

SUPPLEMENTARY APPENDIX

Effect of twice daily inhaled albuterol on cardiopulmonary exercise outcomes, dynamic hyperinflation, and symptoms in secondhand tobacco-exposed persons with preserved spirometry and air trapping: a randomized controlled trial

Running title: Bronchodilators for treatment of air trapping sequelae in pre-COPD

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TABLE OF CONTENT:

DETAILED METHODS	2
SECONDHAND TOBACCO SMOKE EXPOSURE CHARACTERIZATION	2
PULMONARY FUNCTION TESTING (PFT)	2
CARDIOPULMONARY EXERCISE TESTING (CPET)	3
EXPIRATORY FLOW LIMITATION AND END EXPIRATORY LUNG VOLUME MEASUREMENTS DURING EXERCISE	4
SUPPLEMENTAL TABLES	7
SUPPLEMENTAL FIGURE	18
REFERENCES	20

DETAILED METHODS

Secondhand tobacco smoke Exposure Characterization

Secondhand tobacco smoke (SHS) exposure was characterized by an exposure questionnaire that was developed by our UCSF Flight Attendant Medical Research Institute (FAMRI) Center of Excellence,¹ and modified to acquire information on airline-related occupational history, as described previously.^{2,3} Briefly, this included employer airlines, duration of employment, and flight routes (domestic vs. international) with quantification of “cabin SHS exposure” as the number of years of employment before the smoking ban, the period during which the flight crew were exposed to SHS in the aircraft cabin. Other possible sources of exposure to SHS (non-cabin SHS exposure) were also explored by questioning participants about their non-cabin SHS exposure in additional settings, as described previously.⁴

Pulmonary Function Testing (PFT)

Routine PFTs were performed in the seated position using a model Vmax 229 CareFusion (CareFusion Corp., Yorba Linda, CA) and nSpire body plethysmograph (nSpire Health Inc., Longmont, CO). This included measurement of the low-volume curve and spirometry,⁵ lung volume by single breath dilution,^{6,7} and plethysmography,⁸ airway resistance during panting at functional residual capacity (FRC),^{9,10} and single breath carbon monoxide diffusing capacity.¹¹ Air trapping, which is inferred from an increased in residual volume (RV), was quantified using RV to total lung capacity (TLC) ratio (RV/TLC). Pulmonary function studies were conducted according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.¹²⁻¹⁷ Participants did not undergo bronchodilator administration.

Cardiopulmonary Exercise Testing (CPET)

Participants performed physician-supervised, symptom-limited, progressively increasing stepwise maximal exercise tests in the seated position on an electromagnetically braked, seated cycle ergometer (Corvial cpet, Lode B.V., Groningen, The Netherlands). Participants were encouraged to give their best effort, and during testing, were encouraged to continue exercise until a VO_2 plateau effect on a breath-to-breath analysis of oxygen consumption was visually observed; however, they were advised that they could stop voluntarily at any time they believed they could not continue. We continuously monitored heart rate (HR), blood pressure (BP), electrocardiogram (ECG), and breath-by-breath gas exchange.

The protocol consisted of 3-min rest, 1-min unloaded (freewheeling) cycling at 60 rpm, followed by increasing work rate of 20 to 40 Watts per step at 2-minute intervals to the maximum tolerated, and 5-min of recovery. Twelve lead ECGs were monitored continuously; ECGs and blood pressure (measured manually by a physician with a cuff) were recorded every 2 min. Oxyhemoglobin saturation (SpO_2 or O_2sat), determined by pulse oximetry, was recorded continuously.

Minute ventilation (V_E), oxygen uptake (VO_2) and carbon dioxide output (VCO_2) were measured breath-by-breath with an open-circuit metabolic cart (model Vmax 229, CareFusion, Yorba Linda, CA). The volumes of the flow meter, mouthpiece, and filter (70 mL x breathing frequency) were subtracted from V_E for the V_E/VCO_2 calculations. Anaerobic threshold (AT) was determined by the V-slope method.^{18,19} Immediately before all tests, the gas analyzers were calibrated using reference gases of known concentrations and the ventilometer was calibrated using a 3-liter syringe (Hans Rudolph, Kansas, MO). The metabolic system was verified using

four trained technicians who provided monthly exercise values as biological standards for the Laboratory.

Expiratory Flow Limitation and End Expiratory Lung Volume Measurements during Exercise

To determine whether dynamic hyperinflation contributed to the level of maximum exercise achieved, the participants underwent a separate dynamic hyperinflation exercise testing protocol for measurement of end-expiratory lung volume (EELV) and expiratory flow limitation (EFL) approximately 45 minutes after completing their maximum effort exercise testing. This protocol included tidal volume (V_T), inspiratory capacity (IC), and maximal expiratory flow (MEF) measurements in seated position at 2-minute steps with increasing work rates corresponding to 20%, 40%, 60%, and 80% of the peak VO_2 they attained during the maximum effort exercise testing, as described by O'Donnell et al.^{20,21} Measurements of IC and MEF were made three times during the second minute at each step and work rate while recording tidal flow-volume loops to assess for evidence of expiratory flow limitation. The volume of the tidal breath that is flow-limited on expiration (V_{FL}) was measured on flow-volume loop graphics using ImageJ (version 1.44, NIH, Bethesda, MD, USA) and used to calculate %EFL according to formula $[(V_{FL}/V_T)*100]$ at each work rate. EELV and RV (TLC- IC) were similarly calculated using ImageJ at each work rate.

