The 50% $\dot{V}_{O_2 peak}$ test was not included in the study protocol at study start but was added later to obtain a second level of constant work rate exercise; therefore, not all participants completed this test.

2.6 | Graded 'peak' exercise test

Participants performed a graded cycling test to volitional exhaustion. For females, the initial work rate was 20 W, which was increased by 20 W each minute. For males, the initial work rate was 30 W, which was increased by 30 W each minute.

2.7 | Measurements during exercise

Heart rate and pulse oxygen saturation were assessed with a Nellcor N-595 monitor (Medtronic, Minneapolis, MN, USA). Oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), and minute ventilation ($\dot{V}_E$) were measured using the Douglas bag technique (Bhammar et al., 2016). Flow was measured continuously using an inspiratory pneumotachograph (model 4813, Hans Rudolph, Shawnee, KS, USA) and a heated expiratory pneumotachograph (model 3850A, Hans Rudolph) connected to a Hans Rudolph valve (model 2700) via large-bore tubing (Strozza et al., 2020). Inspiratory capacity (IC) manoeuvres were completed to assess operating lung volumes and for placement of tidal flow–volume loops within the maximal flow–volume loop. Participants practiced IC manoeuvres repeatedly during the study and were coached to provide their best effort each time. End-expiratory lung volume (EELV) was calculated as total lung capacity (TLC) − IC. End-inspiratory lung volume (EILV) was calculated as EELV + tidal volume (V_T). EFL was calculated as the percentage of V_T where tidal expiratory flow impinged on maximal expiratory flow corrected for gas compression artifact (Babb, 1997; Strozza et al., 2020). A 150 ml decrease in IC from rest to exercise was indicative of dynamic hyperinflation (O'Donnell et al., 2001).

We corrected for the effects of apparatus (i.e., Hans Rudolf 2700 valve assembly with attached mouthpiece) dead space volume (V_D) by subtracting 0.155 litre from V_T and then calculating $\dot{V}_E$ as $V_T \times f_B$. The ventilatory response to exercise was calculated as corrected $\dot{V}_E$ (exercise − rest)/$\dot{V}_{CO_2}$ (exercise − rest) (Wood et al., 2008) and reported as the $\dot{V}_E/\dot{V}_{CO_2}$ slope. $\dot{V}_E/\dot{V}_{CO_2}$ ratios were also corrected for apparatus V_D.

Partial pressure of CO_2 in arteries (P_{aCO_2}) was estimated from measurements of end-tidal CO_2 (P_{ETCO_2}) using the equation from Jones et al. (Bernhardt et al., 2013; Jones et al., 1979) as:

$$P_{JCO_2} = 5.5 + 0.9 \times P_{ETCO_2} - 2.1 \times V_T$$

Partial pressure of CO_2 in expired air (P_{ECO_2}) was calculated as fraction of expired CO_2 × (barometric pressure − 47). The physiological dead space to tidal volume ratio (V_D/V_T) was estimated as ($P_{JCO_2} - P_{ECO_2}$)/P_{JCO_2} (Enghöff, 1938; Nunn & Holmdahl, 1979).

Borg ratings of perceived breathlessness and exertion (RPB, 0 to 10 scap and RPE) (Borg, 1982) were assessed during exercise. After exercise was completed, affective (i.e., unpleasantness) and emotional responses (i.e., depression, anxiety, frustration, anger and fear) to breathlessness were assessed using visual analogue scales (Wade et al., 1996).

2.8 | MRI

Multiple MRI scans through the chest (sternal notch to xiphoid process) and abdomen (xiphoid process to pubic symphysis) were used to assess fat distribution (Babb, Ranasinghe et al., 2008; Babb, Wyrick et al., 2008; Bhammar et al., 2016).

2.9 | Statistical analysis

Data were expressed as means ± SD, except if otherwise specified. Normality was assessed using a Shapiro–Wilk test. Sex differences were tested by an independent Student's *t*-test for data that were normally distributed and by Wilcoxon's rank-sum test for data that were not normally distributed. Differences by sex and EFL status were tested with a two-way ANOVA. Relationships among variables were investigated with Pearson's correlation coefficient for data that were normally distributed and by Spearman's correlation coefficient for data that were not normally distributed. Sex differences during the peak exercise test were compared using linear mixed models at matched $\dot{V}_E$ ranges of 10–40, 40–60, and 60–80 l/min because ~45% of females had a $\dot{V}_{Emax}$ below 80 l/min. Sex differences during the peak exercise test were also compared using linear mixed models at matched relative $\dot{V}_E$ ranges of 20–40, 40–60, 60–80 and 80–100% $\dot{V}_{Epeak}$. Ranges of ventilation, sex, and ranges × sex interaction were included as fixed effects in the model, subject ID was included as a repeated effect, and the autoregressive(1) covariance structure was utilized. Significant interaction effects were followed by pairwise comparisons by sex using the Bonferroni correction. A *P*-value <0.05 was considered statistically significant. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

3 | RESULTS

The data reported are from 73 participants who completed both constant work rate exercise tests. Males had 7% lower body fat compared with females (Table 1). Males also had a lower forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC), a lower peak expiratory flow, and a higher maximal voluntary ventilation (MVV). FRC (%TLC) was not statistically different between the males and females. The increase in FEV_1 after 360 μg of albuterol was higher in males compared with females. However, lung function was within normal limits in both the males and females.

A subset of 38 females (age: 33.2 ± 7.0 years, BMI: 35.3 ± 3.8 kg/m^2) and 17 males (age: 34.8 ± 5.8 years, BMI: 34.8 ± 3.8 kg/m^2) completed the MRI scans. Abdominal fat distribution differed by sex; in females, visceral fat was lower and subcutaneous fat was higher (Table 2). In males, higher percentage fat was significantly correlated with lower FRC (%TLC) (r = −0.406, P = 0.044). In females, a taller stature was associated with a higher FRC (%TLC) (r = 0.363, P = 0.011) while greater visceral abdominal fat mass was associated with a lower FRC (%TLC) (r = −0.432, P = 0.007).

