SUPPLEMENTAL MATERIAL

Data S1.

Additional details on statistical analysis

Analysis was based on a long-formatted database, as the sample below:

ID	Order	Product	Timing	Measurement
1	1	A	Baseline	Y1
1	2	A	Post	Y2
1	3	B	Baseline	Y3
1	4	B	Post	Y4
1	5	C	Baseline	Y5
1	6	C	Post	Y6
2	1	B	Baseline	Y7
2	2	B	Post	Y8
2	3	C	Baseline	Y9
2	4	C	Post	Y10
2	5	A	Baseline	Y11
2	6	A	Post	Y12
…	…	…	…	…

The model for the within-product before-after analysis was:

$Y_{ij} = \beta_0 + \beta_1 Time + \upsilon_1 ID + \upsilon_2 Order + \varepsilon$

with β representing the fixed effects, υ the random effects, and ε the Gaussian error term.

The Stata code for the within-product before-after analysis was:

```
mixed Measurement Timing || ID:, || Order:, covariance(identity)
```

Conversely, the model for the between-product interaction analysis was:

$Y_{ij} = \beta_0 + \beta_1 Time + \beta_2 Product + \beta_3 Time*Product + \upsilon_1 ID + \upsilon_2 Order + \varepsilon$

with β representing the fixed effects, υ the random effects, and ε the Gaussian error term.

Accordingly, the Stata code for the between-product interaction analysis was:

```
mixed Measurement Timing##Product || ID:, || Order:, covariance(identity)
```

A sample screenshot for the Stata output is the following:

```
. mixed FMD Pre0Post1##TC1EC2HNS3 || ID:, || Order:, covariance(identity)

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -248.25534
Iteration 1:   log likelihood = -246.75537
Iteration 2:   log likelihood = -246.71072
Iteration 3:   log likelihood = -246.71072

Computing standard errors:

Mixed-effects ML regression                     Number of obs      =       115
```

Group Variable	No. of Groups	Observations per Group Minimum	Average	Maximum
ID	20	3	5.8	6
Order	58	1	2.0	2

```
                                                Wald chi2(5)       =     91.50
Log likelihood = -246.71072                     Prob > chi2        =    0.0000
```

FMD	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
1.Pre0Post1	-3.8114	.5404618	-7.05	0.000	-4.870685	-2.752114
TC1EC2HNS3						
2	-.0707635	.5545494	-0.13	0.898	-1.15766	1.016133
3	-.1178998	.5404618	-0.22	0.827	-1.177185	.9413859
Pre0Post1#TC1EC2HNS3						
1 2	1.389178	.7785131	1.78	0.074	-.1366801	2.915035
1 3	1.5004	.7580794	1.98	0.048	.0145915	2.986208
_cons	6.2149	.6280043	9.90	0.000	4.984034	7.445766

