Supplementary Material

Kazuya Yamada, Yoshiharu Matahira, Nagisa Takuwa, Yuri Yoshioka, Shin-ichi Matsumura, Mayo Higashihara, Nobuhiro Zaima, and Naoki Unno: Evidence of Improvements to Arterial Stiffness Among Regular Users of Combustible Cigarettes – Effect of Inhalation of β-Caryophyllene: A Randomized, Double-Blind, Placebo-Controlled Study –; Contrib. Tob. Nicotine Res. 34 (2025) 107–116.
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Table S1. Secondary endpoints

Amount and rate of change in % vital capacity
Amount and rate of change in forced expiratory volume in 1 s (%FEV1.0)
Amount and rate of change in high-sensitivity C-reactive protein (hsCRP)
Amount and rate of change in fibrinogen
Amount of change in questionnaire survey scores
Amount of change in SF-36 scores after 12 weeks
Rate of change in baPWV
Amount of change in baPWV after 4 and 8 weeks
Amount of change in ABI
Amount of change in blood pressure
Amount of change in pulse pressure
Amount of change in heart rate
Amount of change in blood test values
Amount of change in urine test values

The endpoints were measured on day 0 and after 4, 8, and 12 weeks unless indicated otherwise.

Table S2. Recruitment criteria

A smoking history of ≥5 pack-years (pack-years = number of smoked packs [20 cigarettes] per day × number of smoking years)
Age < 59 years
Smoking of a cigarette brand listed in an additional table [see Additional file 3]
Not taking any medicines
Not being treated for a disease
Not pregnant or breastfeeding
Not wishing to become pregnant during the trial period
No daily consumption of health foods (excluding products whose active ingredients are only vitamins and minerals)
Not intending to quit smoking

Table S3. Nicotine and tar amounts of cigarette brands smoked by the placebo and BCP groups at the time of recruitment

Brand name	Nicotine amount (mg)	Tar amount (mg)	Placebo group (number of users)	BCP group (number of users)
Winston	0.9	12	1	0
Winston Caster White 3	0.3	3	0	0
Winston Caster White 3 box	0.3	3	1	0
Winston Caster White 5	0.4	5	0	0
Winston Caster White 5 box	0.4	5	1	1
Winston Caster White One 100's box	0.1	1	0	1
Winston Caster White One box	0.1	1	1	0
Winston Cabin Red 2 box	0.2	2	0	0
Winston Cabin Red 5 box	0.4	5	0	0
Winston Cabin Red 8 100's box	0.7	8	0	1
Winston Cabin Red 8 box	0.6	8	0	0
Winston Cabin Red One 100's box	0.1	1	1	0
Camel Menthol Light box	0.5	5	7	4
Camel Light box	0.5	6	0	2
Seven Stars	1.2	14	2	2
Seven Stars 10 box	0.9	10	0	0
Seven Stars 4	0.4	4	0	0
Seven Stars 7 box	0.6	7	0	0
Seven Stars box	1.2	12	1	0
Seven Stars Menthol 12 box	1	12	0	1
Seven Stars Menthol 5 box	0.5	5	0	0
Peace	1.9	21	0	1
Peace Aroma Infinity	0.7	8	1	0
Hope	1.1	14	0	0
Hope Super Light	0.5	6	0	0
Hope Menthol	0.6	8	1	0
Hope Light	0.8	9	0	0
Mevius	0.8	10	0	3
Mevius 100's box	0.8	10	0	0
Mevius Extra Light	0.3	3	0	1
Mevius Extra Light 100's box	0.3	3	1	1