TABLE 1 Participant characteristics, body composition and pulmonary function

Characteristic	Females (*n* = 48)	Males (*n* = 25)	*P*
Age (years)	33.9 ± 6.6	33.9 ± 6.3	0.9818
Height (cm)	162.6 ± 6.9	177.3 ± 9.0	**<0.0001**
Mass (kg)	92.8 ± 11.9	113.7 ± 19.2	**<0.0001**
BMI (kg/m^2)	35.07 ± 3.94	36.00 ± 4.21	0.3518
Waist (cm)	104.9 ± 11.4	115.3 ± 9.5	**0.0002**
Waist:hip ratio	0.89 ± 0.08	0.98 ± 0.06	**<0.0001**
Fat (%)	46.4 ± 4.7	38.7 ± 5.0	**<0.0001**
Fat mass (kg)	43.3 ± 8.6	44.4 ± 10.9	0.6548
Lean mass (kg)	49.4 ± 5.7	69.3 ± 11.0	**<0.0001**
FVC (l)	3.55 ± 0.50	5.01 ± 1.11	**<0.0001**
FVC (%pred)	101.9 ± 12.2	96.4 ± 12.6	0.0722
FEV_1 (%pred)	100.9 ± 12.4	95.4 ± 11.8	0.0732
FEV_1/FVC (%)	83.46 ± 4.10	80.96 ± 5.14	**0.0388**
PEF (%pred)	105.0 ± 14.0	97.5 ± 13.6	**0.0313**
$FEF_{25–75}$ (l/min)	3.41 ± 0.88	4.15 ± 1.11	**0.0024**
$FEF_{25–75}$ (%pred)	103.8 ± 25.0	95.6 ± 21.1	0.1632
TLC (l)	4.66 ± 0.55	6.48 ± 1.30	**<0.0001**
TLC (%pred)	96.8 ± 9.0	94.6 ± 9.8	0.3487
IC (l)	2.79 ± 0.41	4.05 ± 0.88	**<0.0001**
IC (%pred)	107.2 ± 15.5	107.3 ± 12.5	0.9805
FRC (%TLC)	39.93 ± 6.58	37.38 ± 7.25	0.0654
ERV (l)	0.73 ± 0.35	0.95 ± 0.54	0.0675
RV (%pred)	67.1 ± 12.5	72.3 ± 12.6	**0.0328**
DL_{CO}/V_A (%pred)	115.1 ± 14.4	119.0 ± 15.5	0.4359
R_{aw} (%pred)	123.3 ± 37.9	140.6 ± 47.5	0.0937
MVV (l/min)	116.6 ± 16.4	157.8 ± 31.3	**<0.0001**
MVV (%pred)	104.6 ± 15.4	90.9 ± 15.6	**0.0009**
Post-bronchodilator			
ΔFEV_1 (%)	1.84 ± 2.68	2.95 ± 3.62	0.1505
ΔFEV_1 (ml)	52 ± 78	125 ± 145	**0.0076**

Values are means ± SD. *P*-values shown in bold indicate statistical significance. Abbreviations: BD, bronchodilator; BMI, body mass index; DLco, diffusing capacity of the lung for carbon monoxide; ERV, expiratory lung volume; $FEF_{25–75}$, forced expiratory flow from 25% to 75% of FVC; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; MVV, maximal voluntary ventilation; PEF, peak expiratory flow; %pred, percent predicted; TLC, total lung capacity; R_{aw}, airway resistance; RV, residual volume; V_A, alveolar volume.

TABLE 2 Fat mass and fat distribution in the chest wall in a subset of participants

	Females ($n = 38$)	Males ($n = 17$)	P
Fat mass			
Chest (kg)	5.1 ± 1.2	5.6 ± 3.8	0.6101
Abdomen, ant. SQ + post. SQ + visceral, (kg)	19.3 ± 4.1	17.5 ± 4.9	0.1716
Abdominal ant. SQ (kg)	6.8 ± 1.7	4.8 ± 1.6	**0.0002**
Abdominal post. SQ (kg)	8.2 ± 2.1	6.4 ± 2.3	**0.0056**
Abdominal visceral (kg)	4.3 ± 1.5	6.3 ± 1.9	**0.0002**
Total chest wall, chest + abdomen (kg)	24.4 ± 5.1	23.1 ± 5.3	0.4139
Fat distribution (% of total fat mass)			
Chest (%)	12.0 ± 2.2	13.6 ± 7.1	1.0000
Abdomen, ant. SQ + post. SQ + visceral, (%)	45.3 ± 5.3	44.0 ± 9.4	0.9274
Abdominal ant. SQ (%)	15.8 ± 2.4	12.0 ± 2.9	<**0.0001**
Abdominal post. SQ (%)	19.2 ± 2.6	16.0 ± 4.2	**0.0005**
Abdominal visceral (%)	10.2 ± 3.6	16.0 ± 5.1	**0.0001**
Total chest wall, chest + abdomen (%)	57.3 ± 6.8	57.6 ± 6.7	0.9149

Values are means ± SD. *P*-values shown in bold indicate statistical significance. Abbreviations: Ant., anterior; post., posterior; SQ, subcutaneous.

