



# OPEN Improved aerobic capacity in a randomized controlled trial of noncombustible nicotine and tobacco products

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Smoking negatively impacts aerobic capacity, primarily by reducing  $\dot{V}O_{2\max}$ , the gold standard measure of cardiorespiratory fitness. While smoking cessation is known to improve vascular function, exercise performance, and oxygen uptake, its specific impact on  $\dot{V}O_{2\max}$  remains underexplored. Specifically, no research has yet evaluated  $\dot{V}O_{2\max}$  changes following a switch to electronic cigarettes (ECs) or heated tobacco products (HTPs). This is a secondary analysis of the CEASEFIRE trial, a 12-weeks randomized controlled switching trial comparing the impact of ECs or HTPs on changes in smoking behaviour. The trial offers a unique opportunity to prospectively examine the relationship between smoking behavior and aerobic capacity, and to examine—for the first time—the specific impact of exclusive EC or HTP use on  $\dot{V}O_{2\max}$ . Changes in  $\dot{V}O_{2\max}$  were analyzed across three smoking phenotypes: continuous smokers, those who reduced smoking, and those who abstained from smoking. Additionally,  $\dot{V}O_{2\max}$  was also evaluated specifically in participants who completely abstained from smoking tobacco cigarettes, evaluating outcomes in exclusive EC and HTP users. Quitters showed the greatest improvement in  $\dot{V}O_{2\max}$  at both week 4 ( $2.4 \pm 1.7 \text{ mL kg}^{-1} \text{ min}^{-1}$ ) and week 12 ( $2.7 \pm 1.9 \text{ mL kg}^{-1} \text{ min}^{-1}$ ). Reducers also exhibited significant  $\dot{V}O_{2\max}$  increases ( $1.3 \pm 1.9 \text{ mL kg}^{-1} \text{ min}^{-1}$  at week 4;  $1.9 \pm 1.8 \text{ mL kg}^{-1} \text{ min}^{-1}$  at week 12), while Failures (i.e. those who continued smoking) showed no change. Exclusive use of EC and HTP resulted in statistically significant and clinically relevant improvements in  $\dot{V}O_{2\max}$ . Compared to baseline,  $\dot{V}O_{2\max}$  significantly increased at week 4 (EC:  $38.4 \pm 5.9$  to  $41.0 \pm 6.1 \text{ mL kg}^{-1} \text{ min}^{-1}$ ; HTP:  $39.2 \pm 6.7$  to  $41.4 \pm 6.4 \text{ mL kg}^{-1} \text{ min}^{-1}$ , both  $p < 0.0001$ ) and week 12 (EC:  $38.4 \pm 5.9$  to  $41.4 \pm 6.3$ ; HTP:  $39.2 \pm 6.7$  to  $41.6 \pm 6.5 \text{ mL kg}^{-1} \text{ min}^{-1}$ , both  $p < 0.0001$ ). No significant differences between EC and HTP were observed at either time point. Rapid improvements in  $\dot{V}O_{2\max}$  can happen when healthy smokers switch to exclusive use of ECs or HTPs. These findings reinforce the potential cardiorespiratory benefits of smoking cessation and harm reduction strategies.

**Keywords** e-cigarettes, Heated tobacco products, Smoking cessation, Aerobic capacity,  $\dot{V}O_{2\max}$

Chronic exposure to the harmful chemicals in tobacco cigarette smoke significantly impairs physical fitness, primarily by reducing oxygen availability at the tissue level and diminishing both aerobic and anaerobic exercise capacity<sup>1,2</sup>.

Smoking is well-documented to decrease endurance performance in healthy individuals and negatively impacts physical fitness test outcomes, with reduced oxygen uptake capacity playing a central role<sup>3,4</sup>. Furthermore,

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an inverse relationship has been observed between smoking history and maximal aerobic capacity (VO<sub>2</sub>max)<sup>2,5</sup>, the gold standard for assessing cardiorespiratory fitness<sup>6</sup>.

VO<sub>2</sub>max represents the maximum rate of oxygen consumption measured during incremental exercise and reflects the efficiency of the respiratory, cardiovascular, musculoskeletal, and metabolic systems in oxygen transport and utilization. A higher VO<sub>2</sub>max indicates improved aerobic capacity, which is associated with better cardiorespiratory fitness and reduced cardiovascular and all-cause mortality risk<sup>7,8</sup>.

Importantly, the negative effects of smoking on cardiorespiratory performance can be reversed upon cessation. Studies have shown that smoking cessation leads to significant improvements in vascular endothelial function, exercise performance and cardiovascular responses to physical activity<sup>9–12</sup>. These benefits can be observed as early as 12 weeks post-cessation and persist for up to three years<sup>9–12</sup>. Notably, the rapid improvements in VO<sub>2</sub>max observed post cessation suggest that this parameter may serve as a sensitive biomarker of physiological recovery, reflecting early changes in cardiorespiratory health. This makes VO<sub>2</sub>max particularly valuable in the context of smoking cessation and switching trials involving alternative nicotine and tobacco products. However, the physiological effects and health benefits of smoking cessation—especially those measured by VO<sub>2</sub>max—remain underexplored, with only one study to date having rigorously assessed this outcome<sup>11</sup>. Moreover, no research has yet evaluated VO<sub>2</sub>max changes following a switch to electronic cigarettes (ECs) or heated tobacco products (HTPs), representing a critical gap in the literature.

