



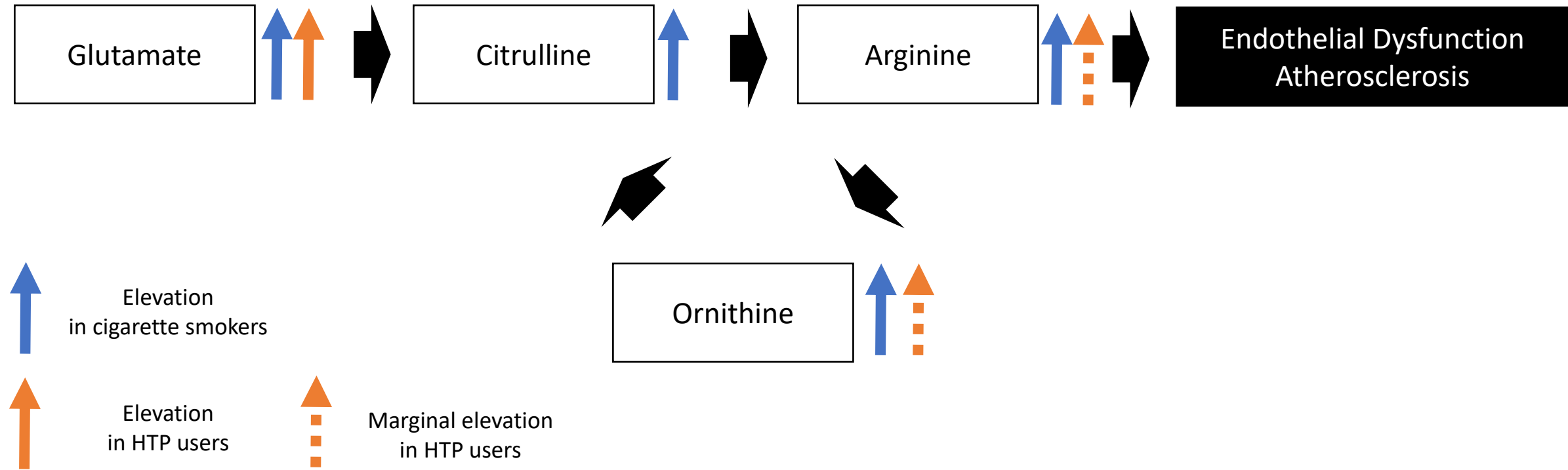
56	HMDB0000271	Sarcosine	1.07	2.3E-02	1.05	1.0E-01	1.00	9.3E-01	0.99	8.4E-01	1.11	5.6E-02	1.11	7.9E-02	0.99	9.1E-01	0.99	8.9E-01	HMDB0000271	Sarcosine
57	HMDB0001539	ADMA	1.05	7.9E-02	1.05	1.0E-01	1.02	5.8E-01	1.02	5.7E-01	1.12	3.9E-02	1.11	7.6E-02	1.03	4.9E-01	1.04	6.0E-01	HMDB0001539	ADMA
58	HMDB0000126	Glycerophosphate	0.98	5.5E-01	0.96	1.0E-01	1.03	2.9E-01	1.00	9.3E-01	0.93	7.2E-02	0.91	2.3E-02	1.01	9.4E-01	1.01	9.0E-01	HMDB0000126	Glycerophosphate
59	HMDB0000929	Trp	1.02	1.2E-03	1.01	1.2E-01	1.00	7.9E-01	0.99	5.3E-01	1.05	2.2E-04	1.02	8.2E-02	1.01	2.2E-01	1.00	9.9E-01	HMDB0000929	Trp
60	HMDB0000699	1-Methylnicotinamide	1.08	8.4E-02	1.07	1.4E-01	1.05	4.2E-01	1.02	7.8E-01	0.90	1.9E-01	0.86	5.0E-02	0.96	5.5E-01	0.92	4.4E-01	HMDB0000699	1-Methylnicotinamide
61	HMDB0000208	2-Oxoglutarate	1.00	9.4E-01	0.98	1.7E-01	1.03	7.3E-02	1.01	7.5E-01	0.99	7.1E-01	0.99	7.5E-01	1.02	7.7E-01	1.01	9.0E-01	HMDB0000208	2-Oxoglutarate
62	HMDB0000847	Pelargonate	1.02	2.3E-01	1.02	1.7E-01	1.01	4.5E-01	1.01	5.7E-01	1.00	1.0E+00	1.01	7.7E-01	1.01	9.4E-01	1.01	9.0E-01	HMDB0000847	Pelargonate
63	HMDB0000201	o-Acetylcarnitine	1.07	9.1E-02	1.06	1.7E-01	1.08	7.1E-02	1.04	4.7E-01	0.97	7.5E-01	0.98	7.9E-01	1.03	5.8E-01	1.02	8.9E-01	HMDB0000201	o-Acetylcarnitine
64	HMDB0000925	Trimethylamine N-oxide	0.94	1.8E-01	0.94	1.9E-01	0.96	4.6E-01	0.95	4.7E-01	1.03	7.5E-01	1.01	8.8E-01	1.12	4.1E-02	1.09	3.9E-01	HMDB0000925	Trimethylamine N-oxide
65	HMDB0000159	Phe	1.00	9.2E-01	1.01	2.1E-01	1.00	6.1E-01	0.99	4.7E-01	1.02	5.6E-02	1.02	1.3E-01	1.01	2.3E-01	1.01	7.8E-01	HMDB0000159	Phe
66	HMDB0000192	Cystine	0.98	1.2E-02	0.99	2.1E-01	1.00	5.8E-01	1.00	6.5E-01	1.00	8.0E-01	0.99	6.7E-01	1.00	8.3E-01	0.99	5.9E-01	HMDB0000192	Cystine
67	HMDB0000479	3-Methylhistidine	0.96	6.8E-02	0.97	2.4E-01	0.96	1.5E-01	0.96	2.7E-01	0.94	1.9E-01	0.95	2.8E-01	0.99	8.3E-01	0.99	8.9E-01	HMDB0000479	3-Methylhistidine
68	HMDB0000883	Val	1.00	8.6E-01	1.01	2.4E-01	1.00	7.0E-01	0.99	4.7E-01	1.02	8.7E-02	1.01	2.7E-01	1.01	2.2E-01	1.00	8.9E-01	HMDB0000883	Val