Mevius Extra Light box	0.3	3	0	1
Mevius Gold 6	0.5	6	0	1
Mevius Gold Impact One 100's	0.1	1	0	0
Mevius Gold One 100's	0.1	1	1	0
Mevius Super Light	0.5	6	2	1
Mevius Super Light 100's box	0.7	8	3	0
Mevius Light	0.7	8	1	1
Mevius Light 100's box	0.7	8	1	1
Mevius Light box	0.7	8	0	0
Mevius One	0.1	1	1	1
Mevius One 100's box	0.1	1	2	0
Mevius One box	0.1	1	0	1
Philip Morris 14 KS box	1.0	14	0	0
Philip Morris 10 KS box	0.7	10	0	1
Philip Morris 6 KS box	0.4	6	0	0
Philip Morris 3 KS box	0.3	3	1	0
Philip Morris Menthol 8 KS box	0.8	10	0	0
Philip Morris Menthol 5 KS box	0.4	5	0	0
Philip Morris Menthol 1 100's box	0.1	1	0	2
Philip Morris Purple 5 KS box	0.4	5	1	0
Marlboro	0.9	12	0	1
Marlboro box	0.9	12	2	0
Marlboro Medium box	0.7	8	0	0
Marlboro Gold box	0.5	6	1	0
Marlboro Gold 100's box	0.5	6	0	0
Marlboro Gold original	0.5	6	0	0
Marlboro Menthol 12 box	0.8	12	0	0
Marlboro Menthol 8 box	0.6	8	2	1
Marlboro Menthol 8 100's box	0.6	8	0	1
Marlboro Menthol 4 box	0.3	4	1	1
Marlboro Black Menthol 8 box	0.5	8	1	0
Lark KS box	0.9	12	0	1
Lark 100 box	0.9	12	1	0
Lark Mild KS box	0.7	9	0	1
Lark Mild 100 box	0.7	9	0	0
Lark Super Mild 100 box	0.5	6	1	1
Lark Classic Mild KS box	0.7	9	1	0
Kool Light box	0.4	5	1	1
Kool FK box	0.9	12	0	0

Kool Mild box	0.7	8	0	2
JPS box	1.0	11	0	0
Lucky Strike FK	1.0	11	0	0
Lucky Strike box	1.0	11	0	1
Lucky Strike Light box (new)	0.5	6	0	1
Lucky Strike Expert Cut 14	1.2	14	0	0
Lucky Strike Expert Cut 10	0.9	10	0	0
Lucky Strike Expert Cut 6	0.5	6	0	1
Lucky Strike Expert Cut 1 100	0.1	1	0	1

Table S4. Screening test items

Interview exploring the background of the study participant (age, sex, race, smoking history)
Interview determining complications and pre-existing conditions
Height and weight measurements
For premenopausal women, pregnancy test (hCG antibody test)
Measurement of baPWV
Measurement of ABI
% Vital capacity measurement
%FEV1.0 measurement
Carotid ultrasonography
Chest X-ray examination
Electrocardiogram examination
Salivary cotinine measurement
Blood tests: red blood cells, white blood cells, platelets, hematocrit, hemoglobin, MCH, MCHC, MCV, TP, TG, TC, HDL-C, LDL-C, ALP, GOT, GPT, γ-GTP, total bilirubin, albumin, LDH, uric acid, urea nitrogen, creatinine, FBS, HbA1c
Urinalysis: pH, ketone bodies, protein (qualitatively), glucose (quantitatively), occult blood, specific gravity, urobilinogen, bilirubin
Blood pressure, pulse pressure, and heart rate measurements
Examination by a medical doctor

Table S5. Inclusion criteria in the screening tests

Those who have the capacity to consent and provided written consent to participate in this research
Those who are healthy adult smokers
Those with a smoking history of ≥5 pack-years
Those who are under 59 years of age at the time of enrollment
Those who regularly smoke a particular brand of cigarettes listed in an additional table [see Additional file 2]
Those with baPWV ≥ 1300 cm/s and < 1800 cm/s
Those with ABI ≥ 1.0 and < 1.4
Those with %FEV1.0 ≥ 70% and % vital capacity ≥ 80%
Those whose blood and urine test results are within the normal range
Those with cotinine detected in saliva

Table S6. Exclusion criteria in the screening tests

Smokers with tobacco use other than cigarette smoking (e.g., smoking pipes)
Those with systolic blood pressure at rest ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg
Those with plaques in a carotid artery as detected by ultrasonography
Those with abnormal chest X-ray findings
Those with electrocardiogram findings that make them unsuitable for participating in the study as attested by a medical doctor
Those who are pregnant, breastfeeding, or wish to become pregnant during this period
Those who regularly consume healthy food (excluding products whose active ingredients are only vitamins and minerals)
Those who intend to quit smoking
Those who are judged by a doctor to be unsuitable for participating in research