Physical Activity Monitoring using Actigraphy

Physical activity was monitored using a triaxial accelerometer-based activity monitor (ActiGraph GT3X, Actigraph Corporations, Pensacola, FL) as described previously.²² Accelerometer data was recorded in 10-second epochs and in the three “vertical”, “horizontal”,

and “perpendicular” axes representing forward, sideways, and upward/downward motion, respectively.

The ActiGraph monitor was initialized to continuously collect data over a seven-day period. It was then mailed to participants along with a daily diary to keep a log of the time the monitor was worn and the activities the participants performed during that time. All participants received the ActiGraph monitors at least seven days prior to the in-laboratory visit, during which data on respiratory symptom questionnaire, PFT and CPET was collected. Participants were instructed to wear the ActiGraph monitor on the waist upon awakening using a waist band provided and to keep it on continuously for at least eight hours for seven consecutive days beginning the first day of their work week and beginning the start of their day. The seven-day monitoring was chosen to allow for adequate number of weekday data collection.²³ All participants were carefully instructed on how the device should be positioned.

Actigraphy data was processed using the ActiLife software program (Version 6.11.9; ActiGraph LLC) and saved in raw format as GT3X files. The ActiLife software generates a total of 52 variables in the distance, time (activity and sedentary) and energy domains. ActiLife outputs use direct measurement of distance, steps, and time for quantifying activity, but quantifying of energy expenditure (EE) requires translation of activity using different prediction models.

Actigraphy data had a repeated measure design as each participant wore the monitor for seven consecutive days in the week prior to their second and third visits. Thus, the data was further summarized into seven-day average values (weekly “mean” values) and the highest values of “maximum” values (maximum per epoch) across all seven days (weekly “highest” values). The actigraphy data was matched against the diary to ascertain the appropriate usage of

the monitor, and the data was considered to be acceptable if the participants wore the monitor for a minimum of 3 days and for greater than 5 hours (300 minutes) per day. The total amount of the time that the monitor was worn was included in the regression models as *total time worn*.

A final set of variables selected based on a combination of the machine learning and literature-guided approaches to provide meaningful variables of highest predictive value for our proposed analysis was used for the purpose of this analysis as described previously.²²

Respiratory Symptom Assessment

Patient-reported respiratory symptoms, physical activity, and quality of life assessments were conducted using the COPD Assessment Test (CAT),²⁴ modified Medical Research Council (mMRC) Dyspnea Scale,²⁵ the Short Form 12-Item Health Survey (SF-12),²⁶ International Physical Activity Questionnaire (IPAQ),²⁷ Airway Questionnaire 20 (AQ20),²⁸ and a self-reported questionnaire (UCSF Flight Attendant Medical Research Institute FAMRI SHS Questionnaire) that elicited symptoms of dyspnea, cough, and participants' perception of a decreased level of exertion compared to peers over the year preceding enrollment.¹ A dichotomous indicator of respiratory symptoms was defined by mMRC ≥ 1 or report of at least one respiratory symptom on the UCSF FAMRI SHS Questionnaire. A dichotomous cause of exercise cessation (dyspnea versus fatigue or effort; Dyspnea_{Peak}) was determined based on the highest score reported by the participants at the end of the maximum effort exercise testing using the modified Borg Rating of Perceived Exertion (Borg), with the Category-Ratio Scale anchored at number 10 (CR10).²⁹

SUPPLEMENTAL TABLES

Table S1- Participant characteristics at baseline for the groups.

Participant characteristics	Participants completed the study (N=42)	Participants with available data (N=49)	Participants with air trapping and 90% adherence (N=27)
Demographics and anthropometrics			
Age (years)	66.0±7.8	66.2±8.0	67.1±8.2
Female sex [n (%)]	38 (90.5%)	43 (87.8%)	26 (96.3%)
Height (cm)	166.4±7.7	166.4±8.1	164.9±7.3
Weight (kg)	65.9±11.8	66.9±12.9	63.0±11.6
BMI (kg/m ²)	23.7±3.2	24.0±3.7	23.1±3.4
Hemoglobin (g/dL)	13.5±0.4	13.5±0.4	13.4±0.2
Having EFL	15 (35.7%)	17 (34.7%)	11 (40.7%)
SHS Exposure			
Ever Cabin SHS exposure [n (%)]	34 (81.0%)	41 (83.7%)	21 (77.8%)
Cabin SHS exposure among exposed (years)	18.0±8.9	17.6±9.0	19.4±8.4
Any form of non-cabin SHS exposure [n (%)]	42 (100%)	49 (100%)	27 (100%)
Childhood home SHS exposure [n (%)]	25 (59.5%)	29 (59.2%)	17 (63.0%)
Adult home SHS exposure [n (%)]	19 (45.2%)	21 (42.9%)	12 (44.4%)
Non-airline occupational SHS exposure [n (%)]	35 (83.3%)	42 (85.7%)	24 (88.9%)
Other SHS Exposure [n (%)]	37 (88.1%)	43 (87.8%)	24 (88.9%)
Symptoms			
mMRC Dyspnea Scale ≥1 [n (%)]	6 (27.3%)	10 (34.5%)	5 (31.3%)
SF12			
Physical component score	38.2±4.9	38.5±4.9	39.4±3.3
Mental component score	48.6±4.7	48.9±4.6	49.1±4.0
IPAQ score			
High [n (%)]	37 (88.1%)	43 (87.8%)	23 (85.2%)
Moderate [n (%)]	5 (11.9%)	5 (10.2%)	4 (14.8%)
Low [n (%)]	0 (0%)	1 (2.0%)	0 (0%)
CAT	6.22±5.34	6.60±5.68	5.67±4.66
Participants with any respiratory symptoms [n (%)]	40 (95.2%)	45 (91.8%)	25 (92.6%)
Participants ever experiencing shortness of breath [n (%)]	11 (26.2%)	13 (26.5%)	7 (25.9%)