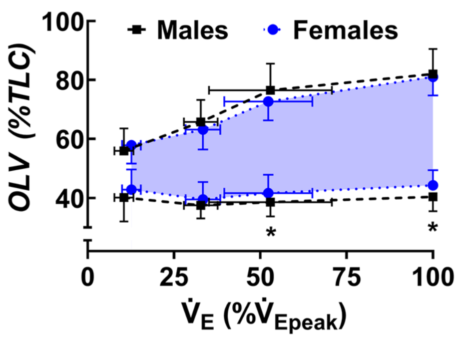

FIGURE 1 Means ± SD operating lung volumes (OLV) as a percentage of total lung capacity (TLC) at rest and during constant work rate exercise at 50% of peak oxygen uptake and 60 W (females) and 105 W (males), and at peak exercise. *$P < 0.05$ between males ($n = 25$) and females ($n = 48$). Raw data can be found in Dataset 1

3.1 | Constant work rate exercise tests

Sixty watts for females and 105 W for males elicited a relative $\dot{V}_{O_2}$ of approximately 70% $\dot{V}_{O_2peak}$ (Table 3). Consistent with the higher absolute work rate and related oxygen requirements, ventilatory demand was higher in males, although, as a percentage of MVV, both males and females were using the same proportion of their ventilatory capacity. The larger V_T in males was also reflected in the pattern of operational lung volumes; EELV was lower and EILV tended to be higher (Figure 1). Since males were initiating inspiration from a lower lung volume, they experienced greater EFL (i.e., >0% V_T overlap; Babb, 2013a) compared with females (48% vs. 19%, $P = 0.0088$). After correcting $\dot{V}_E$ for apparatus V_D, the $\dot{V}_E/\dot{V}_{CO_2}$ ratio and slope were higher in females when compared with males (Table 3). End-tidal CO_2 (P_{ETCO_2}) was lower in females, reflecting the increase in $\dot{V}_E/\dot{V}_{CO_2}$ slope. V_D/V_T was not different between males and females at rest or during exercise (Table 3).

Table 4 shows that the work rate to elicit 50% $\dot{V}_{O_2peak}$ was higher in males. V_T and V_T (%FVC) were higher in males, while f_B did not differ by sex. After correcting $\dot{V}_E$ for apparatus V_D, the $\dot{V}_E/\dot{V}_{CO_2}$ slope was higher and P_{ETCO_2} was lower at 50% $\dot{V}_{O_2peak}$ in females when compared with males. EELV and EILV did not differ by sex.

RPB and RPE from both of the constant work rate exercise tests were similar between females and males. When compared with females, males rated unpleasantness, frustration, and anger higher during constant work rate exercise at 50% $\dot{V}_{O_2peak}$ (Table 4).

3.2 | Peak exercise

Males had a higher absolute $\dot{V}_{O_2peak}$ but similar cardiorespiratory fitness (i.e., $\dot{V}_{O_2peak}$ quantified as a % of predicted; Riddle et al., 1980) compared with females (Table 5). Females used a smaller proportion of their ventilatory capacity (i.e., MVV) at peak exercise compared with males. Peak V_T as an absolute value and expressed relative to FVC and TLC was higher in males, while peak breathing frequency (f_B) did not differ by sex. The $\dot{V}_E/\dot{V}_{CO_2}$ ratio was not different between males and females. EELV was lower in males, but there were no sex differences in EILV (Figure 1).

The magnitude of EFL (i.e., percentage of tidal volume that overlapped with the maximal flow–volume loop) was higher in males compared with females (Table 5). Also, more males experienced EFL (defined as >0% V_T overlap) at peak exercise compared with females (72% vs. 48%, $P = 0.0491$). Higher severity of EFL defined as the percentage V_T overlap in males was correlated with a higher fat mass

TABLE 3 Gas exchange, breathing parameters and perceptual responses for the 6-min constant work rate exercise test at a work rate of 60 W for women and 105 W for men

	Females ($n = 48$)	**Males ($n = 25$)**	***P***
HR (bpm)	145.2 ± 14.82	140.6 ± 19.98	0.2718
HR (%peak)	79.02 ± 7.18	76.83 ± 11.55	0.0662
Lactate (mmol)	4.28 ± 1.53	5.16 ± 1.70	**0.0281**
$\dot{V}_{O_2}$ (l/min)	1.23 ± 0.08	1.95 ± 0.16	**<0.0001**
$\dot{V}_{O_2}$ (%peak)	70.51 ± 10.07	71.42 ± 12.97	0.7413
$\dot{V}_{CO_2}$ (l/min)	1.27 ± 0.11	2.04 ± 0.19	**<0.0001**
RER	1.03 ± 0.06	1.05 ± 0.08	0.2068
$\dot{V}_E$ (l/min)	41.2 ± 5.23	59.52 ± 10.06	**<0.0001**
$\dot{V}_E$ (%MVV)	35.76 ± 8.08	39.38 ± 12.56	0.4057
f_B (bpm)	29.62 ± 6.49	26.62 ± 9.85	**0.0344**
V_T (l)	1.43 ± 0.23	2.42 ± 0.64	**<0.0001**
V_T (%FVC)	40.88 ± 7.32	49.21 ± 10.95	**0.0016**
V_T (%TLC)	31.00 ± 5.28	37.88 ± 8.28	**0.0004**
P_{ETCO_2}	41.21 ± 3.66	43.63 ± 4.77	**0.0186**
T_i/T_{tot}	0.46 ± 0.03	0.48 ± 0.03	**0.0072**
$\dot{V}_E/\dot{V}_{CO_2}$ ratio	28.94 ± 2.52	27.11 ± 3.40	**0.0114**
$\dot{V}_E/\dot{V}_{CO_2}$ slope	27.93 ± 2.80	26.07 ± 3.58	**0.0166**
V_D/V_T – seated on bike	39.46 ± 2.44	39.04 ± 3.86	0.6260
V_D/V_T – exercise	38.89 ± 3.23	38.91 ± 3.81	0.9888
IC (l) – seated on bike	2.65 ± 0.34	3.89 ± 1.00	**<0.0001**
IC (l) – exercise	2.71 ± 0.38	3.98 ± 0.88	**<0.0001**
IC (%TLC) – exercise	58.35 ± 6.11	61.42 ± 4.86	**0.0116**
IC (%FVC) – exercise	76.73 ± 6.95	79.7 ± 5.97	0.0733
EELV (%TLC) – seated on bike	42.8 ± 6.8	40.1 ± 8.1	0.1390
EELV (%TLC) – exercise	41.7 ± 6.1	38.6 ± 4.9	**0.0116**
EILV (%TLC) – seated on bike	57.8 ± 6.3	55.9 ± 7.6	0.2492
EILV (%TLC) – exercise	72.7 ± 6.4	76.5 ± 9.1	0.0696
EFL (%V_T)	24.9 ± 16.3	33.7 ± 17.5	0.2594
RPB (Borg units)	3.46 ± 1.96	3.38 ± 2.06	0.6978
RPE (Borg units)	11.79 ± 2.76	12.04 ± 2.54	0.7091
Unpleasantness (VAS score)	2.7 ± 2.4	3.6 ± 2.8	0.2492
Depression (VAS score)	0.3 ± 0.9	0.4 ± 0.7	0.0621
Anxiety (VAS score)	1.7 ± 2.3	2.1 ± 2.6	0.5732
Frustration (VAS score)	0.8 ± 1.5	1.7 ± 2.4	0.1035
Anger (VAS score)	0.3 ± 1.2	1.0 ± 2.1	**0.0090**
Fear (VAS score)	0.6 ± 1.4	0.8 ± 1.5	0.0502