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
ID: Identity				
var(_cons)	4.871662	1.691218	2.467056	9.620007
Order: Identity				
var(_cons)	1.25e-17	6.91e-17	2.56e-22	6.14e-13
var(Residual)	2.825853	.4095205	2.127131	3.754094

```
LR test vs. linear regression:       chi2(2) =    70.26   Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Table S1. Additional inferential analysis.

Feature	Point estimate of effect (95% confidence interval)		
	EVC vs TC	**EVC vs HNBC**	**TC vs HNBC**
Primary endpoints			
Soluble Nox2-derived peptide (pg/mL)	-4.30 (-12.74; 4.14)	**-9.55 (-16.00; -3.10)**	**-13.85 (-22.29; -5.41)**
Flow-mediated dilation (%)	1.39 (-0.14; 2.92)	0.11 (-1.25; 1.47)	**1.50 (0.02; 2.97)**
Additional endpoints			
Nitric oxide bioavailability (µM)	5.18 (-4.77; 15.13)	3.35 (-5.73; 12.42)	8.52 (-1.42; 18.48)
H_2O_2 production (µmol/L)	-4.58 (-9.89; 0.74)	-0.94 (-3.81; 1.94)	**-5.51 (-10.83; -0.20)**
H_2O_2 breakdown activity (%)	**11.63 (0.64; 22.61)**	8.76 (-1.40; 18.91)	**20.38 (9.40; 31.37)**
8-iso-prostaglandin F-2α-III (pmol/L)	**-44.4 (-66.1; -22.7)**	**-31.0 (-52.2; -9.8)**	**-75.4 (-97.1; -53.7)**
Vitamin E (µmol/mmol)	**1.09 (0.03; 2.15)**	**1.25 (0.22; 2.29)**	-0.16 (-1.22; 0.90)
Soluble CD40 ligand (ng/mL)	**-1.38 (-2.74; -0.02)**	0.13 (-1.21; 1.47)	-1.25 (-2.61; 0.11)
Soluble P-selectin (ng/ml)	**-3.30 (-4.92; -1.68)**	-0.13 (-1.21; 0.96)	**-3.43 (-5.04; -1.81)**
Systolic blood pressure (mm Hg)	-2.05 (-4.64; 0.54)	-1.95 (-4.42; 0.52)	**-4.00 (-6.59; -1.41)**