ECs and HTPs, battery-powered devices that deliver nicotine without combustion, have gained popularity as alternatives to conventional cigarettes<sup>13,14</sup>. These products are widely used by smokers aiming to reduce their exposure to harmful chemical emissions from combustion<sup>15–17</sup>. The key to their reduced harm potential lies in the elimination of combustion<sup>18</sup>, which is the primary source of toxicants in cigarette smoke. Although HTPs contain tobacco and may not offer the same level of harm reduction as ECs, both products have been explored for their potential to lower smoking-related harm<sup>19,20</sup> and their effectiveness as smoking cessation aids remains subject to ongoing research<sup>21,22</sup>.

We hypothesize that smokers who transition from combustible tobacco cigarettes to non-combustible nicotine/tobacco products (N-C NTPs) such as ECs and HTPs may experience measurable improvements in cardiorespiratory performance as a result of eliminating tobacco smoke exposure<sup>23</sup>. While previous research has documented the physiological effects and health improvements associated with switching to these products<sup>24–26</sup> the specific impact on VO<sub>2</sub>max remains insufficiently explored. Given that VO<sub>2</sub>max is a well-established indicator of aerobic capacity, any observed improvements following smoking cessation could provide valuable insights into the potential respiratory and cardiovascular benefits of smoking substitution.

This study examines changes in VO<sub>2</sub>max, measured using the sub-maximal Chester Step Test, in relation to smoking reduction and smoking abstinence among participants in the CEASEFIRE trial<sup>27</sup>. CEASEFIRE is a large prospective randomized controlled trial designed to assess smoking reduction and cessation rates among adult smokers transitioning from conventional cigarettes to N-C NTPs (ECs and HTPs). VO<sub>2</sub>max was assessed at baseline and monitored at multiple follow-up visits.

The CEASEFIRE trial offers a unique opportunity to prospectively investigate the impact of smoking reduction or cessation on aerobic capacity. This study presents a secondary analysis of the trial data, specifically examining changes in VO<sub>2</sub>max across three groups: continuous smokers, those who reduced smoking, and those who abstained from smoking. Additionally, no research has ever documented VO<sub>2</sub>max changes after switching to ECs or HTPs. Therefore, we conducted a separate analysis to assess the differential impact of exclusive EC use versus exclusive HTP use on VO<sub>2</sub>max, offering unique insights into the effects of these non-combustible nicotine and tobacco products.

## Methods

The current study serves as a secondary analysis of a large prospective randomized control non-inferiority trial that focused on examining the quit and reduction rates among adult smokers who transitioned from conventional tobacco cigarettes to non-combustible nicotine/tobacco products (N-C NTP) namely HTPs and ECs. The specifics regarding the population sample, study design, Ethics Review Board approval, study registration, and CONSORT reporting standards were previously detailed<sup>28</sup>.

Research was performed in accordance with the relevant guidelines/regulations and according to the Declaration of Helsinki. Informed consent was obtained from all participants and/or their legal guardians.

The de-identified datasets from the trial were sourced from the open science repository maintained by the Center of Excellence for the Acceleration of Harm Reduction (CoEHAR) at the University of Catania, and subsequently utilized for this analysis: <https://zenodo.org/records/7941030>

Since the study exclusively used publicly available, de-identified data, it was exempt from ERB review. Only complete and reliable data were extracted to ensure analytical integrity.

## Study participants

Adult smokers of  $\geq 10$  cigarettes per day (regularly smoking for at least the past year) and with exhaled carbon monoxide (eCO) levels of  $\geq 7$  ppm, not planning to quit soon (within the next 30 days from screening), but open to switching to HTPs or ECs were recruited from hospital and university staff, via social media, and through word of mouth. They confirmed no quit intention by answering “No” to these two questions: “Do you plan to quit smoking within the next 30 days?” and “Do you wish to participate in a smoking cessation program?” They also met specific exclusion criteria including: (1) history of mental disease, (2) history of alcoholism or drug abuse, (3) presence of clinical diseases that, in the opinion of the investigator, would jeopardize the safety of the participant or impact the validity of the study results, (4) use of any N-C NTPs within the last 3 months, and (5) use of nicotine replacement therapy or other smoking cessation therapies within the last 3 months. Subjects were informed that the purpose of the study was to quantify the impact of reductions in cigarette consumption

on cardio-respiratory performance. The study was approved by the local Ethical Review Board (Comitato Etico, Azienda Ospedaliero Universitaria “Policlinico-V. Emanuele,” Università di Catania, Italy; approval no. 215/2017/PO). All participants provided written informed consent prior to participation in the study. The study was registered at ClinicalTrials.gov (trial registration ID: NCT03569748).

### Trial design and study visits

Eligible subjects were enrolled into a 12-week, randomized, two parallel arm, controlled trial consisting of seven study visits (one screening visit and six study visits) at smoking cessation clinics of the University of Catania (Centro per la Prevenzione e Cura del Tabagismo – CPCT) designed to compare cessation and reduction rates between HTPs and ECs study arms. The trial also measured maximal aerobic capacity by Chester step test at baseline, week-4, and week-12.