69	HMDB0000064	Creatine	1.01	7.9E-01	0.97	2.4E-01	0.99	7.0E-01	0.96	1.8E-01	0.99	7.2E-01	0.98	4.8E-01	0.96	8.5E-02	0.94	4.2E-02	HMDB0000064	Creatine
70	HMDB0000134	Fumarate	0.98	5.8E-01	0.97	2.7E-01	1.05	1.0E-01	1.04	4.6E-01	1.03	5.4E-01	1.04	4.3E-01	0.99	9.4E-01	1.00	9.4E-01	HMDB0000134	Fumarate
71	HMDB0000731	Cysteine S-sulfate	0.96	2.9E-01	0.96	2.7E-01	0.98	5.8E-01	0.98	7.5E-01	1.11	9.8E-02	1.10	1.8E-01	1.07	3.3E-01	1.07	6.2E-01	HMDB0000731	Cysteine S-sulfate
72	HMDB0000510	alpha-Aminoadipate	0.96	1.6E-01	0.97	2.7E-01	1.00	9.3E-01	0.99	8.0E-01	1.00	9.4E-01	0.97	6.3E-01	1.04	4.5E-01	1.01	8.9E-01	HMDB0000510	alpha-Aminoadipate
73	HMDB0000190	Lactate	1.03	2.2E-02	1.01	2.9E-01	1.03	2.6E-02	1.01	7.2E-01	1.04	1.3E-01	1.04	1.6E-01	1.00	9.4E-01	1.00	9.0E-01	HMDB0000190	Lactate
74	HMDB0000251	Taurine	0.99	4.2E-01	0.99	3.0E-01	0.99	5.8E-01	1.00	8.0E-01	1.01	5.1E-01	1.00	8.4E-01	1.01	3.8E-01	1.01	5.9E-01	HMDB0000251	Taurine
75	HMDB0000641	Gln	0.99	3.0E-02	1.01	3.4E-01	0.98	6.0E-04	1.00	6.5E-01	1.01	6.5E-01	1.01	2.8E-01	0.99	4.8E-02	0.99	5.4E-01	HMDB0000641	Gln
76	HMDB0032538	Triethanolamine	1.03	6.4E-01	1.05	3.9E-01	1.04	5.8E-01	1.05	5.7E-01	0.95	7.2E-01	0.97	7.7E-01	0.95	4.9E-01	0.95	7.8E-01	HMDB0032538	Triethanolamine
77	HMDB0003334	SDMA	0.97	2.1E-01	0.98	4.4E-01	0.98	5.8E-01	0.99	8.0E-01	0.93	1.9E-01	0.92	1.7E-01	1.00	9.7E-01	1.00	9.9E-01	HMDB0003334	SDMA
78	HMDB0000812	N-Acetylaspartate	0.99	6.3E-01	0.99	4.9E-01	0.99	7.1E-01	0.99	7.8E-01	1.01	8.7E-01	1.01	7.1E-01	1.01	9.4E-01	1.02	9.0E-01	HMDB0000812	N-Acetylaspartate
79	HMDB0000289	Urate	1.00	9.3E-01	0.99	4.9E-01	1.04	8.3E-05	1.02	7.9E-02	1.04	8.3E-02	1.01	7.6E-01	1.06	8.0E-05	1.03	4.4E-01	HMDB0000289	Urate
80	HMDB0000193	Isocitrate	1.01	4.0E-01	1.01	5.7E-01	1.04	2.1E-03	1.02	2.6E-01	1.00	9.7E-01	1.01	7.6E-01	1.02	4.3E-01	1.02	7.6E-01	HMDB0000193	Isocitrate
81	HMDB0061881	4-Acetylbutyrate	1.03	5.5E-01	1.03	5.8E-01	1.01	7.1E-01	1.02	7.5E-01	1.04	6.4E-01	1.02	7.6E-01	1.01	9.4E-01	1.01	9.0E-01	HMDB0061881	4-Acetylbutyrate