Table S7. Discontinuation criteria

If the study participant withdraws consent
If it becomes impossible to comply with the research plan
If the entire study is discontinued
If the study participant dies
If an adverse event is observed and the research director determines that it is not advisable to continue the research
If the participant deviates from the inclusion criteria or conflicts with the exclusion criteria
If the study participant no longer visits the hospital
If the study participant is found to be pregnant
If the research director or somebody similar determines that it is difficult to continue the research

Supplementary method 1

The BCP content in the capsule core was analyzed using gas chromatography–mass spectrometry (Agilent 7890A-5975C MSD; Agilent Technologies, Santa Clara, CA, USA). MSD ChemStation v.E.02.01. 1177 (Agilent) was used for data analysis. An InertCap PureWAX column (length: 60 m, df: 0.25 μm, I.D.: 0.25 mm; GL Sciences, Inc., Tokyo, Japan) was used for component separation. The temperature was programmed as follows: initial temperature, 50° C; ramp rate, 50°C for 2 min, 2.5° C/min (50° C to 240° C); final temperature, 240° C for 272 min. The He inlet pressure was controlled using an electronic pressure control system to achieve a constant column flow rate of 1 mL/min. MS analysis was performed in the ionization mode at a voltage of 70 eV.

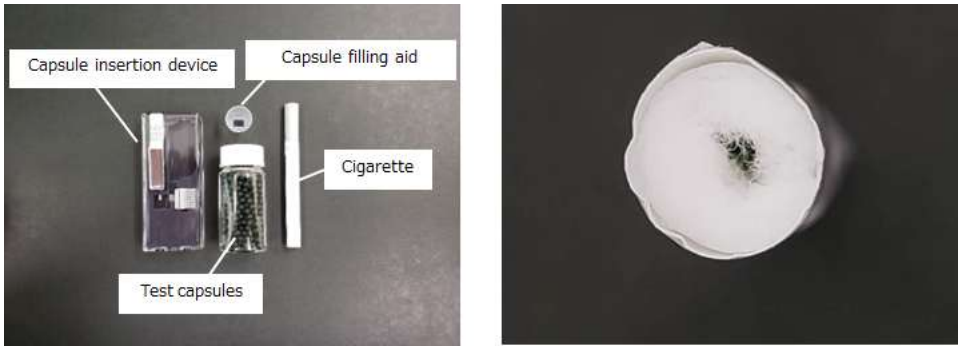

Figure S1. The capsules and the capsule insertion device loaned to the study participants (left). Cigarette filter with an inserted capsule (right).

Supplementary method 2

BCP and nicotine concentrations in the blood were analyzed using gas chromatography–mass spectrometry (Agilent 7890B-5977B MSD; Agilent Technologies) with a thermal desorption unit (TDU2), programmable temperature vaporization inlet (CIS4), and multipurpose sampler (MPS) with dynamic headspace (DHS) option (Gerstel GmbH & Co.KG, Mülheim an der Ruhr, Germany). MSD ChemStation vs. F.01.03. 2357 and Mass Hunter v.B.07.05.2479 (both Agilent) were used for data analysis. Tenax TA cartridges were released from Tenax TA traps using a thermal desorption cold-trap setup (thermal desorption spectrometer [TDS]; Markes International, Ltd., Llantrisant, RCT, UK). An InertCap PureWAX column (length: 60 m, df: 0.25 μm, I.D.: 0.25 mm; GL Sciences, Inc.) was used for component separation. The temperature was programmed as follows: initial temperature, 50°C; ramp rate, 50°C for 2 min, 5°C/min (50–160°C) and 20°C/min (160–240°C); and final temperature, 240°C for 20 min. The He inlet pressure was controlled using an electronic pressure control system to achieve a constant column flow of 1 mL/min. MS analysis was performed in the ionization mode at a voltage of 70 eV.