At the baseline visit, subjects were randomized to either the HTP (IQOS 2.4) group or the EC (JustFog Q16 Starter Kit) group and were instructed to use the assigned product to assist in abstaining from cigarette smoking. Participants were asked to return to the CPCT for follow-up visits to obtain regular supplies of tobacco sticks (for IQOS 2.4 users) and e-liquid refills (for JustFog Q16 users). During these visits, subjects were required to report their tobacco cigarette and EC/HTP consumption, undergo measurements of eCO levels, and have their blood pressure (BP) and heart rate (HR) assessed. Self-reported use of tobacco cigarette and HTPs or ECs since the previous visit was noted in a study diary and recorded in the electronic case report form at each visit (from V2 to V6). Additionally, EC/HTP consumption was verified through checks of product use (by counting the number of used and unused tobacco sticks and liquid refill containers) and calculated as average consumption on a per daily basis. Additionally, the Chester step test was scheduled to be repeated at weeks 4 and 12.

### Exhaled carbon monoxide measurements

Measurements of exhaled carbon monoxide (eCO) levels, expressed in parts per million (ppm), were taken using a hand-held CO meter (Micro CO; Micro Medical Ltd, UK). Subjects were instructed to exhale slowly into a disposable mouthpiece connected to the CO meter, following the manufacturer’s recommendations. Expiratory maneuvers were taken late in the morning or early in the afternoon with participants sitting comfortably. Participants were requested to refrain from smoking, vaping, or using heated tobacco products (HTPs) for at least 30 min prior to each measurement. Smoking status was objectively confirmed when eCO levels exceeded 10 ppm.

### Chester step test procedure

The Chester Step Test (CST) is a validated test assessing maximal aerobic capacity (maximal oxygen consumption, VO<sub>2</sub>Max) by having subjects step on and off a gym step at gradually increasing stepping rates every two minutes to increase their heart’s rate, which was used to calculate their VO<sub>2</sub> max<sup>29,30</sup>. The test provides good test–retest reliability and is an acceptable method for estimating VO<sub>2</sub>max in the general healthy adult population<sup>31</sup>.

Before the commencing the test, participant’s blood pressure (BP) and resting heart rate (HR) were measured. Participants were then instructed to step in time with the beat of a metronome initially set at 15 beats/minute. Every 2-min, stepping rate was increased by 5 steps/minute (from 15 to 35 bpm, a total of 5 stages). HR and rating of perceived exertion (RPE) were recorded at each stage. The test continues until the participant reaches a specific HR (80% HR max) or a moderately vigorous level of exertion (RPE below 14). Aerobic capacity (VO<sub>2</sub>Max) and fitness rating are determined using a Chester Step Test calculator available at: <https://www.briannmac.co.uk/chester.htm>.

### Smoking phenotypes

The study analyzed the time-course of VO<sub>2</sub>max changes in relation to three different smoking phenotypes: quitters vs. reducers vs. failures.

Smoking abstinence is defined as complete self-reported abstinence from cigarette smoking since the previous study visit, which was biochemically verified by eCO levels of < 10 ppm. Smokers in this category are classified as **quitters**. Continuous abstinence rate from week 2 to week 4 (CAR 2–4 Weeks) and from week 2 to week 12 (CAR 2–12 Weeks) were used as a robust characterization of smoking abstinence. Among the quitters, we employed a further subclassification to distinguish between individuals who achieved abstinence after switching to ECs and those who quit after switching to HTPs. This allowed for a more granular comparison of outcomes based on the type of study product used.

Smoking reduction is defined as self-reported ≥ 50% reduction in the number of cigarettes smoked per day from baseline (eCO levels were measured to verify smoking status and confirm a reduction compared with baseline). Smokers in this category are classified as **reducers**. Continuous reduction rates from week 2 to week 4 (CRR 2–4 Weeks) and from week 2 to week 12 (CRR 2–12 Weeks) were used as a robust characterization of smoking reduction.

Smoking failure is the smoking phenotype that excludes smoking abstinence or smoking reduction. Smokers in this category are classified as **failures**.

### Statistical analysis

In the primary analysis, a total of 220 smokers were enrolled, with 110 participants assigned to the EC Study arm and 110 to the HTP Study arm. For the current secondary analysis, subjects’ VO<sub>2</sub>max measurements from both study arms were pooled and evaluated for changes from baseline at the 4-week and 12-week time points, stratified by smoking behavior phenotype: Failures (continued smokers), Reducers, and Quitters (complete abstainers). In addition, this secondary analysis also investigated possible differential impact of exclusive EC use and exclusive HTP use on VO<sub>2</sub>max, providing novel insights into the cardiorespiratory effects of N–C NTPs.

	Failures (n = 32)	Reducers (n = 88)	Quitters (n = 67)	P value
Sex, F/M, No	8/24	39/49	36/31	0.027
Age (years)	47.2 ± 17.2	39.4 ± 16.5	39.8 ± 15.1	0.113
Body mass index (Kg/m <sup>2</sup> )	24.5 ± 4.2	24.4 ± 4.6	23.8 ± 4.0	0.617
Cigarettes/day (No.)	22 ± 8	23 ± 12	21 ± 9	0.769
Years of smoking	28.8 ± 14.8	21.3 ± 16.1	22.6 ± 14.8	0.073
Pack/years	34.2 ± 21.2	28.6 ± 29.4	25.8 ± 22.1	0.171
eCO (ppm)	28.8 ± 13.9	24.4 ± 11.9	27.5 ± 14.3	0.203
VO <sub>2</sub> max (ml min <sup>-1</sup> kg <sup>-1</sup> )	38.6 ± 5.7	38.6 ± 7.5	38.9 ± 6.3	0.704

**Table 1.** Demographic data, smoking history and maximal oxygen consumption (VO<sub>2</sub>max) at baseline for each smoking phenotype. Values are expressed as frequencies or mean ± standard deviation. eCO Exhaled breath carbon monoxide; ppm Part per million.