Participants with cough ≥ 2 episodes/year [n (%)]	40 (95.2%)	44 (89.8%)	25 (92.6%)
Participants with less activity than peers [n (%)]	3 (7.1%)	4 (8.2%)	2 (7.4%)
Pulmonary Function Tests			
FEV ₁ (% predicted)	103 $\pm$ 16	103 $\pm$ 16	99 $\pm$ 12
FVC (% predicted)	107 $\pm$ 16	107 $\pm$ 16	103 $\pm$ 11
FEV ₁ /FVC	0.75 $\pm$ 0.05	0.75 $\pm$ 0.05	0.75 $\pm$ 0.05
FEV ₁ /FVC (% predicted)	96 $\pm$ 6	96 $\pm$ 6	95 $\pm$ 8
FEF ₂₅₋₇₅ (% predicted)	98 $\pm$ 32	98 $\pm$ 30	95 $\pm$ 35
FEF ₇₅ (% predicted)	124 $\pm$ 56	127 $\pm$ 56	132 $\pm$ 69
D _{LCO} adjusted for Hgb (mL/min/mmHg)	21.6 $\pm$ 4.2	21.4 $\pm$ 4.3	22.0 $\pm$ 4.53
D _{LCO} adjusted for Hgb (% predicted)	84 $\pm$ 11	84 $\pm$ 12	87 $\pm$ 11
D _L /V _A adjusted for Hgb (mL/min/mmHg/L)	4.45 $\pm$ 0.58	4.36 $\pm$ 0.61	4.56 $\pm$ 0.62
D _L /V _A adjusted for Hgb (% predicted)	89 $\pm$ 11	88 $\pm$ 12	92 $\pm$ 11
Alveolar volume (V _A) (L)	4.90 $\pm$ 0.86	4.97 $\pm$ 1.00	4.71 $\pm$ 0.66
Alveolar volume (V _A) (L) (% predicted)	92 $\pm$ 12	93 $\pm$ 12	91 $\pm$ 9
TLC (% predicted)	101 $\pm$ 11	101 $\pm$ 11	101 $\pm$ 9
RV (% predicted)	99 $\pm$ 15	98 $\pm$ 16	105 $\pm$ 12
RV/TLC (%)	39 $\pm$ 7	39 $\pm$ 7	42 $\pm$ 5
RV/TLC (% predicted)	95 $\pm$ 14	94 $\pm$ 13	101 $\pm$ 10
FRC (% predicted)	96 $\pm$ 16	96 $\pm$ 17	99 $\pm$ 16
FRC/TLC (%)	51 $\pm$ 7	51 $\pm$ 7	53 $\pm$ 7
FRC/TLC (% predicted)	92 $\pm$ 12	92 $\pm$ 13	95 $\pm$ 13
Cardiopulmonary Testing Measurements			
VO _{2Peak} (L/min)	1.32 $\pm$ 0.38	1.33 $\pm$ 0.41	1.27 $\pm$ 0.38
VO _{2Peak} (% predicted)	101 $\pm$ 22	99 $\pm$ 21	104 $\pm$ 22
VO _{2Peak} /kg (mL/min.kg)	20.2 $\pm$ 4.9	20.0 $\pm$ 4.8	20.3 $\pm$ 5.1
VO _{2Peak} /kg (% predicted)	86 $\pm$ 20	86 $\pm$ 20	89 $\pm$ 22
RER _{Peak}	1.13 $\pm$ 0.09	1.13 $\pm$ 0.08	1.12 $\pm$ 0.07
RER _{Peak} (% predicted)	103 $\pm$ 8	103 $\pm$ 8	102 $\pm$ 6
VCO _{2Peak} (L/min)	1.50 $\pm$ 0.46	1.52 $\pm$ 0.50	1.43 $\pm$ 0.45
Watts _{Peak} (watts)	112 $\pm$ 32	113 $\pm$ 36	106 $\pm$ 28
Watts _{Peak} (% predicted)	114 $\pm$ 27	115 $\pm$ 28	119 $\pm$ 34
Cumulative work (watt-minute)	516 $\pm$ 233	535 $\pm$ 263	501 $\pm$ 212
Stages completed	4.8 $\pm$ 0.9	4.9 $\pm$ 1.0	5.0 $\pm$ 0.9
Total duration (minute)	9.6 $\pm$ 1.9	9.8 $\pm$ 2.0	9.9 $\pm$ 1.8
Symptoms at peak exercise (Borg Scale 0 to 10)			
Shortness of Breath	5.49 $\pm$ 1.87	5.60 $\pm$ 1.85	5.52 $\pm$ 1.67
Effort	6.17 $\pm$ 2.06	6.29 $\pm$ 2.06	6.00 $\pm$ 1.80
Fatigue	5.66 $\pm$ 1.80	5.83 $\pm$ 1.88	5.67 $\pm$ 1.71
Pulmonary Response			
V _{EPeak} (L/min)	52.7 $\pm$ 15.5	53.0 $\pm$ 16.5	49.1 $\pm$ 11.8
V _{EPeak} (% predicted)	57 $\pm$ 13	56 $\pm$ 12	56 $\pm$ 13