Diastolic blood pressure (mm Hg)	-1.00 (-4.14; 2.24)	-2.20 (-4.87; 0.47)	**-3.20 (-6.34; -0.06)**
Mean blood pressure (mm Hg)	-1.35 (-3.93; 1.23)	-2.12 (-4.26; 0.03)	**-3.47 (-6.05; -0.88)**
Cotinine (ng/mL)	1.70 (-10.32; 13.72)	-2.20 (-14.31; 9.91)	-0.50 (-12.52; 11.52)

EVC=electronic vaping cigarette; H_2O_2=hydrogen peroxide; HNBC=heat-not-burn cigarette; TC=traditional tobacco cigarette

Figure S1. Consolidated Standards of Reporting Trials (CONSORT) subject flow diagram (left panel), and measurement protocol (right panel). BP=blood pressure; EVC=electronic vapng cigarette; FMD=flow-mediated dilation; HNBC=heat-not-burn cigarette; TC=traditional tobacco cigarette.

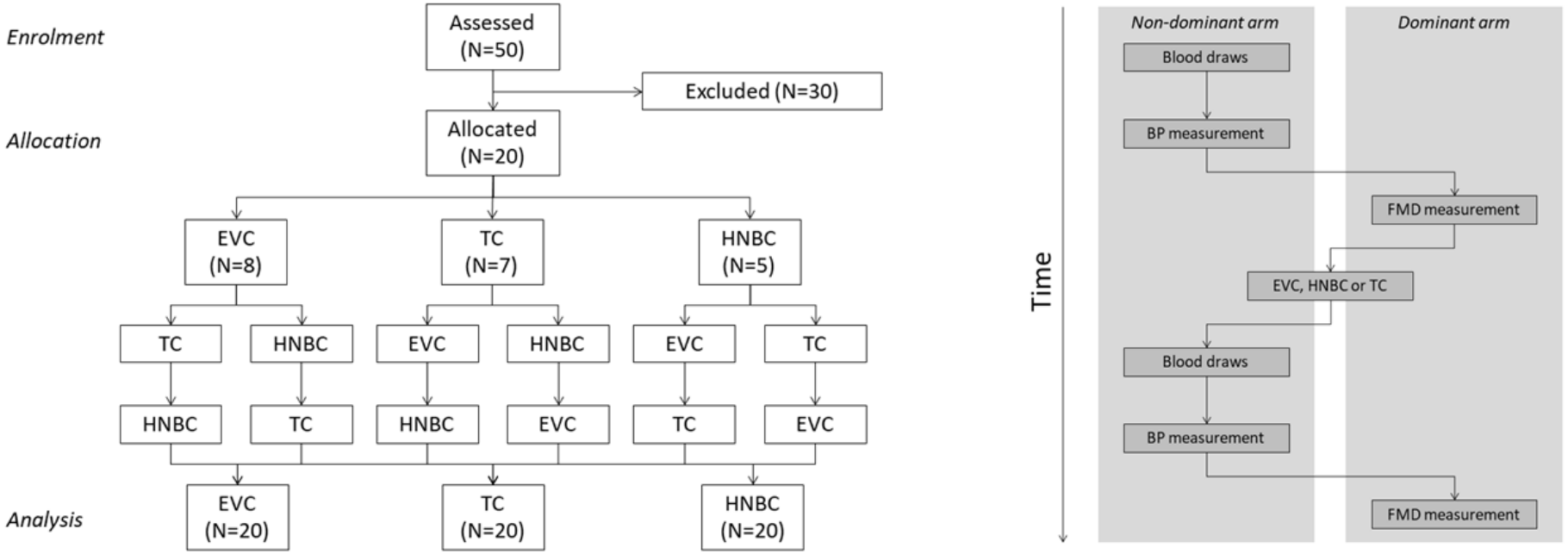