82	HMDB0000784	Azelate	1.01	7.5E-01	1.01	5.8E-01	1.01	7.4E-01	1.01	7.5E-01	1.03	3.7E-01	1.03	5.3E-01	1.00	9.4E-01	1.01	9.0E-01	HMDB0000784	Azelate
83	HMDB0000127	Glucuronate	1.00	9.1E-01	1.02	5.8E-01	1.02	5.0E-01	1.01	7.5E-01	1.06	2.5E-01	1.05	4.3E-01	1.03	7.7E-01	1.02	9.0E-01	HMDB0000127	Glucuronate
84	HMDB0000097	Choline	1.02	5.4E-02	1.00	6.0E-01	1.01	2.6E-01	1.00	8.0E-01	1.02	1.2E-01	1.02	3.4E-01	1.01	4.0E-01	1.00	8.9E-01	HMDB0000097	Choline
85	HMDB0000696	Met	1.00	7.9E-01	1.01	6.4E-01	0.99	5.8E-01	0.99	5.1E-01	1.04	8.7E-02	1.03	2.2E-01	1.01	6.9E-01	1.00	8.9E-01	HMDB0000696	Met
86	HMDB0000482	Octanoate	0.99	7.7E-01	0.98	6.5E-01	1.00	9.5E-01	1.00	9.3E-01	0.91	8.9E-02	0.93	2.6E-01	1.00	9.4E-01	1.02	9.0E-01	HMDB0000482	Octanoate
87	HMDB0000118	Homovanillate	1.05	3.1E-01	1.02	6.8E-01	1.09	3.5E-02	1.06	3.3E-01	1.03	7.1E-01	1.00	9.8E-01	1.00	9.9E-01	0.98	9.0E-01	HMDB0000118	Homovanillate
88	HMDB0000763	Indole-3-acetate	1.00	9.0E-01	0.99	6.8E-01	1.00	9.3E-01	0.99	8.0E-01	0.98	7.8E-01	0.95	5.4E-01	1.04	4.9E-01	1.04	7.7E-01	HMDB0000763	Indole-3-acetate
89	HMDB0000661	Glutarate	0.98	4.3E-01	0.99	8.1E-01	1.01	6.8E-01	1.01	7.2E-01	0.96	2.8E-01	1.00	9.9E-01	0.99	9.4E-01	1.01	9.0E-01	HMDB0000661	Glutarate
90	HMDB0000691	Malonate	1.00	9.6E-01	0.99	8.2E-01	0.99	8.8E-01	0.99	8.5E-01	1.05	5.2E-01	1.05	5.3E-01	1.01	9.4E-01	1.02	9.0E-01	HMDB0000691	Malonate
91	HMDB0000267	5-Oxoprolin	0.99	4.3E-01	1.00	8.2E-01	0.99	3.2E-01	1.00	9.3E-01	1.03	5.7E-02	1.04	2.0E-02	1.01	7.7E-01	1.02	7.6E-01	HMDB0000267	5-Oxoprolin
92	HMDB0000714	Hippurate	0.94	5.2E-01	0.98	8.2E-01	0.85	3.5E-02	0.93	5.7E-01	0.95	7.1E-01	0.96	7.6E-01	0.98	9.4E-01	1.02	9.0E-01	HMDB0000714	Hippurate
93	HMDB0000666	Heptanoate	0.97	4.3E-01	0.99	8.3E-01	0.97	4.5E-01	0.98	7.5E-01	0.99	8.8E-01	0.97	7.6E-01	0.94	5.3E-01	0.93	6.2E-01	HMDB0000666	Heptanoate
94	HMDB0000535	Hexanoate	0.99	6.4E-01	1.00	8.7E-01	0.98	2.1E-01	0.98	5.7E-01	0.93	7.1E-03	0.93	2.0E-02	0.99	9.4E-01	0.99	9.0E-01	HMDB0000535	Hexanoate