	Failures	Reducers	Quitters
Baseline	22.1 ± 8.3	23.2 ± 12.1	21.4 ± 9.3
Week 1	17.7 ± 8.0	4.1 ± 2.0	0
Week 2	17.0 ± 7.9	4.8 ± 2.7	0
Week 4	16.4 ± 7.8	4.7 ± 2.6	0
Week 8	16.9 ± 7.0	5.0 ± 3.1	0
Week 12	17.8 ± 7.1	5.7 ± 3.3	0

**Table 2.** Cigarette consumption (cigarettes/day) data at different time points and for each smoking phenotype (mean ± SD).

Categorical variables were summarized using counts and percentages, while continuous variables with symmetrical distribution were presented as mean and standard deviations (SD). Skewed continuous data were summarized using median and interquartile ranges (IQR). Comparisons were conducted using the  $\chi^2$  test for categorical variables, and one-way Analysis of Variance (ANOVA) and Kruskal–Wallis tests for normally and not normally distributed data, respectively. A two-way ANOVA was used to assess the effects of classification and sex on VO<sub>2</sub> max at baseline. A repeated measures ANOVA model was applied to examine potential effects of classifications and sex on VO<sub>2</sub> max over time. To evaluate the association between smoking phenotypes and changes in VO<sub>2</sub> max from baseline to week 4 and week 12, while accounting for potential confounders, a multiple linear regression analysis was performed. The outcome variable was  $\Delta$ VO<sub>2</sub> max (i.e., the absolute difference in VO<sub>2</sub> max from baseline to weeks 4 and 12), with classification, age, sex and BMI changes from baseline included as independent factors. These variables were selected based on existing evidence indicating their potential influence on cardiorespiratory performance.

The analyses were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) for Windows version 20.0 and *p* values < 0.05 were considered significant.

## Results

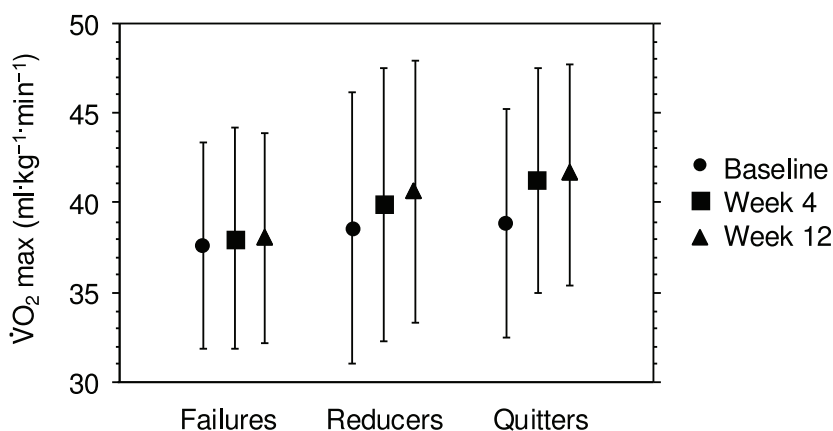
For this secondary analysis, data from 187 subjects were available. This accounted for missing data from subjects who either could not perform the Chester Step Test or did not qualify as continuous smoking phenotypes (Quitters, Reducers, or Failures, based on the provided definitions). Among the 187 evaluated subjects, 32 (17%) were classified as Failures, 88 (47%) as Reducers, and 67 (36%) as Quitters. A description of the evaluated sample is presented in Table 1. Table 2 illustrates the level of cigarette consumption for each smoking phenotype, showing that Reducers had on average a greater than 75% reduction in cigarette consumption from baseline.

At baseline, the frequency distribution of sex among classes (i.e., Failures, Reducers, and Quitters) was significantly different ( $p = 0.027$ ,  $\chi^2$  test). Conversely, no significant difference was found for age among classes and sex (Two-way ANOVA). Additionally, no significant difference was found at baseline for cigarettes per day, pack-years, and the number of years of smoking among sex and classes (Two-way ANOVA). As expected, VO<sub>2</sub>max was significantly different between males and females ( $p < 0.0001$ ) at baseline, while no difference was found among classes ( $p = 0.147$ , Two-way ANOVA).

Regarding the effect of individual smoking history on baseline VO<sub>2</sub>max, strong negative correlations were found between VO<sub>2</sub>max and both the natural log of years of smoking ( $R^2 = 0.469$ ,  $p < 0.0001$ ) and the natural log of pack-years ( $R^2 = 0.389$ ,  $p < 0.0001$ ). In a multiple linear model, both correlations disappeared when corrected for sex and age, which were the only independent variables correlated to VO<sub>2</sub>max at baseline. However, to limit the obvious effect of age on individual smoking history by evaluating a narrower age window, in a subset with age range between 19 and 30 years, we found that in a multiple regression model for VO<sub>2</sub>max at baseline, sex