Figure S2. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on hydrogen peroxide (H_2O_2) production. Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

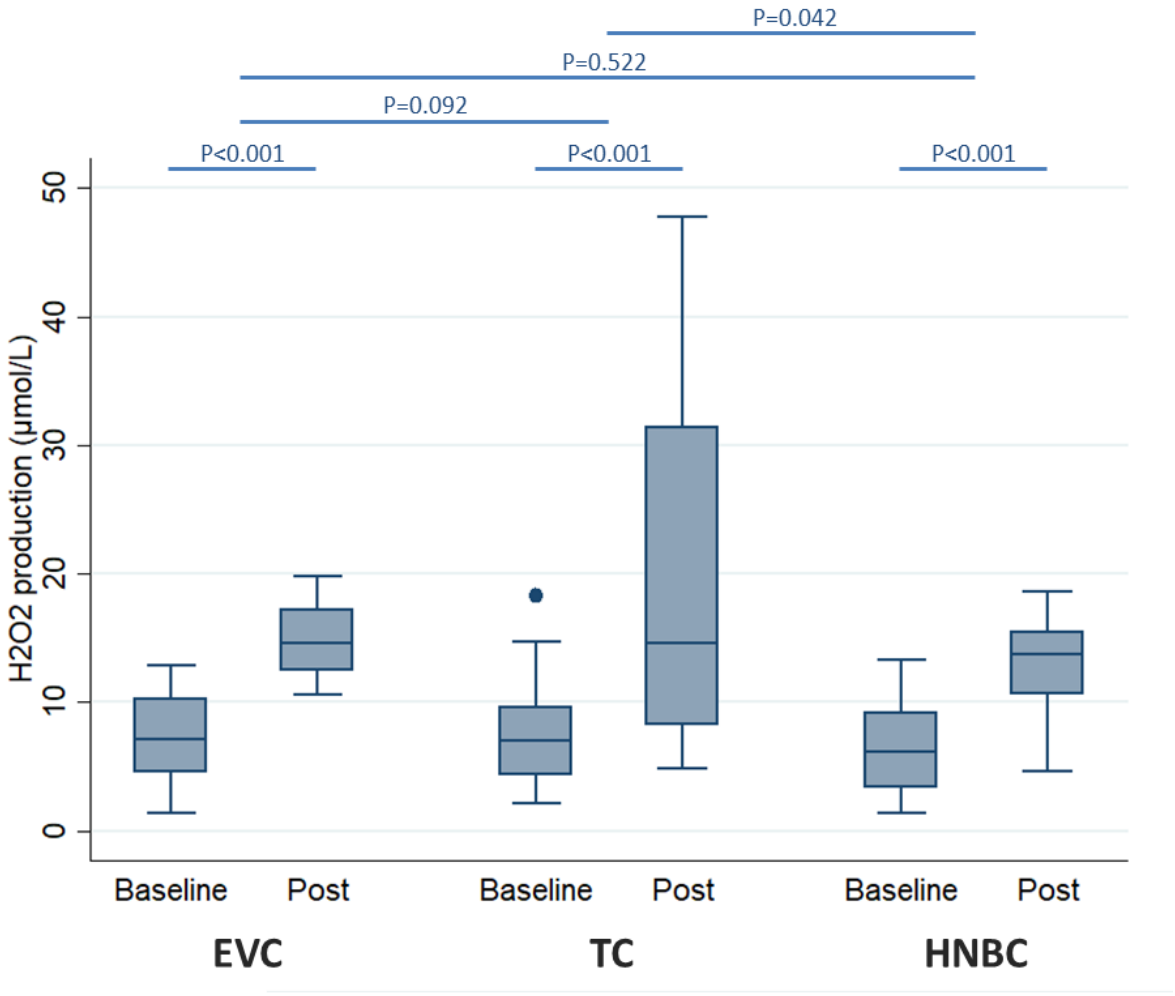

Figure S3. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on 8-iso-prostaglandin F-2α-III (8-iso-PGF2a). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

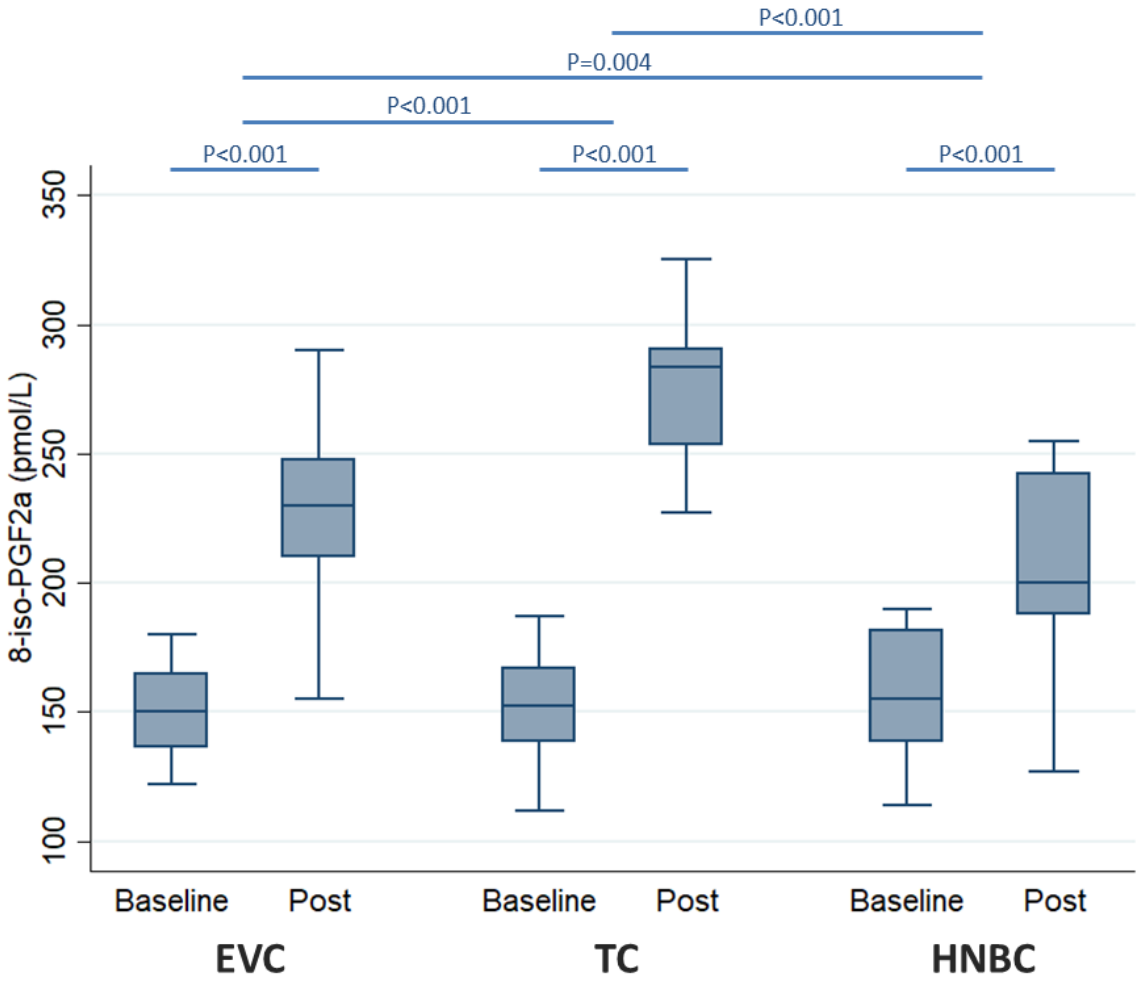

Figure S4. **Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on vitamin E.**

Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

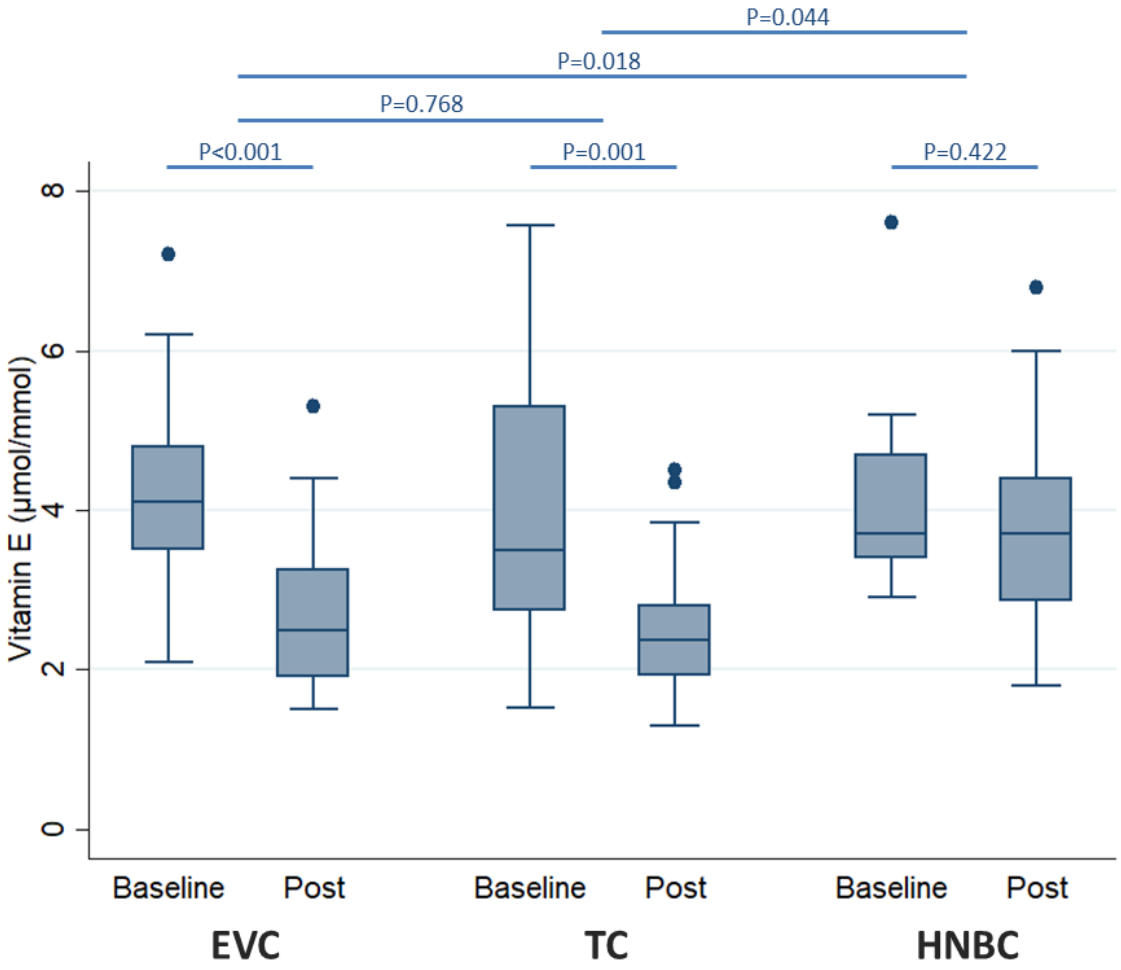

Figure S5. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on hydrogen peroxide (H_2O_2) breakdown activity (HBA). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

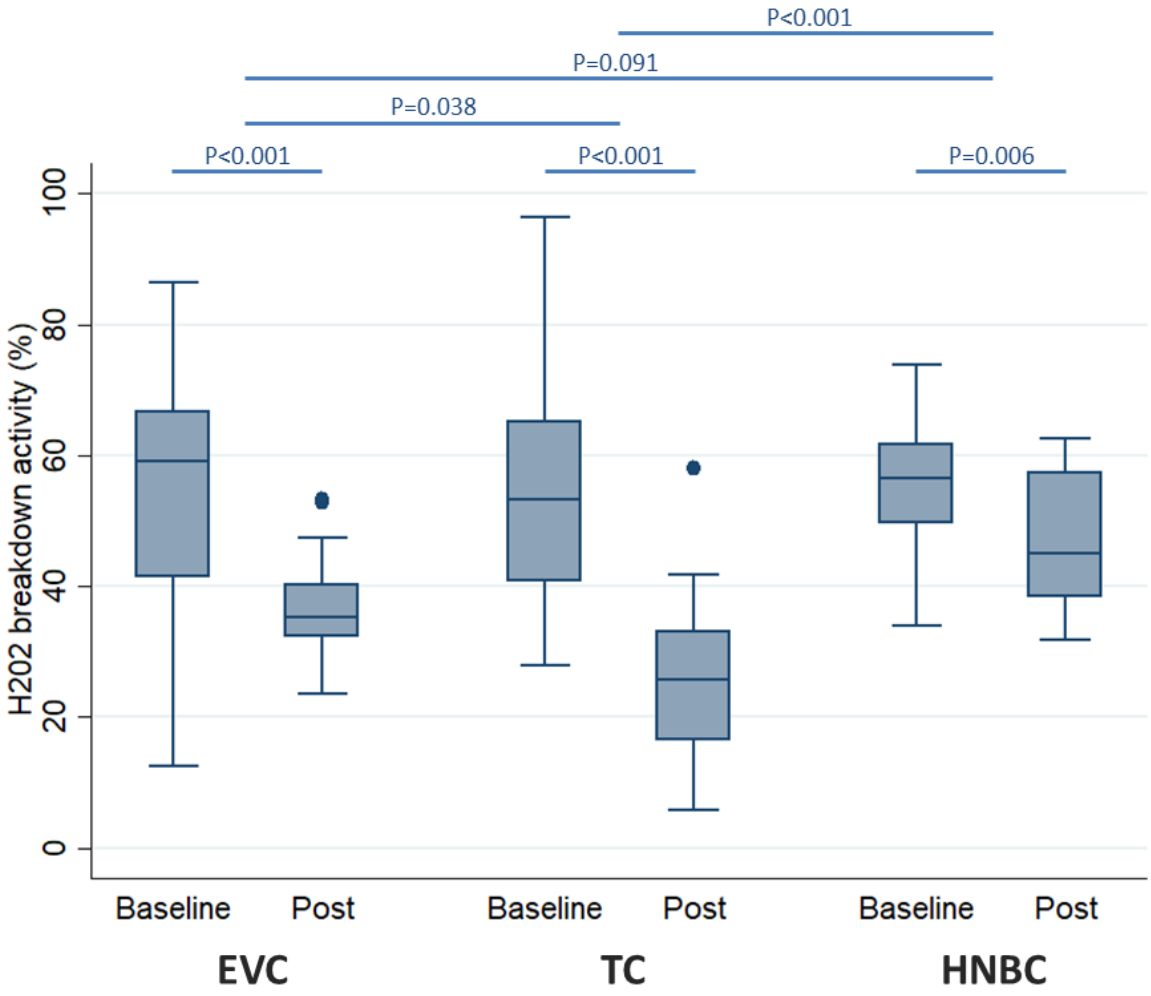