Values are means ± SD. *P*-values shown in bold indicate statistical significance. Abbreviations: EELV, end-expiratory lung volume; EFL, expiratory flow limitation; EILV, end-inspiratory lung volume; f_B, breathing frequency; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; MVV, maximal voluntary ventilation; P_{ETCO_2}, end tidal CO_2; pred, predicted; T_i/T_{tot}, ratio of inspiratory time to total time; RER, respiratory exchange ratio; RPB, ratings of perceived breathlessness; RPE, ratings of perceived exertion; TLC, total lung capacity; VAS, visual analogue scale; $\dot{V}_{CO_2}$, carbon dioxide production; V_D/V_T, ratio of dead space to tidal volume; $\dot{V}_E$, minute ventilation; $\dot{V}_{O_2}$, oxygen uptake; V_T, tidal volume.

TABLE 4 Gas exchange and breathing parameters for the 6-min constant work rate exercise test at the relative work rate selected to elicit 50% $\dot{V}_{O_2peak}$

	Females ($n = 48$)	Males ($n = 25$)	P
Work rate (W)	32.5 ± 10.5	66.0 ± 22.7	**<0.0001**
Lactate (mmol)	2.05 ± 0.75	2.72 ± 0.74	**0.0004**
$\dot{V}_{O_2}$ (l/min)	0.88 ± 0.16	1.39 ± 0.34	**<0.0001**
$\dot{V}_{O_2}$ (%peak)	49.62 ± 3.56	49.40 ± 4.49	0.8203
$\dot{V}_{CO_2}$ (l/min)	0.80 ± 0.15	1.33 ± 0.35	**<0.0001**
RER	0.90 ± 0.06	0.96 ± 0.05	**<0.0001**
$\dot{V}_E$ (l/min)	26.87 ± 4.76	38.72 ± 8.47	**<0.0001**
$\dot{V}_E$ (%MVV)	23.05 ± 4.07	25.09 ± 5.11	0.1366
f_B (bpm)	25.44 ± 5.59	22.83 ± 6.87	0.0851
V_T (l)	1.10 ± 0.27	1.83 ± 0.63	**<0.0001**
V_T (%FVC)	31.15 ± 6.22	36.39 ± 8.90	**0.0047**
V_T (%TLC)	23.73 ± 4.85	28.21 ± 7.22	**0.0084**
P_{ETCO_2}	41.81 ± 2.88	44.74 ± 4.00	**0.0025**
T_i/T_{tot}	0.47 ± 0.03	0.47 ± 0.03	0.3878
$\dot{V}_E/\dot{V}_{CO_2}$ ratio	28.85 ± 2.16	26.62 ± 2.40	**0.0002**
$\dot{V}_E/\dot{V}_{CO_2}$ slope	26.94 ± 2.49	24.85 ± 3.06	**0.0026**
V_D/V_T	40.16 ± 2.67	41.20 ± 3.47	0.1614
IC (l)	2.80 ± 0.38	4.03 ± 0.88	**<0.0001**
IC (%TLC)	60.48 ± 5.93	62.51 ± 4.44	0.1372
IC (%FVC)	79.23 ± 5.94	80.78 ± 5.08	0.2705
EELV (%TLC)	39.5 ± 5.9	37.5 ± 4.4	0.1371
EILV (%TLC)	63.1 ± 6.7	65.7 ± 7.5	0.1403
RPB (Borg units)	2.10 ± 1.42	2.10 ± 1.65	0.7953
RPE (Borg units)	9.54 ± 2.08	9.72 ± 2.49	0.8872
Unpleasantness (VAS score)	0.5 ± 0.7	2.4 ± 2.6	**0.0069**
Depression (VAS score)	0.0 ± 0.1	0.8 ± 1.7	0.1026
Anxiety (VAS score)	0.2 ± 0.5	0.8 ± 1.9	0.4386
Frustration (VAS score)	0.1 ± 0.2	1.4 ± 2.3	**0.0223**
Anger (VAS score)	0.1 ± 0.1	0.7 ± 1.4	**0.0413**
Fear (VAS score)	0.1 ± 0.2	0.9 ± 1.9	0.0758

Values are means ± SD. *P*-values shown in bold indicate statistical significance. Abbreviations: EELV, end-expiratory lung volume; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; MVV, maximal voluntary ventilation; EILV, end-inspiratory lung volume; f_B, breathing frequency; P_{ETCO_2}, end tidal CO_2; pred, predicted; RER, respiratory exchange ratio; RPB, ratings of perceived breathlessness; RPE, ratings of perceived exertion; T_i/T_{tot}; TLC, total lung capacity, ratio of inspiratory time to total time; VAS, visual analogue scale; $\dot{V}_{CO_2}$, carbon dioxide production; V_D/V_T, ratio of dead space to tidal volume; $\dot{V}_E$, minute ventilation; $\dot{V}_{O_2}$, oxygen uptake; V_T, tidal volume.

and percentage fat (r = 0.483, P = 0.042 and r = 0.479, P = 0.045, respectively; n = 18). In females, higher severity of EFL was correlated with a lower peak $\dot{V}_E$ (r = −0.418, P = 0.047; n = 23) and tended to correlate with lower mid-expiratory flows ($MEF_{25–75}$, r = −0.410, P = 0.052; n = 23).