Table S8. Main test items

Measurement of baPWV
Measurement of ABI
% Vital capacity measurement
%FEV1.0 measurement
Blood tests: red blood cells, white blood cells, platelets, hematocrit, hemoglobin, MCH, MCHC, MCV, TP, TG, TC, HDL-C, LDL-C, ALP, GOT, GPT, γ-GTP, total bilirubin, albumin, LDH, uric acid, urea nitrogen, creatinine, FBS, hsCRP, fibrinogen
Urinalysis: pH, ketone bodies, protein (qualitatively), glucose (qualitatively), occult blood, specific gravity, urobilinogen, bilirubin
Blood pressure, pulse pressure, and heart rate measurements
Original questionnaire survey
SF-36 survey
Consultation

Table S9. Questions of the original questionnaire survey

Question 1	For the past four weeks, have you felt easier to relax while smoking?
Question 2	For the past four weeks, have you felt easier to relax?
Question 3	For the past four weeks, have you felt easier to fall asleep at night?
Question 4	For the past four weeks, have you felt that your sleep quality is good?
Question 5	For the past four weeks, have you felt tired easily?
Question 6	For the past four weeks, have you felt cold in your fingers and toes?
Question 7	For the past four weeks, have you felt that your face has a good complexion?
Question 8	For the past four weeks, have you felt that the texture and firmness of your facial skin is good?
Question 9	For the past four weeks, have you felt shortness of breath when you move your body vigorously?
Question 10	For the past four weeks, have you been concerned about bad breath after smoking?
Question 11	For the past four weeks, have you found cigarettes delicious?
Question 12	Based on the overall effect (experience), do you want to continue purchasing and smoking capsule-containing cigarettes?
Question 13	Please state the reason for the above answer.
Question 14	If you have any perceptions regarding your body after smoking cigarettes with capsules, please feel free to describe them, even if they are trivial.
Question 15	Please feel free to write your thoughts, opinions, requests, etc. regarding this examination.

Answers to questions 1 to 12 were given in a 5-point Likert format as shown below; 1: fully disagree, 2: somewhat disagree, 3: neither agree nor disagree, 4: somewhat agree, 5: fully agree. Answers to questions 13 to 15 were written freely in empty boxes.

Table S10. Number of people excluded by reason for screening

Those with ABI < 1.0 and ≥ 1.4	12
Those with %FEV1.0 < 70% or % vital capacity < 80%	26
Those whose blood and urine test results were not within the normal range	61
Those with cotinine not detected in the saliva	3
Those with systolic blood pressure at rest ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg	75
Those with plaques (≥2 mm) in a carotid artery as detected through ultrasonography	21
Those with abnormal chest X-ray findings	6
Those with electrocardiogram findings deemed unsuitable for participation in the study by a medical doctor	4

Table S11. Background information of the study participants

		Placebo group (n = 33)	BCP group (n = 36)
Sex, n (%)	Male	28 (84.8)	31 (86.1)
	Female	5 (15.2)	5 (13.9)
Age at the time of consent (years)		49.9 ± 7.00	49.4 ± 7.72
Height (cm)		168.75 ± 6.753	168.99 ± 6.437
Body weight (kg)		67.15 ± 11.102	67.93 ± 11.529
Smoking history (years)		27.5 ± 8.62	27.1 ± 7.93
Cigarettes smoked per day (n)		16.7 ± 14.5	15.4 ± 5.6
Pack-years		21.8 ± 16.3	20.2 ± 9.6
average left and right baPWV (cm/s)		1454.1 ± 107.14	1453.8 ± 170.73
% Vital capacity (%)		102.67 ± 11.064	110.18 ± 10.731
%FEV1.0 (%)		78.921 ± 6.0595	78.615 ± 6.0728
hsCRP (mg/100 mL)		0.1034 ± 0.21021	0.0413 ± 0.04763
Fibrinogen (mg/100 mL)		278.4 ± 53.33	270.8 ± 39.50
ABI		1.182 ± 0.0948	1.230 ± 0.1024
Systolic blood pressure (mmHg)		122.5 ± 12.66	117.6 ± 12.14
Diastolic blood pressure (mmHg)		76.9 ± 8.90	74.3 ± 8.89
Pulse pressure (mmHg)		45.7 ± 9.92	43.6 ± 5.63
Heart rate (/s)		65.8 ± 10.78	65.3 ± 11.92
Blood tests	Red blood cell count (count/μL)	462.1 ± 53.47	464.6 ± 46.95
	White blood cell count (count/μL)	6351.5 ± 1290.14	6444.4 ± 1999.63
	Platelet count (count/μL)	26.89 ± 6.668	26.49 ± 4.414
	Hematocrit (%)	43.63 ± 4.034	43.42 ± 3.920
	Hemoglobin (g/100 mL)	14.32 ± 1.321	14.22 ± 1.352
	MCH (pg)	31.12 ± 2.046	30.65 ± 1.513
	MCHC (g/100 mL)	32.83 ± 0.821	32.73 ± 0.783
	MCV (fL)	94.8 ± 5.28	93.7 ± 3.71
	TP (g/100 mL)	6.79 ± 0.347	6.77 ± 0.333
	TG (mg/100 mL)	97.2 ± 51.15	150.6 ± 168.65
	TC (mg/100 mL)	190.6 ± 29.66	195.8 ± 27.72
	HDL-C (mg/100 mL)	60.1 ± 18.57	54.0 ± 14.99
	LDL-C (mg/100 mL)	111.0 ± 23.64	113.9 ± 26.58
	ALP (U/L)	71.6 ± 14.28	69.8 ± 15.94
	GOT (AST) (U/L)	22.0 ± 20.23	18.6 ± 5.53
	GPT (ALT) (U/L)	21.2 ± 16.28	19.3 ± 8.76