RR _{Peak} (breaths/min)	31.2±6.7	30.6±6.7	31.2±7.2
V _{TPeak} (L)	1.71±0.45	1.77±0.57	1.61±0.34
V _{TPeak} (% predicted)	94±18	96±19	94±18
V _E /VO _{2Peak}	39.1±12.1	38.8±11.3	38.3±12.7
V _E /VCO _{2Peak}	34.9±10.4	34.4±9.8	34.2±11.7
V _E /VCO _{2Peak} (% predicted)	87±26	86±24	86±29
VO ₂ at Anaerobic Threshold (VO _{2AT}) (L/min)	1.11±0.33	1.11±0.34	1.11±0.32
VO ₂ at Anaerobic Threshold (VO _{2AT}) (% predicted)	81±22	81±23	86±23
VO ₂ at Anaerobic Threshold (VO _{2AT}) (% of VO _{2Peak} achieved)	86±19	86±20	88±18
V _E /VCO ₂ at Anaerobic Threshold	35.3±14.7	35.2±13.7	36.3±17.5
Cardiovascular Response			
HR _{Rest} (beat/min)	75±15	76±19	80±23
HR _{Peak} (beat/min)	141±23	141±22	142±20
HR _{Peak} (% predicted)	92±14	92±14	93±13
HR _{Peak} ≤ 90% predicted [n (%)]	17 (40.5%)	21 (42.9%)	11 (40.7%)
HRR	12.7±21.4	12.8±21.0	11.3±18.8
HRR ≥ 15 [n (%)]	19 (45.2%)	23 (46.9%)	11 (40.7%)
HR _{Slope} (beat/min/10 Watts)	6.44±2.05	6.30±2.06	6.22±1.71
SBP _{Rest} (mmHg)	128±18	128±17	129±19
SBP _{Peak} (mmHg)	186±28	189±29	187±31
SBP _{Slope} (mmHg/10 Watts)	5.60±1.87	5.87±2.13	5.71±2.12
DBP _{Rest} (mmHg)	73±10	73±9	72±11
DBP _{Peak} (mmHg)	83±11	84±11	83±11
DBP _{Slope} (mmHg/10 Watts)	0.98±1.08	1.07±1.11	1.10±1.24
HRE (met at least one criterion) [n (%)]	22 (75.9%)	12 (60.0%)	34 (69.4%)
Rise in SBP ≥ 50 mmHg (≥ 60 mmHg for men)	20 (69.0%)	11 (55.0%)	31 (63.3%)
SBP _{Peak} ≥ 190 mmHg (≥ 210 mmHg for men)	15 (51.7%)	8 (40.0%)	23 (46.9%)
DBP _{Peak} ≥ 105 mmHg	0 (0%)	0 (0%)	0 (0%)
O ₂ -Pulse _{Peak} (mL/beat)	9.64±3.62	9.74±3.80	9.11±2.76
O ₂ -Pulse _{Peak} (% predicted)	107±32	106±30	108±30
O ₂ -Pulse _{Rest} (mL/beat)	3.49±0.94	3.54±1.18	3.45±0.98
O ₂ -Pulse _{Slope} (mL/beat/10 Watt)	0.50±0.20	0.50±0.19	0.49±0.18
O ₂ -Pulse at Anaerobic Threshold (mL/beat)	9.07±2.67	9.15±3.04	9.08±2.57
O ₂ -Pulse at Anaerobic Threshold (% O ₂ -Pulse _{Peak})	97±20	98±21	101±19
SpO _{2Rest}	97.7±1.9	97.5±1.8	97.5±2.0
SpO _{2Peak}	97.4±1.6	97.3±1.5	97.3±1.5
Change in SpO ₂ at peak exercise	-0.29±1.44	-0.20±1.35	-0.26±1.68
Dynamic Hyperinflation			

VFL _{Rest} (L)	0.19±0.25	0.20±0.25	0.23±0.26
VFL _{80% effort} (L)	0.54±0.35	0.55±0.36	0.54±0.36
VFL _{Slope} (mL/watt)	3.71±3.50	3.80±3.38	3.41±3.23
EFL _{Rest} (%)	19.4±25.6	19.5±24.7	21.6±24.7
EFL _{80% effort} (%)	29.8±18.9	29.7±18.4	31.2±20.6
EFL _{Slope} (%/watt)	0.091±0.247	0.091±0.230	0.084±0.223
EFL at rest [n (%)]	19 (45.2%)	23 (46.9%)	14 (51.9%)
EFL at rest or during exercise [n (%)]	36 (85.7%)	43 (87.8%)	22 (81.5%)
EELV _{Rest}	2.83±0.55	2.82±0.64	2.88±0.56
EELV _{80% effort}	2.78±0.52	2.76±0.59	2.80±0.47
Slope of EELV across exercise stages	-0.59±3.89	-0.69±3.74	-1.09±2.66
No. with increase in EELV slope [n (%)]	19 (45.2%)	21 (42.9%)	11 (40.7%)

Footnote: Demographics, secondhand smoke (SHS) exposure, symptoms, and lung function in participants with preserved spirometry that underwent exercise testing. Other SHS exposure was defined as non-aircraft cabin SHS exposure outside the work or home environment such as in recreational public places. Data are presented as mean ± standard deviation or number of participants with positive value for the variable (n) out of the total number of participants (N) and percentage of participants (%). Reference equations: percent predicted of normal values of spirometry, diffusing capacity, and lung volumes were calculated using Global Lung Function Initiative (GLI), Crapo, and Stock and Quanjer predicted formulas, respectively.³⁰⁻³³ Percent predicted of normal values of cardiopulmonary outputs were calculated using Wassermann predicted formulas.³⁰ Available measures of the variables at peak exercise, at rest, and at anaerobic threshold were reported. Rate of change in the variables during the exercise testing were assessed by linear regression slope of the variables with respect to the workload.