Figure S6. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on soluble CD40 ligand. Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

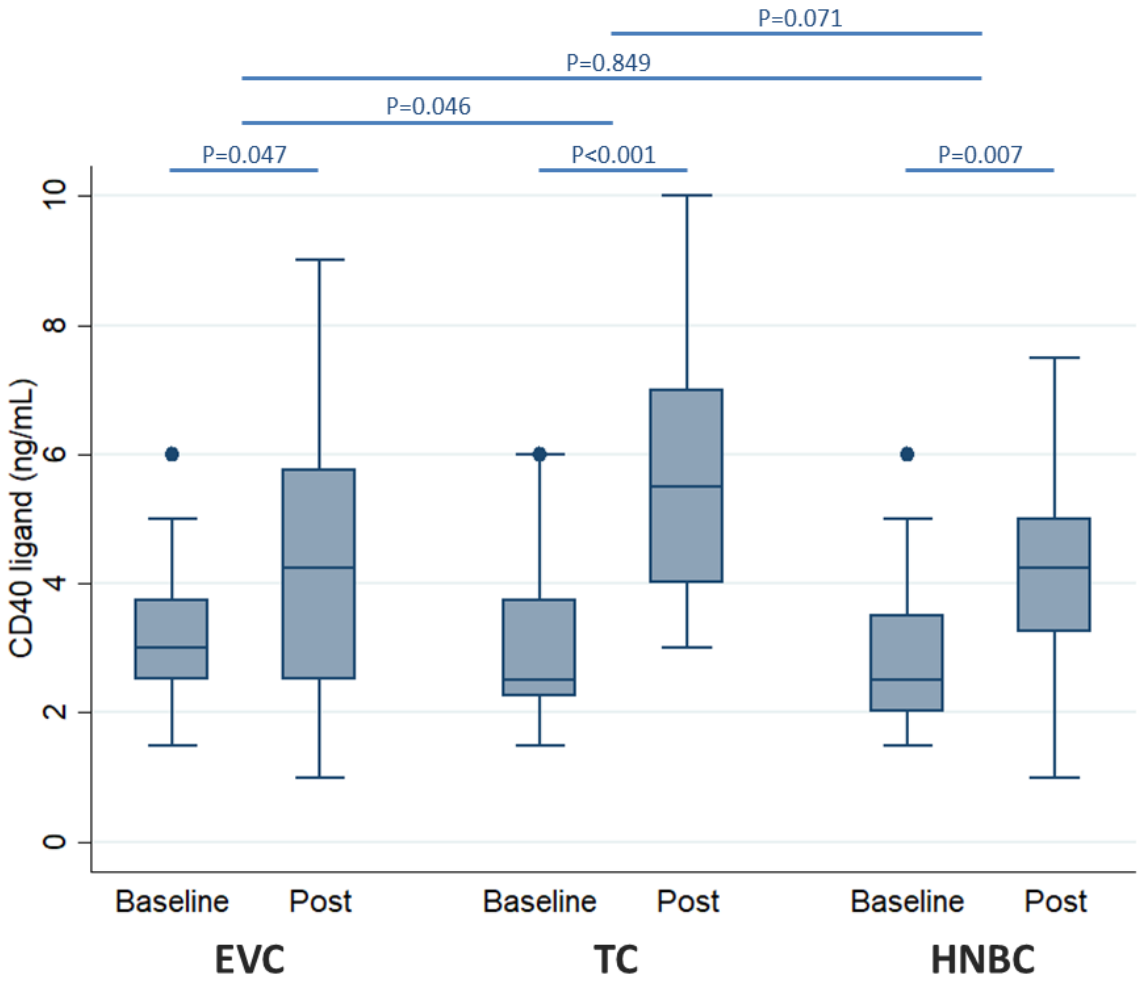

Figure S7. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on soluble P-selectin. Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

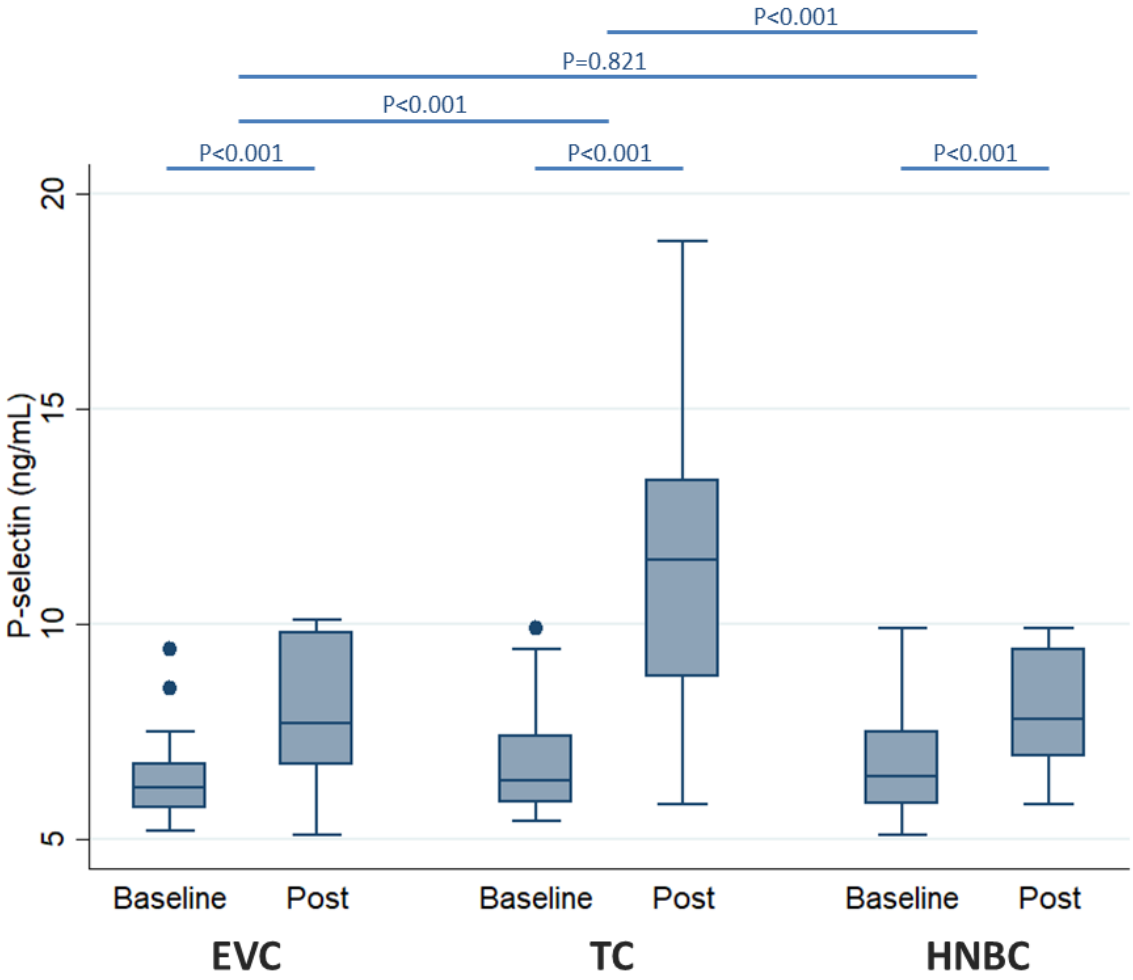

Figure S8. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on systolic blood pressure (SBP). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

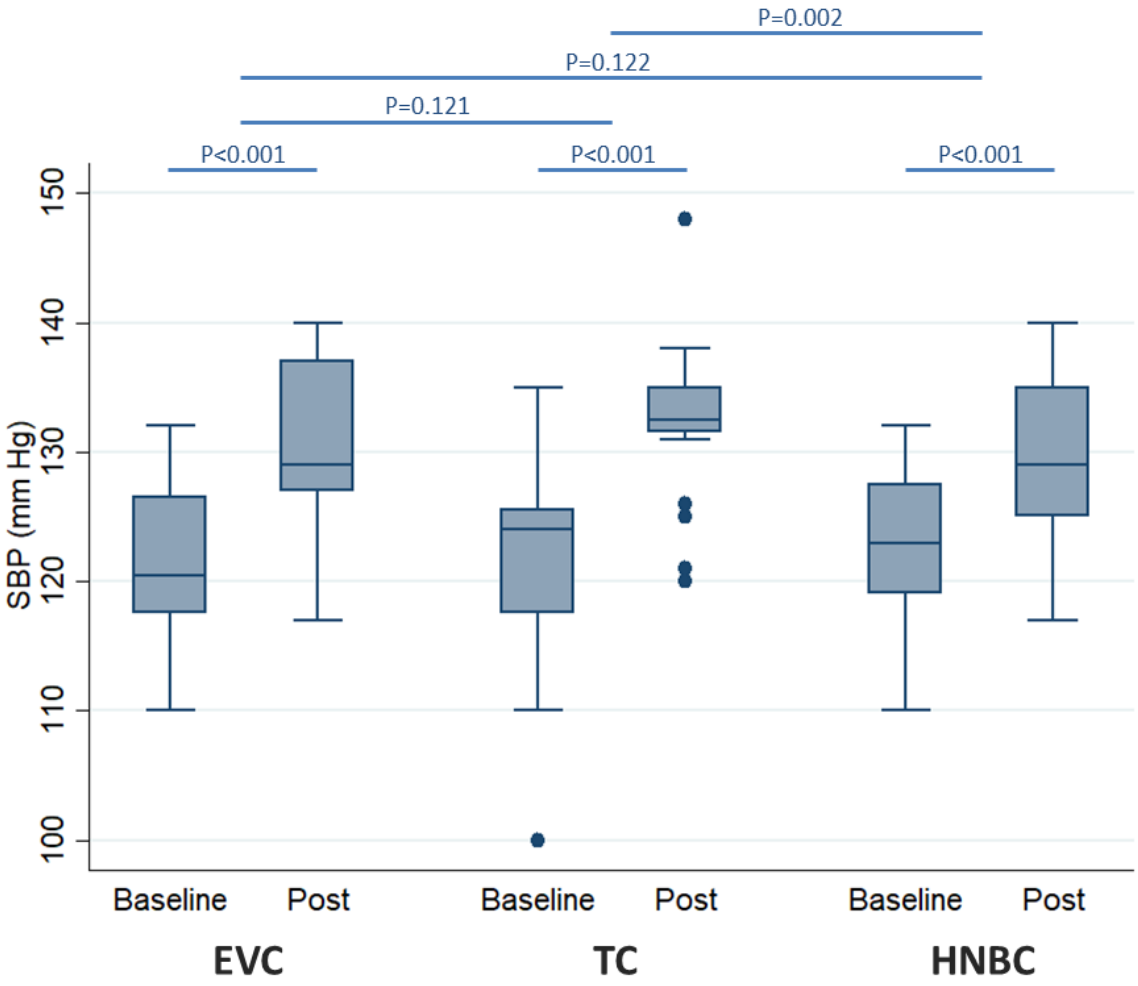

Figure S9. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on diastolic blood pressure (DBP). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

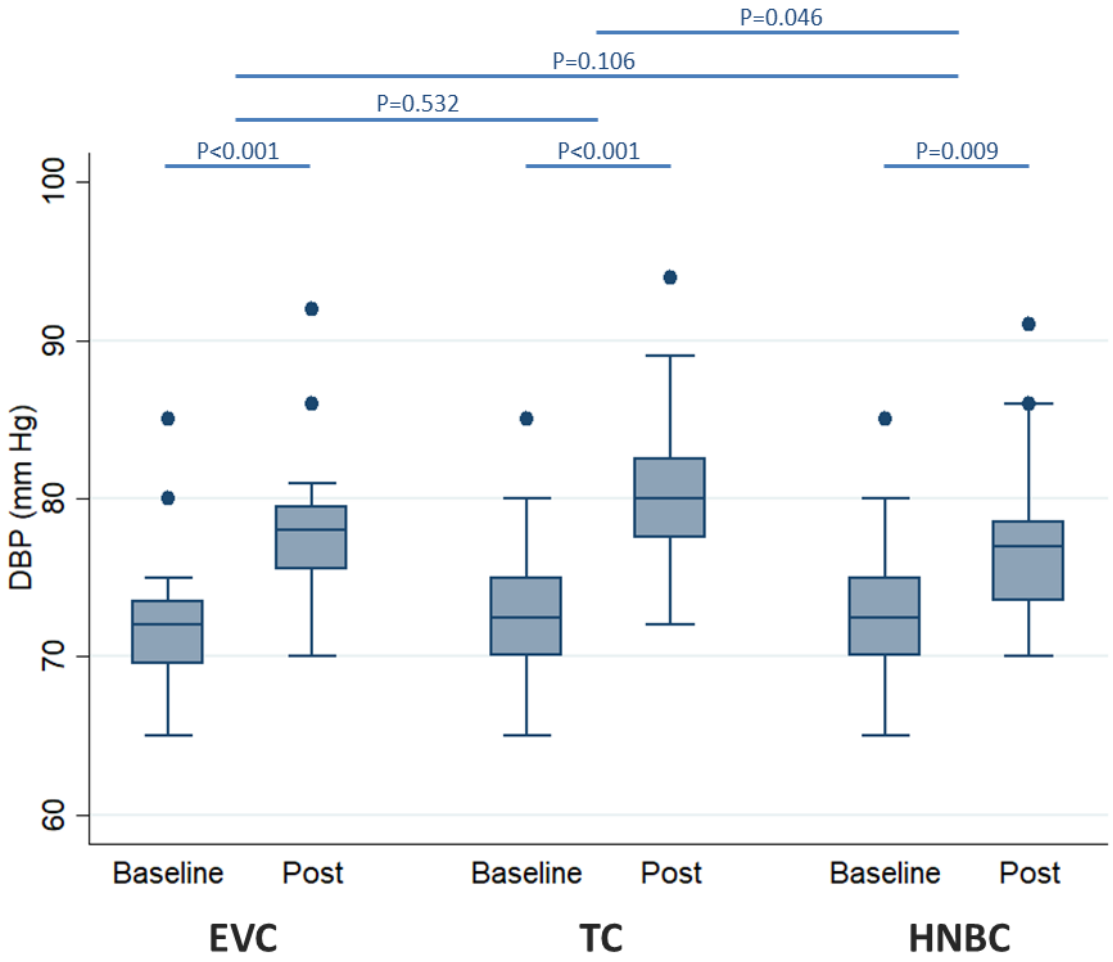