	γ-GTP (U/L)	31.4 ± 25.93	34.9 ± 28.96
	Total bilirubin (mg/100 mL)	0.74 ± 0.266	0.73 ± 0.313
	Albumin (g/100 mL)	4.20 ± 0.287	4.26 ± 0.238
	LDH (U/L)	166.2 ± 31.35	162.2 ± 24.94
	Uric acid (mg/100 mL)	5.91 ± 1.320	6.32 ± 1.112
	Urea nitrogen (BUN) (mg/100 mL)	11.88 ± 3.298	12.17 ± 3.321
	Creatinine (mg/100 mL)	0.799 ± 0.1256	0.822 ± 0.1316
	FBS (mg/100 mL)	93.5 ± 8.70	98.0 ± 12.19
Urinalysis	pH	6.11 ± 0.622	5.93 ± 0.599
	Ketone bodies, n (%)	(-) 32 (97.0) (±) 0 (0.0) (1+) 1 (3.0) (2+) 0 (0.0)	(-) 36 (100.0) (±) 0 (0.0) (1+) 0 (0.0) (2+) 0 (0.0)
	Specific gravity (g/mL)	1.0178 ± 0.00820	1.0177 ± 0.00754
	Urobilinogen, n (%)	(±) 33 (100.0) (1+) 0 (0.0) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)	(±) 35 (97.2) (1+) 1 (2.8) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)
	Bilirubin, n (%)	(±) 33 (100.0) (1+) 0 (0.0) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)	(±) 36 (100.0) (1+) 0 (0.0) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)
	Protein, qualitative, n (%)	(-) 29 (87.9) (±) 4 (12.1) (1+) 0 (0.0) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)	(-) 32 (88.9) (±) 2 (5.6) (1+) 2 (5.6) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)
	Glucose, qualitative, n (%)	(-) 33 (100.0) (±) 0 (0.0) (1+) 0 (0.0) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)	(-) 36 (100.0) (±) 0 (0.0) (1+) 0 (0.0) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)
	Occult blood, n (%)	(-) 31 (93.9) (±) 2 (6.1)	(-) 30 (83.3) (±) 4 (11.1)

		(1+) 0 (0.0) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)	(1+) 2 (5.6) (2+) 0 (0.0) (3+) 0 (0.0) (4+) 0 (0.0)

Table S12. BCP blood concentrations

		Placebo group (n = 33)	BCP group (n = 36)
Before smoking	Mean ± SD	0.67 ± 0.438	0.88 ± 0.978
	Range	0.2–1.8	0.2–3.4
10 min after starting to smoke	Mean ± SD	0.71 ± 0.586	4.43 ± 3.249
	Range	0.2–2.7	0.2–13.3
20 min after starting to smoke	Mean ± SD	0.64 ± 0.483	2.67 ± 2.022
	Range	0.2–2.4	0.3–8.4
40 min after starting to smoke	Mean ± SD	0.63 ± 0.418	1.94 ± 1.246
	Range	0.2–1.9	0.3–5.8