Abbreviations- BMI: body mass index; mMRC: modified medical research council; SF12: Short Form 12-Item Health Survey; IPAQ: International Physical Activity Questionnaire; CAT: COPD Assessment Test; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF₂₅₋₇₅: maximum airflow at mid-lung volume; FEF₇₅: maximum airflow at low-lung volume; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; D_{LCO}: single-

breath diffusing capacity of carbon monoxide; Hgb: hemoglobin; VO_2 : oxygen uptake; $\text{VO}_{2\text{Peak.kg}}$: peak oxygen uptake per kilogram of body weight; Watts: work stage completed in watts; VCO_2 : carbon dioxide production; V_E : minute ventilation value; RER: respiratory exchange ratio (VCO_2/VO_2) at peak exercise; RR: respiratory rate; V_T : tidal volume; HR: heart rate; HRR: heart rate reserve; SBP: systolic blood pressure; DBP: diastolic blood pressure; O_2 -Pulse: oxygen uptake per heartbeat; SpO_2 : oxygen saturation; VFL: volume of the tidal breath that is flow limited on expiration; EFL: expiratory flow limitation; EELV: end-expiratory lung volume; Slope of EELV across exercise stages: estimate of regression coefficient of three EELV measurements at each of baseline (rest), 20%, 40%, 60%, and 80% of the load intensity (watts) of the peak exercise stage achieved.

Table S2- Participant characteristics at baseline.

Participant characteristics	Albuterol w/ V2 Placebo w/ V3 (N=29)	Placebo w/ V2 Albuterol w/ V3 (N=20)	Overall (N=49)
Demographics and anthropometrics			
Age (years)	66.2±8.9	66.3±6.5	66.2±8.0
Female sex [n (%)]	25 (86.2%)	18 (90.0%)	43 (87.8%)
Height (cm)	165.5±7.8	167.9±8.6	166.5±8.1
Weight (kg)	65.3±13.5	69.1±12.0	66.9±12.9
BMI (kg/m ²)	23.7±3.5	24.5±3.9	24.0±3.7
Hemoglobin (g/dL)	13.6±0.4	13.5±0.4	13.5±0.4
SHS Exposure			
Ever Cabin SHS exposure [n (%)]	27 (93.1%)	14 (70.0%)	41 (83.7%)
Cabin SHS exposure among exposed (years)	16.1±9.6	20.4±7.5	17.6±9.0
Any form of non-cabin SHS exposure [n (%)]	29 (100%)	20 (100%)	49 (100%)
Childhood home SHS exposure [n (%)]	18 (62.1%)	11 (55.0%)	29 (59.2%)
Adult home SHS exposure [n (%)]	12 (41.4%)	9 (45.0%)	21 (42.9%)
Non-airline occupational SHS exposure [n (%)]	24 (82.8%)	18 (90.0%)	42 (85.7%)
Other SHS Exposure [n (%)]	26 (89.7%)	17 (85.0%)	43 (87.8%)
Symptoms			
mMRC Dyspnea Scale ≥1 [n (%)]	5 (31.3%)	5 (38.5%)	10 (34.5%)
SF12			
Physical component score	37.9±4.3	39.3±5.7	38.5±4.9
Mental component score	48.9±3.8	48.9±5.7	48.9±4.6
IPAQ score			
High [n (%)]	25 (86.2%)	18 (90.0%)	43 (87.8%)
Moderate [n (%)]	4 (13.8%)	1 (5.0%)	5 (10.2%)
Low [n (%)]	0 (0%)	1 (5.0%)	1 (2.0%)
CAT	6.04±5.55	7.40±5.90	6.60±5.68
Participants with any respiratory symptoms [n (%)]	28 (96.6%)	17 (85.0%)	45 (91.8%)
Participants ever experiencing shortness of breath [n (%)]	9 (31.0%)	4 (20.0%)	13 (26.5%)
Participants with cough ≥2 episodes/year [n (%)]	28 (96.6%)	16 (80.0%)	44 (89.8%)
Participants with less activity than peers [n (%)]	2 (6.9%)	2 (10.0%)	4 (8.2%)
Pulmonary Function Tests			
FEV ₁ (% predicted)	102±18	105±9	103±16