	Baseline	VO <sub>2</sub> max week 4	ΔVO <sub>2</sub> max week 4	VO <sub>2</sub> max week 12	ΔVO <sub>2</sub> max week 12
Failures (ml kg <sup>-1</sup> min <sup>-1</sup> )	37.6 ± 5.7	38.1 ± 6.2	0.4 ± 2.0	37.9 ± 5.9	0.3 ± 1.7
Reducers (ml kg <sup>-1</sup> min <sup>-1</sup> )	38.6 ± 7.5	39.9 ± 7.6	1.3 ± 1.9	40.5 ± 7.3	1.9 ± 1.8
Quitters (ml kg <sup>-1</sup> min <sup>-1</sup> )	38.9 ± 6.3	41.2 ± 6.3	2.4 ± 1.7	41.5 ± 6.2	2.7 ± 1.9

**Table 3.** Values of VO<sub>2</sub> max (ml min<sup>-1</sup> kg<sup>-1</sup>) at baseline, week 4, and week 12 separately per each continuous smoking phenotypes along with absolute changes in VO<sub>2</sub> max from baseline at weeks 4 and 12 (means ± SD). Time ( $p < 0.0001$ ), smoking phenotype classification ( $p = 0.004$ ), and sex ( $p < 0.0001$ ) all had a significant effect on VO<sub>2</sub> max changes over the time (Repeated measures ANOVA). In the model, no significant effect was produced by the product used (EC or HTP,  $p = 0.144$ ). ΔVO<sub>2</sub> max: Absolute change in VO<sub>2</sub> max with respect to baseline.



**Fig. 1.** Means ± SDs relevant to the values of VO<sub>2</sub> max at baseline, week 4 and week 12 separately for smoking phenotype classification. Time ( $p < 0.0001$ ), smoking phenotype classification ( $p = 0.01$ ) and sex  $p < 0.0001$  had a significant effect on VO<sub>2</sub> max (Repeated Measures ANOVA model, adopting time as within factor and classification and sex as between factors).

( $B = -4.834$  [95% CI  $-6.218/-3.451$ ], reference: Males,  $p < 0.0001$ ) and the natural log of pack-years ( $B = -1.269$  [95% CI  $-2.469/-0.069$ ],  $p = 0.038$ ) showed a significant correlation, but not age ( $p = 0.820$ ).

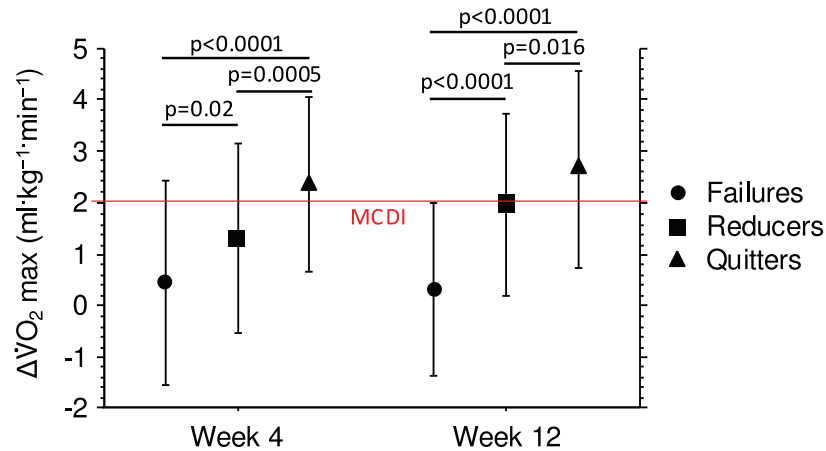
The correlation between VO<sub>2</sub>max and the natural log of eCO at baseline was significant ( $R^2 = 0.055$ ,  $p = 0.0013$ ). Additionally, the correlation between changes in VO<sub>2</sub>max (ΔVO<sub>2</sub>max) at week 12 and at week 4 was also significant ( $R^2 = 0.77$ ,  $p < 0.0001$ ).

Table 3 and Fig. 1 present the means and standard deviations (SDs) of VO<sub>2</sub>max at baseline, week 4, and week 12, separately for each continuous smoking phenotypes. A Repeated Measures ANOVA model, using time as the within-subject factor and classification and sex as between-subject factors, showed that time ( $p < 0.0001$ ), phenotype classification ( $p = 0.004$ ), and sex ( $p < 0.0001$ ) all had significant effects on VO<sub>2</sub>max changes over time. In the model, no significant effect was produced by the product used (EC or HTP,  $p = 0.144$ ).