There were no statistical sex differences in the magnitude or prevalence of dynamic hyperinflation (ΔIC exercise-rest; males (n = 12, 48%): −387 ± 138 ml vs. females (n = 18, 38%): −323 ± 118 ml; P = 0.1808 (t-test for mean differences); P = 0.3869 (chi-square test for frequency differences)) at peak exercise. In females, a greater decrease in IC from rest to peak exercise (or dynamic hyperinflation) was associated with a higher BMI, waist circumference, and peak f_B (r = −0.452, P = 0.001, r = −0.435, P = 0.002, and r = −0.369, P = 0.01, respectively; n = 48). In males, a greater decrease in IC from rest to peak exercise (or dynamic hyperinflation) was associated with a lower resting FRC %TLC (r = 0.620, P = 0.001) and a higher BMI and waist

TABLE 5 Gas exchange and breathing parameters measured at peak exercise

	Females ($n = 48$)	Males ($n = 25$)	P
Work rate (W)	139 ± 21	224 ± 43	**<0.0001**
HR (bpm)	182 ± 11	184 ± 13	0.5272
HR (%pred)	97.88 ± 5.93	96.39 ± 5.99	0.3133
Lactate (mmol)	8.69 ± 1.97	10.57 ± 1.93	**0.0002**
$\dot{V}_{O_2}$ (l/min)	1.78 ± 0.26	2.80 ± 0.56	**<0.0001**
$\dot{V}_{O_2}$ (%pred)	91.29 ± 12.9	97.33 ± 14.30	0.1061
$\dot{V}_{CO_2}$ (l/min)	2.21 ± 0.34	3.51 ± 0.79	**<0.0001**
RER	1.24 ± 0.08	1.25 ± 0.08	0.6964
$\dot{V}_E$ (l/min)	81.25 ± 17.14	117.40 ± 31.15	**<0.0001**
$\dot{V}_E$ (%MVV)	69.13 ± 14.49	77.41 ± 17.06	**0.0374**
f_B (bpm)	48.98 ± 11.65	46.17 ± 11.05	0.3227
V_T (l)	1.71 ± 0.36	2.70 ± 0.77	**<0.0001**
V_T (%FVC)	48.51 ± 9.29	54.12 ± 10.43	**0.0218**
V_T (%TLC)	36.79 ± 6.75	41.63 ± 7.58	**0.0068**
P_{ETCO_2}	33.48 ± 4.71	33.78 ± 4.76	0.8210
T_i/T_{tot}	0.48 ± 0.03	0.48 ± 0.03	0.8805
$\dot{V}_E/\dot{V}_{CO_2}$ ratio	33.6 ± 4.0	32.3 ± 4.6	0.2184
IC (l)	2.59 ± 0.33	3.86 ± 0.84	**<0.0001**
IC (%TLC)	55.71 ± 5.06	59.6 ± 4.89	**0.0047**
IC (%FVC)	73.26 ± 5.61	77.34 ± 6.08	**0.0099**
EELV (%TLC)	44.3 ± 5.1	40.4 ± 4.9	**0.0024**
EILV (%TLC)	81.1 ± 6.3	82.0 ± 8.5	0.4639
EFL (%V_T)	29.0 ± 16.2	44.9 ± 19.3	**0.0065**

Values are means ± SD. P-values shown in bold indicate statistical significance. Abbreviations: EELV, end-expiratory lung volume; EFL, expiratory flow limitation; EILV, end-inspiratory lung volume; f_B, breathing frequency; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; MVV, maximal voluntary ventilation; P_{ETCO_2}, end tidal CO_2; pred, predicted; RER, respiratory exchange ratio; T_i/T_{tot}, ratio of inspiratory time to total time; TLC, total lung capacity; $\dot{V}_{CO_2}$, carbon dioxide production; $\dot{V}_E$, minute ventilation; $\dot{V}_{O_2}$, oxygen uptake; V_T, tidal volume.

circumference ($r = -0.537$, $P = 0.006$ and $r = -0.497$, $P = 0.012$, respectively; $n = 25$).

During the peak exercise test, there were no sex differences in $\dot{V}_E$ at any given range of absolute $\dot{V}_E$ ($P = 0.1291$). $\dot{V}_E$ was higher in males compared with females at higher ranges of relative $\dot{V}_E$ including 40–60, 60–80 and 80–100% $\dot{V}_{Emax}$ (interaction $P < 0.0001$; *post hoc* sex differences $P < 0.0001$ for all three comparisons). Females relied on a higher f_B and a lower V_T at higher levels of $\dot{V}_E$ (Figure 2a,c). V_T (%TLC) did not differ by sex at any given range of absolute $\dot{V}_E$ (Figure 2e). However, at similar relative $\dot{V}_E$, f_B did not differ by sex but V_T and V_T (%TLC) were higher in males compared with females (Figures 2b,d,f). For any given range of absolute or relative $\dot{V}_E$, females had a higher $\dot{V}_E/\dot{V}_{CO_2}$ ratio when compared with males (Figures 2g,h). At $\dot{V}_E$ between 60 and 80 l/min, females had higher ratings of perceived exertion when compared with males (Figure 3a). However, ratings of perceived exertion and breathlessness did not differ by sex at any relative level of $\dot{V}_E$ (Figures 3b,d).