FVC (% predicted)	106±19	110±8	107±16
FEV ₁ /FVC	0.75±0.05	0.75±0.04	0.75±0.05
FEV ₁ /FVC (% predicted)	96±6	95±6	96±6
FEF ₂₅₋₇₅ (% predicted)	99±33	96±26	98±30
FEF ₇₅ (% predicted)	127±55	127±59	127±56
D _{LCO} adjusted for Hgb (mL/min/mmHg)	20.7±4.4	22.3±4.1	21.4±4.3
D _{LCO} adjusted for Hgb (% predicted)	82±12	85±13	84±12
D _L /V _A adjusted for Hgb (mL/min/mmHg/L)	4.35±0.65	4.36±0.58	4.36±0.61
D _L /V _A adjusted for Hgb (% predicted)	88±13	87±10	88±12
Alveolar volume (V _A) (L)	4.87±1.02	5.12±0.99	4.97±1.00
Alveolar volume (V _A) (L) (% predicted)	91±14	95±7	93±12
TLC (% predicted)	99±12	103±11	101±11
RV (% predicted)	96±15	100±18	98±16
RV/TLC	0.39±0.07	0.38±0.05	0.39±0.07
RV/TLC (% predicted)	95±15	92±10	94±13
FRC (% predicted)	94±15	99±20	96±17
FRC/TLC	0.51±0.08	0.51±0.07	0.51±0.07
FRC/TLC (% predicted)	92±13	92±13	92±13
Cardiopulmonary Testing Measurements			
VO _{2Peak} (L/min)	1.27±0.40	1.42±0.43	1.33±0.41
VO _{2Peak} (% predicted)	96±22	104±18	99±21
VO _{2Peak} /kg (mL/min.kg)	19.7±5.4	20.4±3.8	20.0±4.8
VO _{2Peak} /kg (% predicted)	82±17	92±24	86±20
RER _{Peak}	1.14±0.08	1.13±0.09	1.13±0.08
RER _{Peak} (% predicted)	103±7	103±8	103±8
VCO _{2Peak} (L/min)	1.45±0.49	1.62±0.52	1.52±0.50
Watts _{Peak} (watts)	110±35	116±37	113±36
Watts _{Peak} (% predicted)	116±28	114±29	115±28
Cumulative work (watt-minute)	503±232	582±303	535±263
Total duration (minute)	9.6±1.9	10.2±2.2	9.8±2.0
Stages completed	4.8±0.9	5.1±1.1	4.9±1.0
Symptoms at peak exercise (Borg Scale 0 to 10)			
Shortness of Breath	5.43±1.73	5.85±2.03	5.60±1.85
Effort	6.00±1.91	6.70±2.25	6.29±2.06
Fatigue	5.50±1.64	6.30±2.13	5.83±1.88
Pulmonary Response			
V _E Peak (L/min)	52.9±16.7	53.2±16.7	53.0±16.5
V _E Peak (% predicted)	56±12	55±13	56±12
RR _{Peak} (breaths/min)	31.4±6.1	29.4±7.4	30.6±6.7
RR _{Peak} (% predicted)	63±12	59±15	61±13
V _T Peak (L)	1.72±0.58	1.84±0.56	1.77±0.57
V _T Peak (% predicted)	94±20	99±18	96±19
V _E /VO _{2Peak}	40.9±13.5	35.7±5.9	38.8±11.3
V _E /VCO _{2Peak}	36.2±11.9	31.9±4.4	34.4±9.8

V_E/VCO_{2Peak} (% predicted)	90±30	80±11	86±24
$V_E/VCO_{2Lowest}$	33.2±12.4	29.0±4.1	31.5±10.0
$V_E/VCO_{2Lowest}$ (% predicted)	83±31	73±10	79±25
VO_2 at Anaerobic Threshold (VO_{2AT}) (L/min)	1.03±0.28	1.24±0.38	1.11±0.34
VO_2 at Anaerobic Threshold (VO_{2AT}) (% predicted)	76±23	89±21	81±23
VO_2 at Anaerobic Threshold (VO_{2AT}) (% VO_{2Peak})	84±22	88±16	86±20
V_E/VCO_2 at Anaerobic Threshold	37.8±17.2	31.4±3.6	35.2±13.7
Cardiovascular Response			
HR_{Rest} (beat/min)	77±14	76±26	76±19
HR_{Peak} (beat/min)	143±24	139±20	141±22
HR_{Peak} (% predicted)	93±15	90±12	92±14
$HR_{Peak} \leq 90\%$ predicted [n (%)]	11 (37.9%)	10 (50.0%)	21 (42.9%)
HRR	11.4±23.0	14.9±18.1	12.8±21.0
$HRR \geq 15$ [n (%)]	12 (41.4%)	11 (55.0%)	23 (46.9%)
HR_{Slope} (beat/min/10 Watts)	6.59±2.22	5.89±1.77	6.30±2.06
SBP_{Rest} (mmHg)	130±17	125±16	128±17
SBP_{Peak} (mmHg)	191±29	185±29	189±29
SBP_{Slope} (mmHg/10 Watts)	5.94±2.39	5.76±1.75	5.87±2.13
DBP_{Rest} (mmHg)	72±10	74±9	73±9
DBP_{Peak} (mmHg)	85±11	83±11	84±11
DBP_{Slope} (mmHg/10 Watts)	1.25±1.20	.0.81±0.95	1.07±1.11
O_2 -Pulse $_{Rest}$ (mL/beat)	3.43±1.19	3.70±1.18	3.54±1.18
O_2 -Pulse $_{Peak}$ (mL/beat)	9.32±4.15	10.4±3.21	9.74±3.80
O_2 -Pulse $_{Peak}$ (% predicted)	100±29	114±31	106±30
O_2 -Pulse $_{Slope}$ (mL/beat/10 Watt)	0.48±0.19	0.53±0.18	0.50±0.19
O_2 -Pulse at Anaerobic Threshold (mL/beat)	8.36±2.53	10.3±3.41	9.15±3.04
O_2 -Pulse at Anaerobic Threshold (% O_2 -Pulse $_{Peak}$)	96±26	100±13	98±21
SpO_{2Rest}	97.7±2.1	97.3±1.5	97.5±1.8
SpO_{2Peak}	97.4±1.5	97.2±1.5	97.3±1.5
Change in SpO_2 at peak exercise	-0.28±1.56	-0.10±1.02	-0.20±1.35
Dynamic Hyperinflation			
VFL_{Rest} (L)	0.23±0.24	0.16±0.27	0.20±0.25
$VFL_{80\% \text{ effort}}$ (L)	0.60±0.33	0.49±0.40	0.55±0.36
VFL_{Slope} (mL/watt)	3.93±3.43	3.62±3.38	3.80±3.38
EFL_{Rest} (%)	21.9±23.6	15.8±26.4	19.5±24.7
$EFL_{80\% \text{ effort}}$ (%)	32.8±16.4	24.9±20.7	29.7±18.4
EFL_{Slope} (%/watt)	0.10±0.25	0.08±0.21	0.09±0.23
EFL at rest [n (%)]	16 (57.1%)	7 (35.0%)	23 (46.9%)
EFL at rest or during exercise [n (%)]	27 (93.1%)	16 (80.0%)	43 (87.8%)
$EELV_{Rest}$	2.68±0.47	3.04±0.80	2.82±0.64