Figure S10. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on mean blood pressure (MBP). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

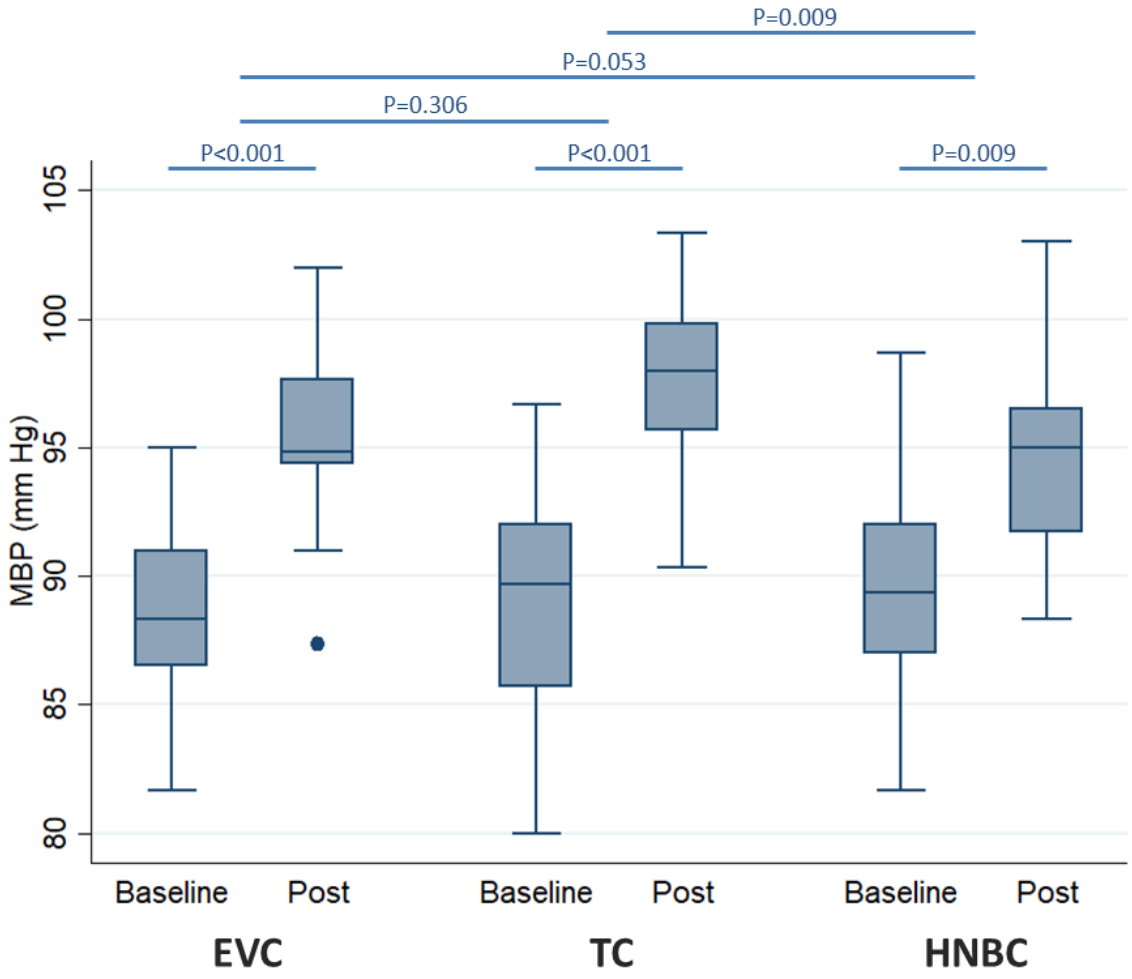

Figure S11. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on nitric oxide (NO) bioavailability. Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

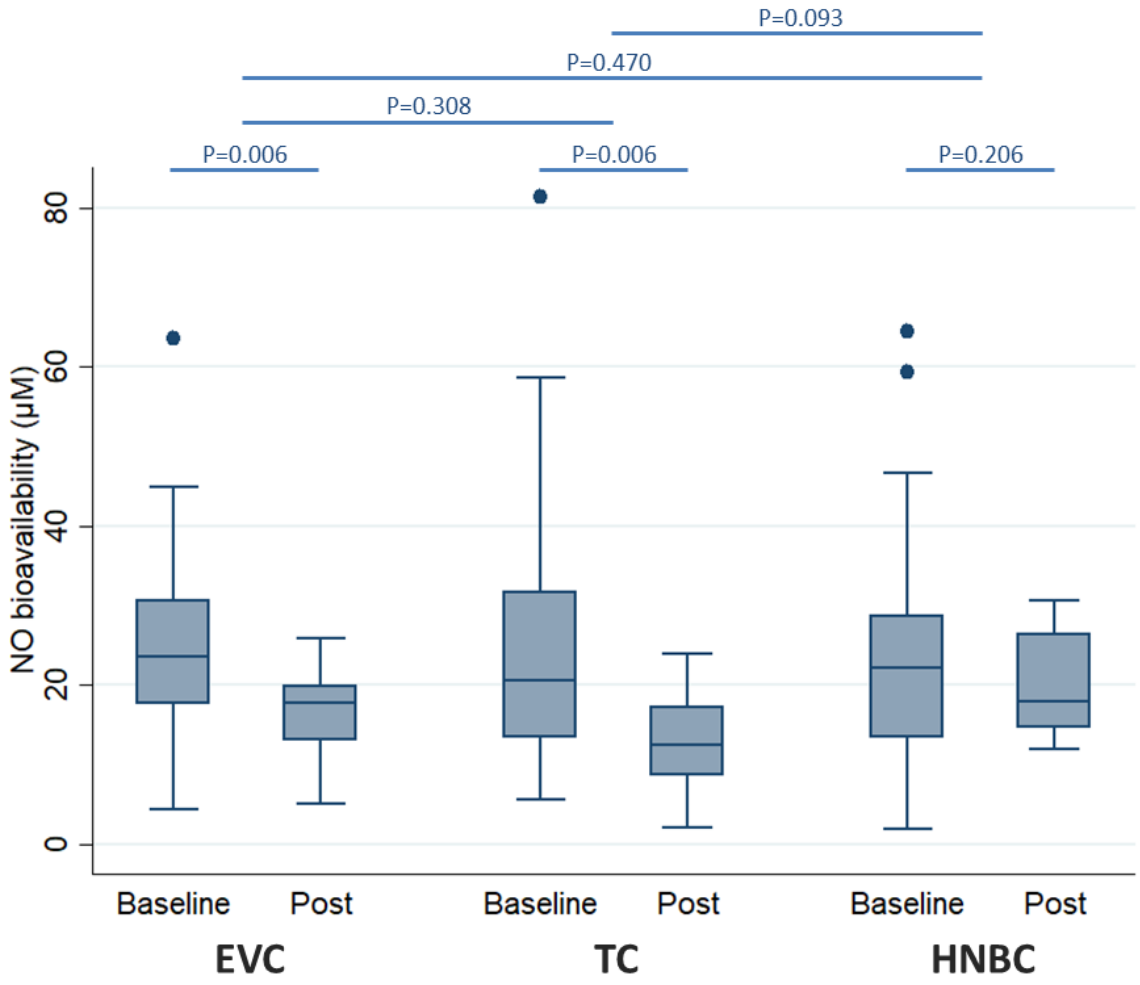

Figure S12. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on smoking satisfaction, appraised with the explicit question "Was the cigarette enjoyable?", and answers scored using a subjective scale from 0 (no effect) to 100 (maximum effect). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

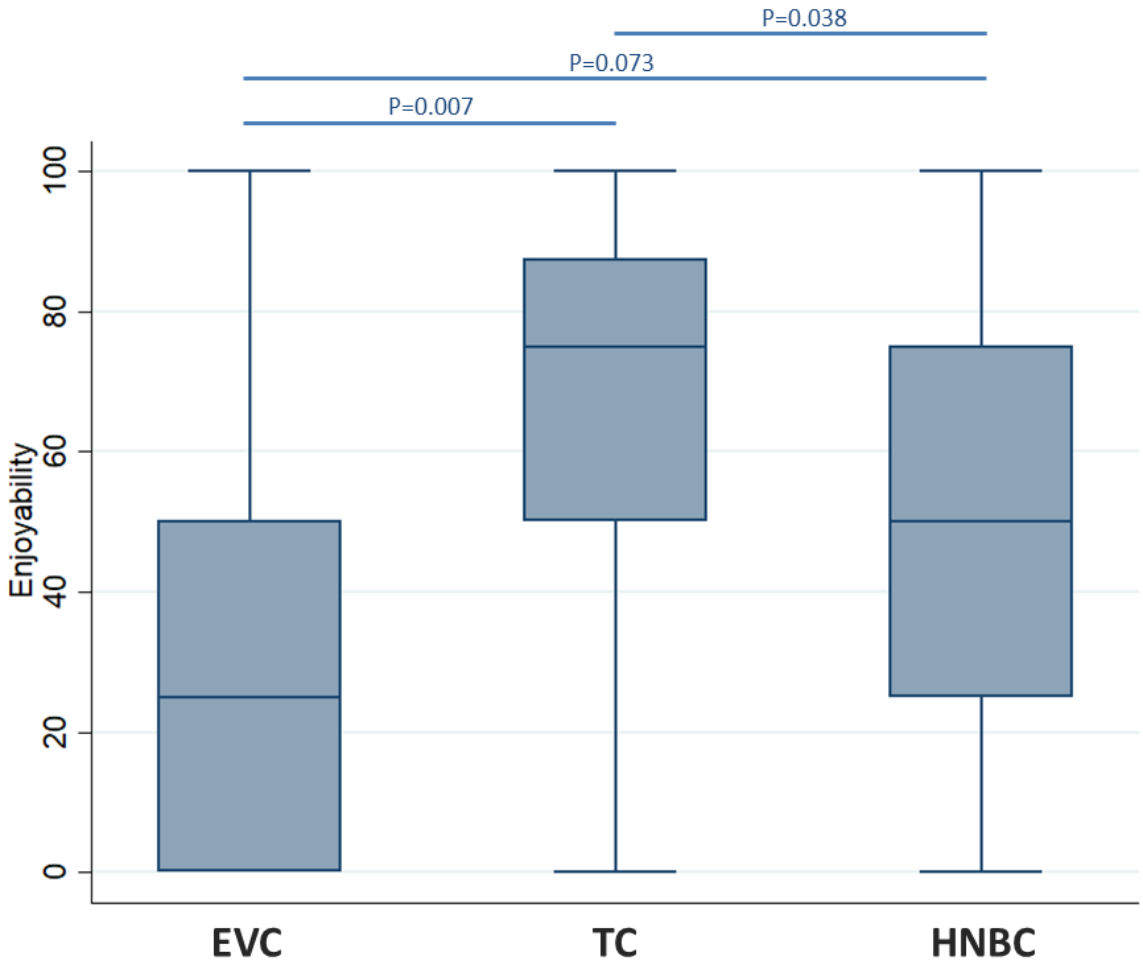