4 | DISCUSSION

This is the first study to comprehensively investigate sex differences in ventilatory responses in otherwise healthy males and females with mild-to-moderate obesity. The major findings of this study are that females compared with males had (1) higher EELV during exercise; (2) shallower breathing pattern; (3) smaller peak $\dot{V}_E$ as a percentage of maximal voluntary ventilation; and (4) higher $\dot{V}_E/\dot{V}_{CO_2}$ ratio during the peak exercise test and higher ventilatory response to submaximal exercise. In contrast to our initial hypothesis, EFL was more prevalent in males compared with females and there were no sex differences in dynamic hyperinflation. However, EFL in females was associated with a lower peak $\dot{V}_E$.

Females with obesity used ~8% less of their ventilatory capacity and ~10% less of their vital capacity at peak exercise, possibly due to an inability to increase expiratory flows at higher levels of ventilation despite small increases in EELV. Studies in adults without obesity with sample sizes ranging from 18 to 231 and ages ranging from 19 to 80 years have reported lower values of $\dot{V}_{Epeak}$ as a fraction of capacity in females (range of difference, males–females: 0–8%MVV or maximal ventilatory capacity), although these sex differences did not reach statistical significance (Blackie et al., 1991; Cory et al., 2015; Dominelli, Molgat-Seon et al., 2015; Dominelli, Render et al., 2015; Mitchell et al., 2018; Ofir et al., 2008; Schaeffer et al., 2014). Some studies have also reported lower values of V_T as a fraction of FVC in females (range of difference, males–females: 1.9–6.1%FVC), although statistical comparisons were either not performed or reported differences did not reach statistical significance (Blackie et al., 1991; Dominelli, Molgat-Seon et al., 2015; Dominelli, Render et al., 2015; Ofir et al., 2008; Schaeffer et al., 2014).

The incidence and magnitude of EFL were higher in males with obesity at peak exercise and were correlated with fat mass and percentage fat. Higher percentage fat was associated with a lower FRC in males and breathing at lower lung volumes could have predisposed males to greater risk of EFL. The finding of higher EFL in males was contrary to the expectation that EFL would be higher in females who have lower maximal expiratory flow rates (American Thoracic Society, 1991) and a smaller maximal flow–volume envelope. It is possible that the smaller airways in females elicited a reflex mechanism that curtailed expiration prematurely and increased EELV in the presence of EFL (Pellegrino et al., 1993). This notion was supported by results showing that although resting FRC normalized to lung size was not statistically different between females and males, EELV normalized to lung size remained 2–4% higher in females during exercise. EILV did not differ by sex and thus, theoretically, females had access to greater inspiratory and expiratory reserves than males, but they still adopted a shallower breathing pattern and experienced a limited $\dot{V}_{Epeak}$ at a relatively lower percentage of MVV. Sex differences in respiratory musculature (or inspiratory muscle weakness) could limit females in