EELV _{80% effort}	2.68±0.49	2.87±0.72	2.76±0.59
Slope of EELV across exercise stages (mL/watts)	0.06±4.21	-1.78±2.66	-0.69±3.74
No. with increase in EELV slope [n (%)]	16 (55.2%)	5 (25.0%)	21 (42.9%)

Footnote: Demographics, secondhand smoke (SHS) exposure, symptoms, and lung function in participants with preserved spirometry that underwent exercise testing. Other SHS exposure was defined as non-aircraft cabin SHS exposure outside the work or home environment such as in recreational public places. Data are presented as mean ± standard deviation or number of participants with positive value for the variable (n) out of the total number of participants (N) and percentage of participants (%). Reference equations: percent predicted of normal values of spirometry, diffusing capacity, and lung volumes were calculated using Global Lung Function Initiative (GLI), Crapo, and Stock and Quanjer predicted formulas, respectively.³⁰⁻³³ Percent predicted of normal values of cardiopulmonary outputs were calculated using Wassermann predicted formulas.³⁰ Available measures of the variables at peak exercise, at rest, and at anaerobic threshold were reported. Rate of change in the variables during the exercise testing were assessed by linear regression slope of the variables with respect to the workload.

Abbreviations- BMI: body mass index; mMRC: modified medical research council; SF12: Short Form 12-Item Health Survey; IPAQ: International Physical Activity Questionnaire; CAT: COPD Assessment Test; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF₂₅₋₇₅: maximum airflow at mid-lung volume; FEF₇₅: maximum airflow at low-lung volume; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; D_{LCO}: single-breath diffusing capacity of carbon monoxide; Hgb: hemoglobin; VO₂: oxygen uptake; VO_{2Peak.kg}: peak oxygen uptake per kilogram of body weight; Watts: work stage completed in watts; VCO₂: carbon dioxide production; V_E: minute ventilation value; RER: respiratory exchange ratio (VCO₂/VO₂) at peak exercise; RR: respiratory rate; V_T: tidal volume; HR: heart

rate; HRR: heart rate reserve; SBP: systolic blood pressure; DBP: diastolic blood pressure; O₂-Pulse: oxygen uptake per heartbeat; SpO₂: oxygen saturation; VFL: volume of the tidal breath that is flow limited on expiration; EFL: expiratory flow limitation; EELV: end-expiratory lung volume; Slope of EELV across exercise stages: estimate of regression coefficient of three EELV measurements at each of baseline (rest), 20%, 40%, 60%, and 80% of the load intensity (watts) of the peak exercise stage achieved.