Table S13. Nicotine blood concentrations

		Placebo group (n = 33)	BCP group (n = 36)
Before smoking	Mean ± SD	5.20 ± 4.503	8.40 ± 5.604
	Range	1.0–17.8	0.6–24.3
10 min after starting to smoke	Mean ± SD	10.22 ± 5.313	15.64 ± 6.698
	Range	2.7–24.0	4.5–31.8
20 min after starting to smoke	Mean ± SD	9.07 ± 5.716	13.07 ± 6.365
	Range	2.5–26.3	2.9–28.4
40 min after starting to smoke	Mean ± SD	6.96 ± 5.159	10.81 ± 7.510
	Range	1.7–26.9	1.6–44.5

Supplementary data 1: ***Number of Cigarettes Smoked***

The number of cigarettes smoked per day was tabulated for each group on a weekly basis, and the results were compared between groups using the Mann–Whitney U test. In addition, before–after comparisons were performed within each group using Wilcoxon's signed-rank test with Bonferroni correction. The percentage change in the number of cigarettes smoked was calculated for each week. The mean number of cigarettes smoked from week 1 to week 12 ranged from 32.42 to 33.31 cigarettes/day in the placebo group, with no significant change observed compared with the number at week 1. In the BCP group, the range was similarly 33.54 to 35.06 cigarettes/day, and significant decreases were observed at weeks 5, 7, 8, and 9 compared to week 1 (week 5: P=0.028, week 7: P=0.039, week 8: P=0.037, week 9: P=0.036). Furthermore, no significant difference in the number of cigarettes smoked per day and the rate of change in the number of cigarettes smoked was observed between the two study groups at any time point.

Table S14. Summary statistics of baPWV measurements on day 0 and at weeks 4, 8, and 12 by study group

		Placebo group	BCP group
Day 0	n	33	36
	Mean ± SD	1454.1 ± 107.14	1453.8 ± 170.73
	Range	1199–1729	1151–1856
Week 4	n	33	35
	Mean ± SD	1487.0 ± 127.18	1425.1 ± 154.74
	Range	1285–1881	1199–1779
Week 8	n	32	33
	Mean ± SD	1452.0 ± 162.20	1418.0 ± 128.87
	Range	1184–1805	1115–1746
Week 12	n	32	34
	Mean ± SD	1463.1 ± 137.22	1445.4 ± 146.95
	Range	1228–1816	1175–1832

Table S15. Summary statistics of baPWV changes from day 0 to week 4, 8, and 12 by study group

		Placebo group	BCP group
Week 4	n	33	35
	Mean ± SD	32.9 ± 95.42	-29.8 ± 125.81
	Range	-154–310	-260–232
Week 8	n	32	33
	Mean ± SD	-3.2 ± 143.99	-30.8 ± 125.40
	Range	-333–318	-315–219
Week 12	n	32	34
	Mean ± SD	7.9 ± 113.50	-2.5 ± 138.46
	Range	-224–217	-227–415

Table S16. Results of the repeated measures mixed model

		Placebo group			BCP group			Difference between BCP and placebo groups		
		Mean	95% CI	P-value (vs. day 0)	Mean	95% CI	P-value (vs. day 0)	Mean	95% CI	P-value (vs. placebo)
Day 0	Absolute	1463	1424,9, 1501.2	-	1462	1425.9, 1498.5	-	-	-	-
Week 4	Absolute	1496	1457.8, 1534.1	-	1435	1398.5, 1472.0	-	-	-	-
	Difference	32.9	-8.9, 74.7	0.244	-27	-67.4, 13.4	0.379	-59.9	-118.0, -1.7	0.087
Week 8	Absolute	1461	1422.3, 1499.7	-	1433	1385.6, 1470.7	-	-	-	-
	Difference	-2	-44.3, 40.2	>0.999	-29	-70.2, 12.1	0.331	-27	-86.0, 32.0	0.735
Week 12	Absolute	1472	1433.4, 1510.8	-	1458	1421.4, 1495.4	-	-	-	-
	Difference	9	-33.2, 51.3	0.673	-3.8	-44.5, 37.0	0.855	-12.8	-71.5, 45.9	0.667

Supplementary data 2:

Respiratory function tests (% vital capacity)

On the start date (day 0), the mean value was 106.02% in the placebo group and 106.59% in the BCP group. During the evaluation period, the values remained in the range of 102.57–104.15% in the placebo group and 105.19–106.61% in the BCP group (all least-squares mean values). A within-subject test regarding the change from day 0 showed a significant decrease in the placebo group at week 12 (P = 0.001) but no significant change in the BCP group at any time point. Furthermore, no significant difference was observed between the placebo and BCP groups at any time point.