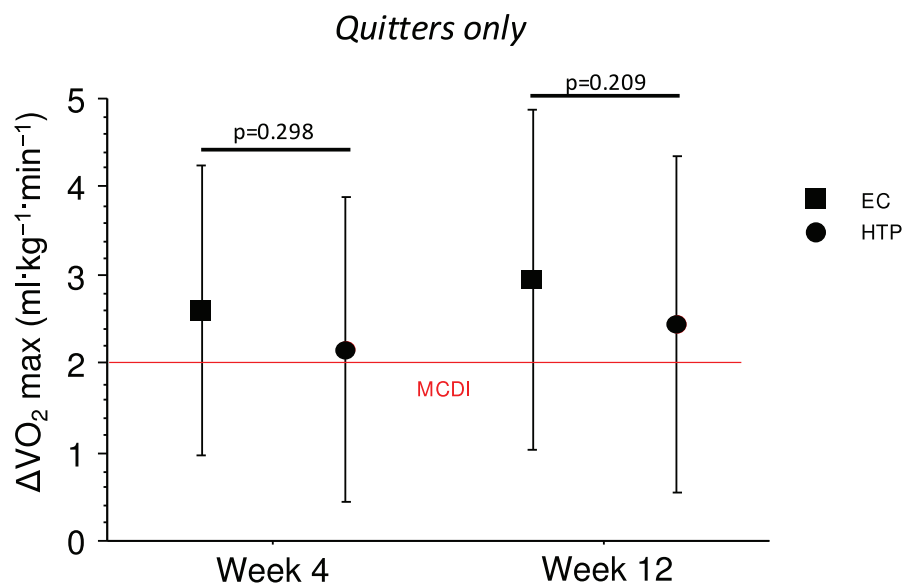
In Fig. 2 and Table 3, the means and SDs of changes in VO<sub>2</sub>max (ΔVO<sub>2</sub>max) at week 4 and week 12 from baseline are shown separately for each continuous smoking phenotypes. A one-way ANOVA model indicated that, among Quitters, ΔVO<sub>2</sub>max was significantly greater at both week 4 ( $2.4 \pm 1.7$  mL kg<sup>-1</sup> min<sup>-1</sup>) and week 12 ( $2.7 \pm 1.9$  mL kg<sup>-1</sup> min<sup>-1</sup>,  $p < 0.0001$  for both). Statistically significant improvements in ΔVO<sub>2</sub>max were also observed among Reducers at both week 4 and week 12, with increases of  $1.3 \pm 1.9$  and  $1.9 \pm 1.8$  mL kg<sup>-1</sup> min<sup>-1</sup>, respectively ( $p < 0.0001$  for both). In subjects who continued to smoke at the same rate as baseline, the estimated VO<sub>2</sub>max remained unchanged.

In Fig. 3 the means and SDs relevant to the comparisons of the changes in ΔVO<sub>2</sub> max at week 4 and week 12 are shown for Quitters using EC or HTP. Both exclusive EC and HTP use caused a statistically significant and clinically relevant amelioration in VO<sub>2</sub>max. Compared to baseline, VO<sub>2</sub>max values were significantly greater at both week 4 (from  $38.4 \pm 5.9$  mL kg<sup>-1</sup> min<sup>-1</sup> to  $41.0 \pm 6.1$  mL kg<sup>-1</sup> min<sup>-1</sup>;  $p < 0.0001$ , Repeated Measures ANOVA) and week 12 (from  $38.4 \pm 5.9$  mL kg<sup>-1</sup> min<sup>-1</sup> to  $41.4 \pm 6.3$  mL kg<sup>-1</sup> min<sup>-1</sup>;  $p < 0.0001$ ) for exclusive EC use. Likewise, VO<sub>2</sub>max values were significantly greater than baseline at both week 4 (from  $39.2 \pm 6.7$  mL kg<sup>-1</sup> min<sup>-1</sup> to  $41.4 \pm 6.4$  mL kg<sup>-1</sup> min<sup>-1</sup>;  $p < 0.0001$ ) and week 12 (from  $39.2 \pm 6.7$  to  $41.6 \pm 6.5$  mL kg<sup>-1</sup> min<sup>-1</sup>;  $p < 0.0001$ ) for exclusive HTP use. No significant differences between EC and HTP usage were found by means of one-way ANOVA at both time points.

Tables 4 and 5 present the multiple linear regression models for ΔVO<sub>2</sub>max at week 4 and week 12, respectively. At both weeks 4 and 12, VO<sub>2</sub>max significantly increased in both Reducers and Quitters, with no significant effects found for age and sex. Being a Reducer or a Quitter resulted in a significantly greater improvement in



**Fig. 2.** Means  $\pm$  SDs relevant to the changes in  $\text{VO}_2$  ( $\Delta\text{VO}_2$ ) max at week 4 and week 12 separately for phenotype smoking classification. *P* values were computed by means of one-way ANOVA and Fisher’s protected Least Significant Difference. MCID; the minimum clinically important difference is defined as an improvement in anaerobic threshold of at least 2 ml O<sub>2</sub>/kg/min.



**Fig. 3.** Means  $\pm$  SDs relevant to the changes in  $\text{VO}_2$  ( $\Delta\text{VO}_2$ ) max at week 4 and week 12 separately for EC and HTP users, in Quitters only. *P* values were computed by means of one-way ANOVA. MCID; the minimum clinically important difference is defined as an improvement in anaerobic threshold of at least 2 ml O<sub>2</sub>/kg/min.

$\text{VO}_{2\text{max}}$ . The number of pack-years (as natural log) was positively correlated to  $\Delta\text{VO}_{2\text{max}}$ , while age was negatively correlated. Changes in BMI from baseline (this information was only available at week 12) were similarly negatively correlated to  $\Delta\text{VO}_{2\text{max}}$ .

### Discussion

Research suggests that abstaining from smoking can improve exercise performance, though the evidence from longitudinal studies is very limited. This 12-week prospective cohort analysis shows significant and clinically relevant improvements in exercise capacity among smokers who were encouraged to quit their cigarette consumption by switching to HTPs or ECs. Improvements were also observed in individuals who reduced their tobacco cigarette consumption. The study specifically shows—for the first time—consistent improvement in  $\text{VO}_{2\text{max}}$ , among quitters exclusively using EC or HTP. Notably, there was a significant increase in aerobic capacity (i.e. maximal oxygen consumption,  $\text{VO}_{2\text{max}}$ ), observable as early as 4 weeks.