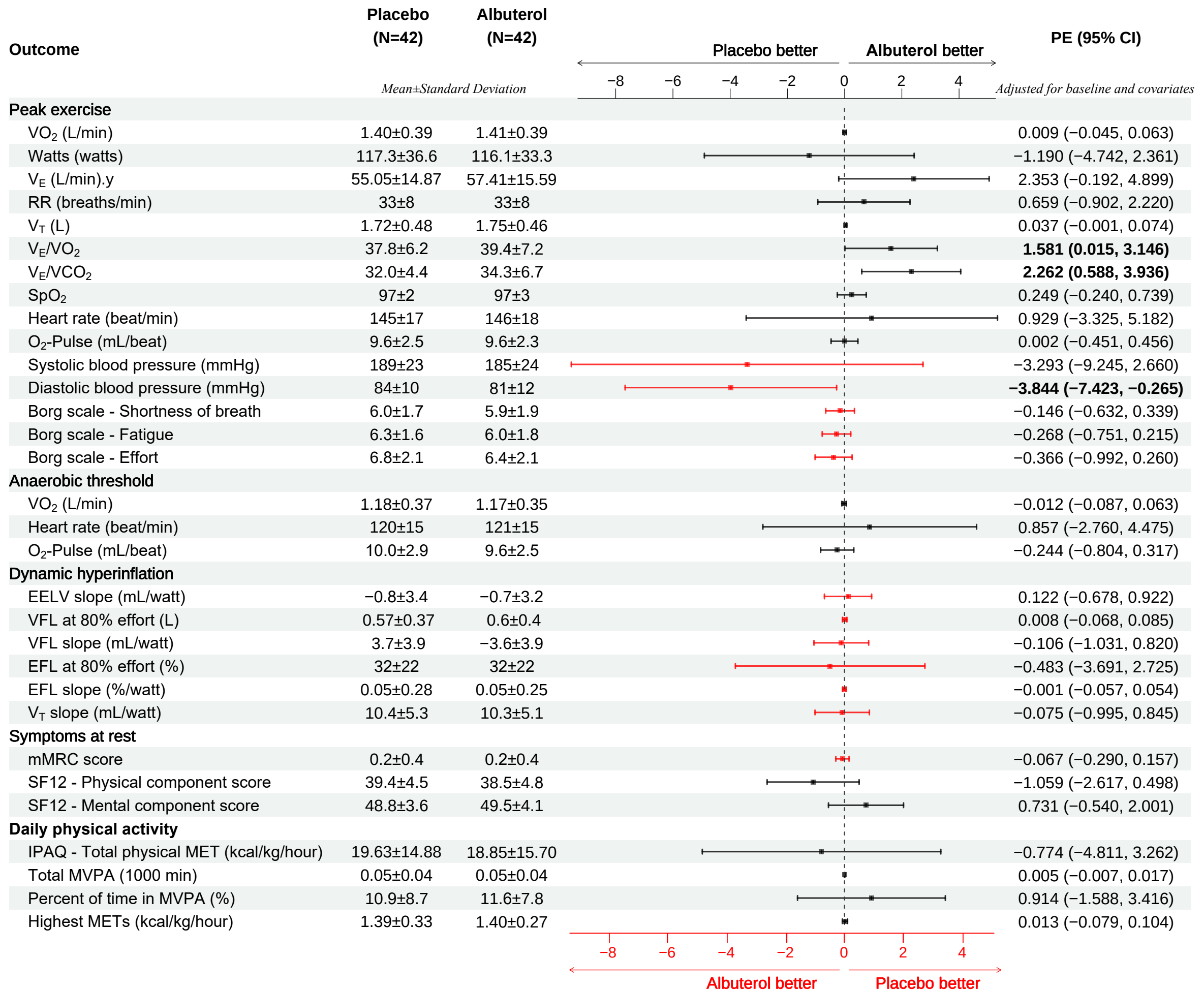
Table S3- Comparison of changes in outcomes after albuterol versus placebo treatments using paired t-test.

Subgroup	Variable	Average change from baseline		P value
		Albuterol	Placebo	
All completed	V_E/VCO_{2Peak}	-0.558	-2.821	0.012
	DBP_{Peak} (mmHg)	-2.2	1.6	0.048
	$RV@80\%$ (L)	-0.049	0.010	0.011
Air trapping by $RV/TLC > 0.35$	V_{TPeak} (L/min)	0.046	-0.017	0.005
	SpO_{2Peak} (%)	0.0	-0.6	0.037
	DBP_{Peak} (mmHg)	-2.9	1.8	0.040
$RV/TLC > 0.35$ and $\geq 90\%$ adherence	V_{EPeak} (L/min)	5.107	-0.565	0.029
	$O_2\text{-Pulse}_{Peak}$ (L/min/beat)	0.600	-0.145	0.005
	VO_{2Slope} (L/min/watt)	0.001	-0.0003	0.039

Footnote: Changes in the outcomes from baseline were calculated by subtracting the subsequent visits (V2 or V3) outcome values from those of baseline visit (V1). Statistical significance was determined by a paired t-test P value of <0.05 . Only outcomes with statistically significant change are shown. Abbreviations- V_E : minute ventilation value; VCO_2 : carbon dioxide production; DBP : diastolic blood pressure; RV : residual volume; V_T : tidal volume; SpO_2 : oxygen saturation; $O_2\text{-Pulse}$: oxygen uptake per heartbeat; VO_2 : oxygen uptake.

SUPPLEMENTAL FIGURE

Supplemental Figure S1- Associations of Albuterol and outcomes in participants who completed the entire study. The effect of Albuterol on the outcome variables was examined with a repeated measure design using mixed-effect linear regression modeling with the random subject effect and fixed effect variables including age, sex, height, weight, and the corresponding baseline measure of the outcome variable. The number of participants (N), the summary statistics (mean±standard deviation) for each outcome variables measured in the placebo visit and the albuterol visit as well as the resulted parameter estimate (PE) representing the adjusted difference and the corresponding 95% confidence interval (CI) are shown. In this intention-to-treat analysis, N represents the number of participants who completed each (albuterol or placebo) arm of the study. The dot-and-whisker plots represent the PE and 95% CI with colors black (scaled on the top) and red (scaled on the bottom) to distinguish outcomes in which higher versus lower values are preferable. The PE and 95% CI for the statistically significant associations were shown in bold. Abbreviations: VO₂: oxygen uptake; Watts: work stage completed in watts; V_E: minute ventilation value; RR: respiratory rate; V_T: tidal volume; VCO₂: carbon dioxide production; SpO₂: oxygen saturation; O₂-Pulse: oxygen uptake per heartbeat; EELV: end-expiratory lung volume; VFL: volume of the tidal breath that is flow limited on expiration; EFL: expiratory flow limitation; SF12: Short Form 12-Item Health Survey; IPAQ: International Physical Activity Questionnaire; MET: metabolic equivalent; MVPA: moderate to vigorous physical activities; PE: parameter estimate; CI: confidence interval.



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