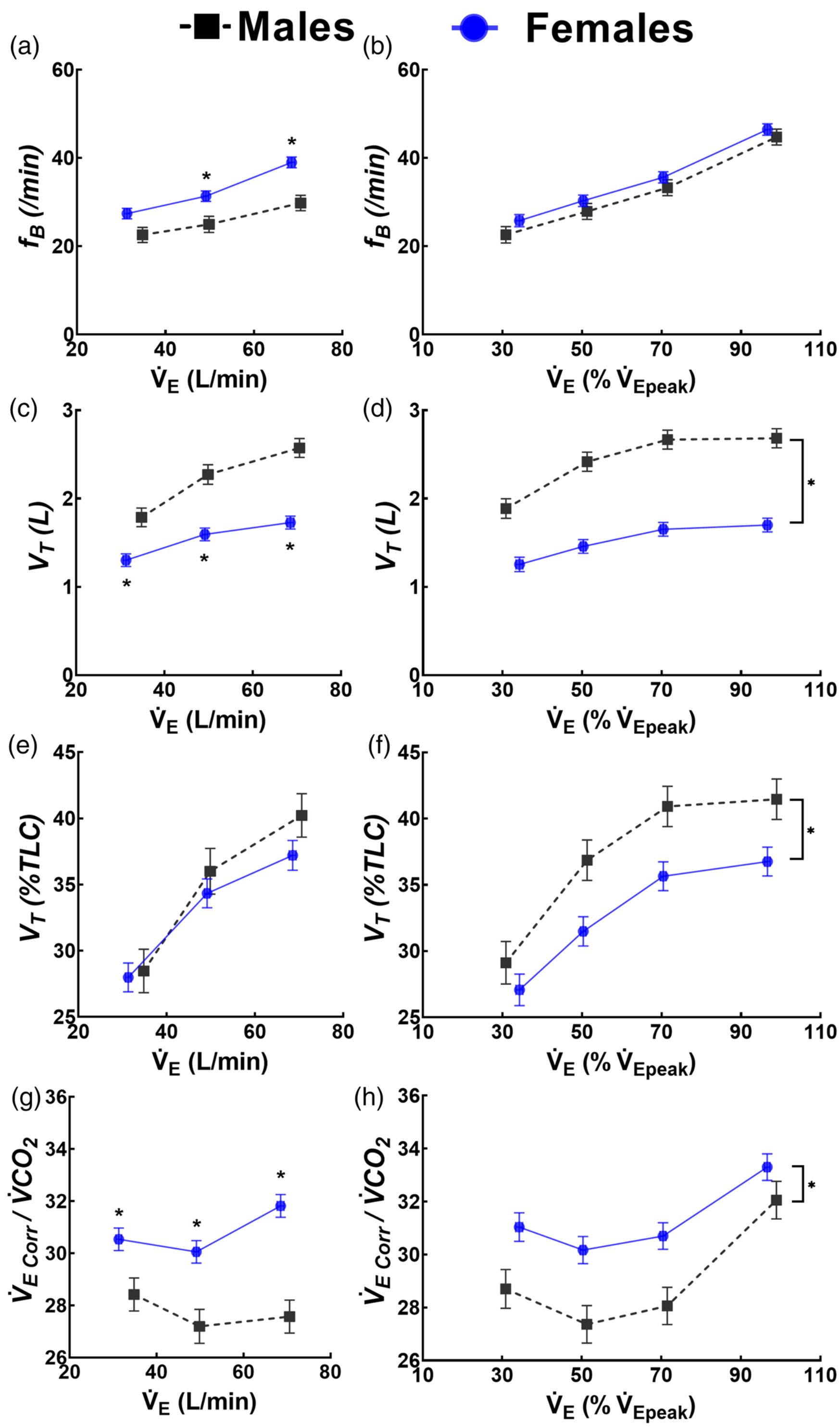

FIGURE 2 Least square means ± SE for breathing frequency (f_B), tidal volume (V_T) in litres and as a percentage of total lung capacity (TLC) and $\dot{V}_E/\dot{V}_{CO_2}$ ratio with $\dot{V}_E$ corrected for apparatus dead space from data collected during the peak exercise test. Variables have been plotted against least square means ± SE of: (1) absolute ventilation ($\dot{V}_E$) for ranges of 10–40, 40–60 and 60–80 l/min because approximately 45% of females had a maximal $\dot{V}_E$ that was below 80 l/min (a, c, e, g; males $n = 24$ because one participant had $\dot{V}_E$ measurements starting after 80 l/min and females $n = 48$), and (2) $\dot{V}_E$ relative to peak $\dot{V}_E$ for ranges of 20–40, 40–60, 60–80, and 80–100%$\dot{V}_{Epeak}$ (b, d, f, h; males $n = 25$ and females $n = 48$). *$P < 0.05$ between males and females. Raw data can be found in Dataset 2

their capacity to access their inspiratory reserves and increase V_T. EFL in females also tended to be inversely associated with $FEF_{25–75}$, implying that a smaller maximal flow–volume envelope increases EFL. EFL, when present, was associated with lower peak $\dot{V}_E$ in females. Lower mid-expiratory flows and lower expiratory reserve volume as a fraction of FVC (indicators of ventilatory capacity) and higher V_T (%FVC) and f_B (indicators of ventilatory demand) can help predict whether EFL occurs during exercise (Molgat-Seon et al., 2022). However, a larger sample would be needed to explore sex differences in how ventilatory capacity and demand interact to produce EFL among males and females with obesity.

Two studies have compared differences in respiratory function between adults with and without obesity, separated by sex. Babb, Wyrick et al. (2008) reported a higher amount of fat mass in the chest wall and a lower FRC in males and females with obesity when compared with males and females without obesity. In males, increasing visceral

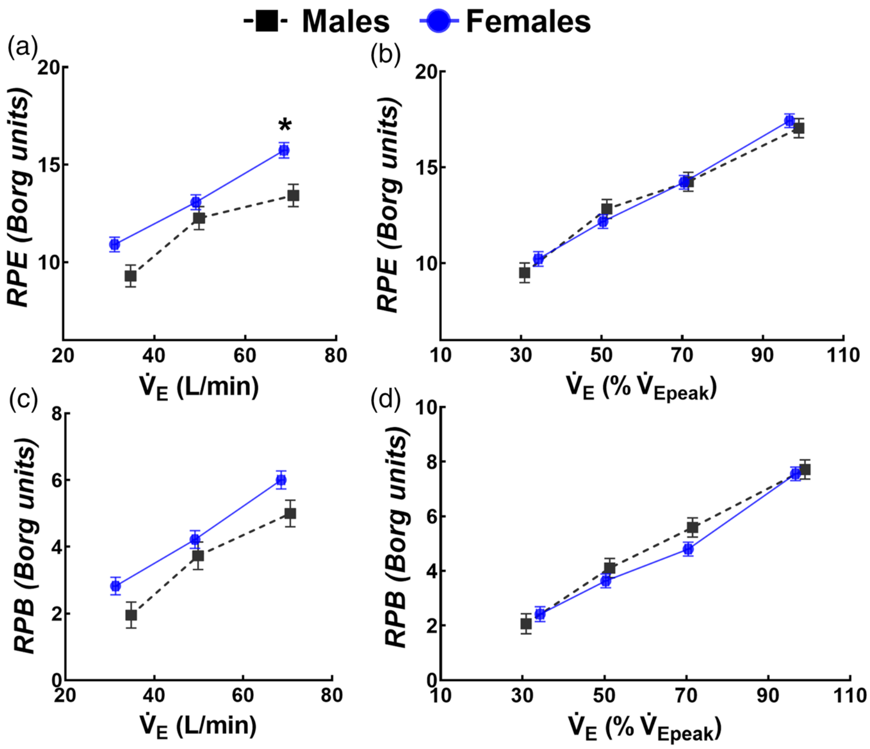

FIGURE 3 Least square mean ± SE ratings of perceived breathlessness (RPB) and exertion (RPE) during the peak exercise test. Variables have been plotted against absolute ventilation ($\dot{V}_E$; a, c) and $\dot{V}_E$ relative to peak $\dot{V}_E$ (b, d). $^*P < 0.05$ between males ($n = 25$) and females ($n = 48$). Raw data can be found in Dataset 2

fat mass was the best predictor of lower FRC, and in females increased anterior subcutaneous abdominal fat mass was the best predictor of lower FRC. However, Babb et al. did not analyse or inform additional outcomes based on examination of sex differences. In the present study and in the absence of a control group without obesity, we identified that higher percentage fat was associated with a lower FRC in males and that higher visceral fat mass was a predictor of lower FRC in females, which supports the idea that an increased mechanical load on the chest wall or abdomen leads to low lung volume breathing. In females only, Ofir et al. (2007) reported higher dyspnoea ratings at 60 and 80 W and more EFL and dynamic hyperinflation during a peak exercise test in participants with obesity when compared with those without obesity. Overall, further study is warranted as the literature is limited on information regarding the sex × obesity interaction on respiratory measures of interest.