	B	95% CI	p Value
Sex (Ref. M)	0.042	-0.509/0.594	0.880
Reducers (Ref. failures)	0.835	0.087/1.583	0.029
Quitters (Ref. failures)	1.837	1.050/2.623	<0.0001
Natural log of pack (Yrs)	0.628	0.186/1.069	0.006
Age (Yrs)	-0.041	-0.073/-0.009	0.012
BMI at baseline (kg/m <sup>2</sup> )	0.044	-0.022/0.110	0.190

**Table 4.** Multiple linear regression model for  $\Delta\text{VO}_2$  max at week 4. B values and relevant 95% confidence interval (95%CI) are reported for each independent variable.

	B	95% CI	p Value
Sex (Ref. M)	0.302	-0.201/0.805	0.238
Reducers (Ref. failures)	1.694	1.013/2.375	<0.0001
Quitters (Ref. failures)	2.550	1.829/3.270	<0.0001
$\Delta\text{BMI}$ at Wk 12 (kg/m <sup>2</sup> )	-0.981	-1.291/-0.670	<0.0001
Natural log of Pack/Yrs	0.650	0.248/1.051	0.002
Age (yrs)	-0.035	-0.064/0.006	0.019
BMI at baseline (kg/m <sup>2</sup> )	0.001	-0.059/0.061	0.980

**Table 5.** Multiple linear regression model for  $\Delta\text{VO}_2$  max at week 12. B values and relevant 95% confidence interval (95%CI) are reported for each independent variable.  $\Delta\text{BMI}$  at Wk 12: absolute change in BMI at week 12 with respect to baseline.

The study used the standardized Chester Step Test (CST) to estimate maximal aerobic capacity (i.e.,  $\text{VO}_2\text{max}$ ). While the CST may not be as accurate as direct  $\text{VO}_2\text{max}$  measurements obtained through standard cardiopulmonary exercise testing (which requires gas analyzers and complex procedures), it offers a simpler and valid alternative that could be easily incorporated into routine clinical practice<sup>29–31</sup>. Additionally, the CST, being sub-maximal, is safer than cardiopulmonary exercise testing and is also more rapid, making it a useful tool for assessing large study samples with repeated measures after interventions aimed at improving the O<sub>2</sub> transport/utilization pathway. For these reasons, CST was considered the ideal test to examine  $\text{VO}_2\text{max}$  changes in the context of a large prospective switching trial of ECs and HTPs.

This study demonstrates that abstaining from smoking can improve  $\text{VO}_2\text{max}$ . Specifically, consistent and clinically relevant improvements were observed among quitters exclusively using EC or HTP. This adds important new information to the current understanding of how stopping smoking and complete substituting tobacco cigarettes with N-C NTPs can reverse the detrimental effects of cigarette smoke exposure on aerobic capacity in relatively young and apparently healthy individuals. The improvement in  $\text{VO}_2\text{max}$  in our study aligns with the findings that the aerobic capacity of current smokers is significantly lower compared to non-smokers and former smokers<sup>32,33</sup>.

Our study shows an improvement in  $\text{VO}_2\text{max}$  of at least 2.2 and 2.6 mL kg<sup>-1</sup> min<sup>-1</sup> from baseline among HTP and EC users, respectively. These changes are statistically significant as early as week 4 and exceed the minimum clinically important difference (MCID) for  $\text{VO}_2\text{max}$  (defined as an increase in anaerobic threshold of at least 2 mL O<sub>2</sub> kg<sup>-1</sup> min<sup>-1</sup>). The reported changes were not significantly different between EC and HTP. This suggests that individuals who quit smoking by switching to ECs or HTPs can achieve an early and clinically meaningful improvement in aerobic capacity. An improvement beyond the MCID reflects enhanced cardiorespiratory fitness, which may translate into better daily functioning and physical performance.

An important additional finding of this present study is that we found statistically significant improvements in  $\Delta\text{VO}_2\text{max}$  among reducers, with increases of 1.3 and 1.9 mL kg<sup>-1</sup> min<sup>-1</sup> at week 4 and week 12, respectively. In this cohort of reducers, daily cigarette consumption was consistently reduced by at least 75% from baseline throughout the entire study duration. By substantially reducing cigarette smoking with N-C NTPs (i.e. HTPs or ECs) use and thereby curtailing exposure to several toxic chemicals, we observed an amelioration in aerobic capacity may have resulted.

The rapid and significant improvements in  $\text{VO}_2\text{max}$  following smoking cessation after switching to N-C NTPs can be attributed to several potential mechanisms, including a reduction in carbon monoxide (CO) levels. Tobacco smoking increases CO in the bloodstream, which binds to hemoglobin with a much higher affinity than oxygen, leading to elevated carboxyhemoglobin (COHb) levels and reduced oxygen-carrying capacity. This compromises oxygen delivery to muscle mitochondria, affecting  $\text{VO}_2\text{max}$  by reducing available binding sites on hemoglobin and slowing oxygen unloading at active muscles<sup>34</sup>. Inhalation of CO sufficient to raise COHb to approximately 4.5% (equivalent to smoking three cigarettes) has been shown to decrease  $\text{VO}_2\text{max}$  by about 7%<sup>35</sup>. Consistently, our study found a small but significant correlation between exhaled CO and estimated  $\text{VO}_2\text{max}$ . The correlation remained modest because smoking influences exercise capacity through multiple mechanisms, including improvements in vascular endothelial function, and reductions in exposure to advanced glycation

end products (AGEs) and nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)<sup>36,37</sup>. For example, years of smoking – a key predictor of reduced physical fitness—was inversely correlated with baseline VO<sub>2</sub>max in our study.