FDR, false discovery rate.

**eTable 2.** Characteristics of the participants at the follow-up survey after matching

	HTP users	Cigarette smokers	Past smokers	Never smokers
N, %	55 (11.9)	119 (25.7)	144 (31.1)	145 (31.3)
Women, n (%)	10 (18.2)	27 (22.7)	30 (20.7)	30 (20.7)
Age, mean (SD)	49.22 (10.57)	54.51 (8.83)	52.72 (10.25)	51.34 (10.08)
Total tobacco products number per day	13.12 (4.82)	14.41 (6.23)		
Cigarette, mean (SD)		14.41 (6.23)		
IQOS, mean (SD)	11.05 (6.41)			
Ploom TECH, mean (SD)	0.27 (2.02)			
glo, mean (SD)	1.80 (5.06)			
Years of using HTPs	1.69 (0.84)			
Cigarette number per day at baseline	15.49 (6.14)	16.08 (6.80)		
Years of smoking	27.47 (10.94)	33.00 (10.23)	23.25 (15.10)	
Years after cessation			8.77 (7.65)	
Daily drinking, %	42 (76.4)	90 (75.6)	104 (72.2)	108 (74.5)
Systolic blood pressure, mean (SD)	128.93 (17.56)	129.93 (17.99)	131.51 (16.44)	128.61 (15.80)
BMI, mean (SD)	23.00 (3.03)	23.05 (3.75)	23.77 (3.66)	23.86 (3.61)
HbA1c, mean (SD)	5.66 (0.60)	5.71 (0.47)	5.75 (0.59)	5.66 (0.56)
Triglyceride, median (IQR]	94.0 (58.0–134.5)	108.0 (79.5–146.5)	92.0 (65.8–144.3)	95.0 (62.0–132.0)

HTP, heated tobacco products; IQR, interquartile range; SD, standard deviation.



**eFigure 1. Glutamate pathway and atherosclerosis development in smokers.**

Previous studies reported that the glutamate transporter encoded by SLC7A11 was activated in cigarette smokers, which increased circulating glutamate, arginine, ornithine, and citrulline.<sup>23,24</sup> In our study, the elevation of these metabolites was confirmed. Previous studies have suggested that elevation of this metabolic pathway can be linked to endothelial cell damage through nitric oxide decline and contribute to atherosclerosis.<sup>25-27</sup>