Figure S13. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on smoking satisfaction, appraised with the explicit question "Was the cigarette satisfying?", and answers scored using a subjective scale from 0 (no effect) to 100 (maximum effect). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.

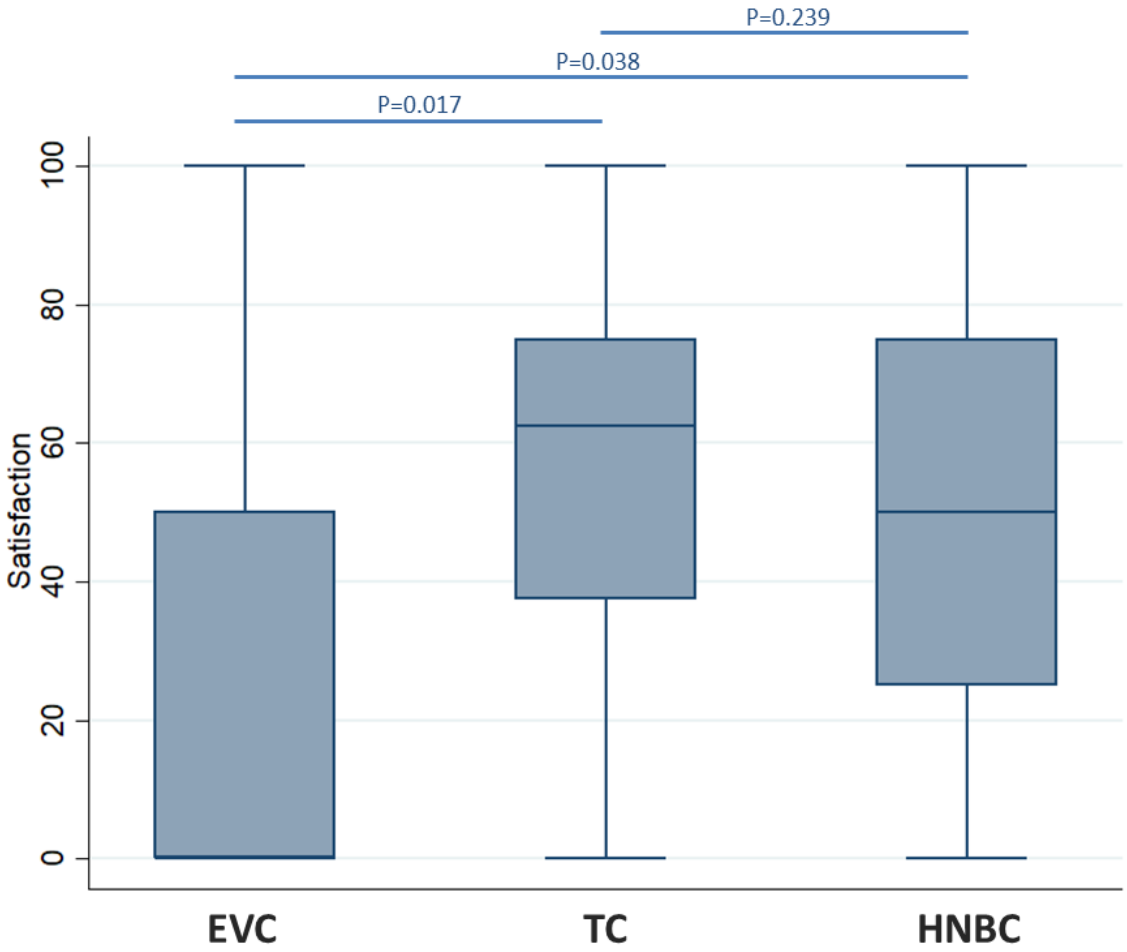

Figure S14. Impact of using electronic vaping cigarette (EVC), traditional tobacco cigarette (TC), and heat-not-burn cigarette (HNBC) on smoking satisfaction, appraised with the explicit question "Soon after smoking did your desire for another cigarette decrease?", and answers scored using a subjective scale from 0 (no effect) to 100 (maximum effect). Boxplots represent median, 1st quartile, 3rd quartile, 5th percentile, 95th percentile, and outliers.