The marked decline in CO and COHb levels following cigarette substitution with combustion-free alternatives<sup>38,39</sup> rapidly restores the oxygen-carrying capacity of the blood, improving oxygen delivery to muscles during exercise. This contributes to the time-dependent improvement in aerobic capacity, with greater improvement observed at 12 weeks due to a higher prevalence of quitters compared to 4 weeks. This aligns with improved exercise tolerance seen in COPD patients who switched to e-cigarettes<sup>26</sup> and heated tobacco products<sup>40</sup>.

The study had both strengths and limitations. The initial RCT provided a large, well-characterized cohort with standardized data collection methods, ensuring careful tracking of physiological changes over time and biochemical verification of smoking status. This approach minimized biases commonly associated with retrospective or cross-sectional studies, enhancing the credibility of our findings, particularly in terms of data quality and consistency. Notably, the use of biochemically verified continuous abstinence rate (CAR) as a measure of abstinence is particularly valuable in this type of study, as continuous abstinence is the key driver of health improvements in a per-protocol analysis. The high CAR in this dataset can be attributed to strong acceptability and effectiveness of the smoking substitution products used in the original study<sup>27</sup>. This, combined with personalized counseling from psychologists specialized in both smoking cessation and harm reduction, played a crucial role in preventing relapse. While we recognize the importance of evaluating unaided cessation in the broader context of harm reduction, our secondary analysis specifically focused on the pathophysiological impact of smoking cessation/reduction, as reflected in measurable improvements in aerobic capacity. Both ECs and HTPs were effective in promoting smoking cessation and improving VO<sub>2</sub>max. However, it is important to emphasize that the original CEASEFIRE trial was specifically designed to compare ECs and HTPs, and therefore did not include a control group to isolate the individual effects of each product. While the inclusion of an unaided quitter control group would certainly enhance future research, its absence in this study does not compromise the validity of the current findings. Another limitation of this study is the limited generalizability of the findings, as the relatively young population with normal weight and no preexisting diseases may not accurately represent the broader patient population. Additionally, study participants were from urban Sicilian settings, which may limit the generalizability due to unique lifestyle factors such as diet, exercise, and genetics. Furthermore, we used only one exercise modality, namely CST, to assess improvement in aerobic capacity, whereas other types of exercise tests may be more precise for this assessment. However, the Chester Step test has previously been demonstrated as an appropriate tool to track changes over the time, which was the purpose of our study. It also has a high test–retest reliability, which lends itself to repeat testing manoeuvres. We also could not control for changes in exercise habits during the study, which is a known factor influencing improvements in VO<sub>2</sub>max and/or VO<sub>2</sub>peak<sup>41</sup> but this is unlikely to have been different between the randomised cohorts to account for the differences seen.

In conclusion, this post-hoc analysis suggests early significant improvements in exercise capacity among healthy smokers who quit smoking by switching to either exclusive ECs or HTPs use. Given that VO<sub>2</sub>max is the key indicator of exercise capacity and a strong predictor of cardiovascular morbidity and all-cause mortality<sup>7,8</sup>, these findings provide valuable insights into the potential benefits of switching from tobacco cigarettes to combustion free nicotine alternatives. However, as this is a post-hoc analysis, causality cannot be established, and further prospective studies are needed to confirm the present findings.

Recognizing changes in VO<sub>2</sub>max as early indicators of health effect will strengthen their value across clinical, regulatory, and research settings. Clinicians can leverage this information to recommend smoking cessation interventions, that may lead to tangible improvements in physical performance and overall well-being. Additionally, researchers may consider including VO<sub>2</sub>max measurements as clinically meaningful outcomes in future studies involving e-cigarettes, heated tobacco products, oral tobacco/nicotine products, smoking cessation medications, and other medicinal products designed to improve physical performance.

## Data availability

The de-identified datasets from the trial were sourced from the open science repository maintained by the Center of Excellence for the Acceleration of Harm Reduction (CoEHAR) at the University of Catania, and subsequently utilized for this analysis: <https://zenodo.org/records/7941030>.

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### Author contributions

Polosa Riccardo: designed research Davide Campagna: performed research Grazia Caci: collected data, Fabio Cibella, Claudio Saitta, Jacob George: analyzed data and revised the manuscript Lucia Spicuzza: wrote paper. Francesco Pennisi: MS second revision and literature revision Giulio Geraci MS second revision and literature revision Yusuff Adebisi: Ms third revision.

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## Declarations

### Competing interests

RP is full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. He has received grants from U-BIOPRED and AIR-PROM, Integral Rheumatology & Immunology Specialists Network (IRIS), Foundation for a Smoke Free World, Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merck Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group Srl., Duska Therapeutics, Forest Laboratories, Ministero dell'Università e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union (EU), and the ministerial grant PON REACT-EU 2021 GREEN- Bando 3411/2021 by Ministero dell'Università e (MUR) – PNRR EU Community. He is founder of the Center for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc., GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbooks royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO); and he is Chair of the European Technical Committee for Standardization on “Requirements and test methods for emissions of electronic cigarettes” (CEN/TC 437; WG4). All other authors declare no conflict of interests.

### Additional information

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