The ventilatory response to exercise ($\dot{V}_E/\dot{V}_{CO_2}$ slope) was higher in females during both constant work rate exercise sessions. Also, the $\dot{V}_E/\dot{V}_{CO_2}$ ratio was higher in females during constant work rate exercise and during the peak exercise test (but not at peak exercise). These findings are consistent with that of a larger study in 145 males and 388 females with obesity, where Balmain et al. (2021) reported that the ventilatory response to exercise below the ventilatory threshold (which occurred at approximately 62% $\dot{V}_{O_2peak}$) was higher in females. These findings are also consistent with Phillips et al. who reported higher $\dot{V}_E/\dot{V}_{CO_2}$ ratio in females without obesity when compared with males with or without added thoracic load carriage during a peak exercise test (Phillips et al., 2019). An increased ventilatory response to exercise in females could be due to smaller V_T and therefore a higher amount of dead space ventilation, although V_D/V_T did not differ by sex in this study. It is possible that females experience alveolar hyperventilation due to the ventilatory stimulant effects of progesterone (Bayliss & Millhorn, 1992; Skatrud et al., 1978), which could explain why P_{ETCO_2} levels were also lower in females during constant-load exercise.

In contrast with reports of higher dyspnoea ratings in females without obesity when compared with males for any given level of absolute $\dot{V}_E$ but not at a relative percentage of maximum capacity (Cory et al., 2015; Ofir et al., 2008; Phillips et al., 2019; Schaeffer et al., 2014), we found no sex differences in dyspnoea ratings in adults with obesity during constant work rate cycling tests or the graded exercise test. Females report higher levels of breathlessness during day-to-day activities when compared with males (Bowden et al., 2011; Currow et al., 2009), which could be a function of the relatively higher intensity of activities in the context of a smaller ventilatory capacity. It could also be a function of an increased ventilatory response to exercise at lower relative intensities. However, this sex difference appears to be attenuated in the context of obesity. Visual inspection of dyspnoea ratings from our current study (Figure 3) with plots from published papers in adults without obesity (Cory et al., 2015; Ofir et al., 2008; Phillips et al., 2019; Schaeffer et al., 2014) suggests that dyspnoea ratings on average were slightly higher among individuals with obesity in our study at any given absolute or relative $\dot{V}_E$. It could be that some adults with obesity have a heightened perception of dyspnoea due to complex psychophysiological mechanisms including the effect of mood or negative emptions on the neural processing of respiratory stimuli (Bernhardt & Babb, 2016). Nevertheless, in the absence of a non-obese control group, we can only cautiously speculate that obesity may play a role in attenuating sex differences at similar levels of absolute $\dot{V}_E$.

4.1 | Limitations

Because of the lack of a control group without obesity, we are limited in drawing firm conclusions regarding the interaction between obesity and sex on outcome measures. We have instead provided data on sex differences in individuals with obesity and compared our findings with published literature in adults without obesity. Although the original intent of including a constant work rate test at 60 W for females and 105 W for males was to assess responses at an intensity that approximated ventilatory threshold, it must be noted that these fixed work rates elicited a $\dot{V}_{O_2}$ that was above the ventilatory threshold for 70–80% of participants. However, the relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ is expected to be linear for work rates below the respiratory compensation point and the independent effect of exercising above the ventilatory threshold on the ventilatory response to exercise may be negligible. Furthermore, reported submaximal responses at similar absolute and relative $\dot{V}_E$ ranges from data collected during the peak exercise test support our study conclusions. The mechanisms underlying the perception of dyspnoea and its associated affective and emotional responses are complex. Our study evaluated sex differences in ventilatory responses using comprehensive resting and exercise measurements in an acute setting. However, we did not investigate the psychological, environmental and social contributors to dyspnoea, which are important to study further. The participants in this study had mild-to-moderate obesity, and these findings may not extend to individuals with morbid obesity where the sex differences in morphometry of the respiratory system combined with the extreme reductions in FRC could worsen airway closure, gas exchange abnormalities, and ventilation–perfusion mismatch in females. Finally, the age range was narrow, and participants were relatively young. Age-related impairments in respiratory function tend to worsen in females without obesity (Ofir et al., 2008); how ageing affects ventilatory responses in older females with obesity remains to be studied.

4.2 | Conclusion

Manifestations of obestity-related mechanical ventilatory constraints are different in females and males with obesity. Morphological differences in lung and airway size in females with obesity appear to produce lower tidal volumes and expiratory flows at higher levels of ventilation despite small increases in EELV. Dyspnoea on exertion closely matches the proportion of ventilatory capacity and levels of ventilation during exercise in males and females with obesity, but dyspnoea perception itself may be increased due to obesity. Our findings suggest that exercise prescriptions should be tailored relative to their individual exercise capacity, and an attempt should be made to enquire about and address dyspnoea on exertion in all adults with obesity.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to the conception of the work, methodology, interpretation, and revising the work critically for important intellectual content. D.M.B. was responsible for writing the original draft, data curation, formal analysis, and visualization. T.G.B. was responsible for funding acquisition, project administration, and supervision. All authors approved the final version of the manuscript, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and all persons designated as authors qualify for authorship and all those who qualify for authorship are listed.

DATA AVAILABILITY STATEMENT

The de-identified numerical datasets used and/or analysed during the current study are available from the corresponding author on reasonable request from a qualified researcher upon completion of a data-use agreement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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