Respiratory function tests (%FEV1.0)

On day 0, the mean value was 78.668% in the placebo group and 78.580% in the BCP group. During the evaluation period, the values remained in the range of 78.836–80.862% in the placebo group and 78.996–79.934% in the BCP group (all least-squares mean values). A within-subject test regarding the change from day 0 showed a significant increase in the placebo group at week 12 (P = 0.015) but no significant change in the BCP group at any time point. Furthermore, no significant difference was observed between the two study groups at any time point.

Blood tests (hsCRP)

On day 0, the mean hsCRP concentration was 0.0929 mg/dL in the placebo group and 0.0474 mg/dL in the BCP group. During the evaluation period, the concentration was in the range of 0.0591–0.1234 mg/dL in the placebo group and 0.0421–0.1447 mg/dL in the BCP group (all least-squares mean values). A within-subject test regarding the change from day 0 revealed no significant change at any time point in either group. Furthermore, no significant difference was observed between the two study groups at

any time point.

Blood tests (fibrinogen)

On day 0, the fibrinogen concentration was 276.7 mg/dL in the placebo group and 274.7 mg/dL in the BCP group. During the evaluation period, the concentration was in the range of 271.2–278.1 mg/dL in the placebo group and 283.6–290.7 mg/dL in the BCP group (all least-squares mean values). A within-subject test of the change from day 0 showed no significant change at any time point in either group. Furthermore, no significant difference was observed between the two study groups at any time point.

Original questionnaire survey

Participants were asked to fill out a self-administered survey form regarding their experience when smoking capsule-containing cigarettes. They were asked to answer each question on a scale using the following items: “I strongly agree,” “I somewhat agree,” “I can't say either way,” “I somewhat disagree,”, and “I strongly disagree,” and the answers were scored on a five-point scale. Question 12 was not included in the survey on day 0; therefore, comparisons vs. day 0 were only conducted for questions 1 to 11. Significant differences were observed for three questions at week 4 (Question 7: $P = 0.037$, Question 10: $P = 0.037$, Question 11: $P = 0.006$), for one question at week 8 (Question 11: $P = 0.007$), and for one question at week 12 (Question 10: $P = 0.038$) in the placebo group. In the BCP group, a significant difference was observed for one question at week 4 (Question 11: $P = 0.002$), and no significant change was observed in any question at weeks 8 and 12. For all questions with significant differences in the before–after comparison, the percentage of people who answered “I can't say either way” or “I somewhat disagree” tended to increase compared with the percentages on day 0. Furthermore, no significant difference was observed between the two study

groups for any question at any time point.

SF-36 questionnaire

The SF-36 v2^{TM} standard version was used to evaluate quality of life. On day 0 and at week 12, participants were asked to fill out this self-administered questionnaire. "Physical component summary: PCS," "Mental component summary: MCS," and "Role/Social component summary: RCS" were tabulated. In the before–after comparisons, no significant changes were observed in any of the scores in the placebo group. In the BCP group, a significant change was observed in PCS ($P = 0.041$), whereas no significant change was observed in MCS and RCS. Furthermore, no significant difference was found between the two study groups in any score on day 0 and at week 12.

Other evaluated items

Regarding ABI, blood pressure, pulse pressure, heart rate, blood test, and urine test, we used a repeated measures mixed model with groups, time points, their interaction terms, dependent variable values on day 0 (secondary endpoints to be analyzed), and stratification factors at randomization (baPWV < 1500 cm/s vs. ≥ 1500 cm/s; %FEV1.0 < 80% vs. ≥ 80%) as a fixed effect and participant as a random effect. Then, test group comparisons were performed for the amount of change. We also performed within-subject tests between day 0 and each time point in both study groups. As a result of the within-subject test, significant changes were observed in ABI (right) ($P = 0.006$), platelets ($P = 0.039$), and hematocrit ($P = 0.040$) in the placebo group at week 12, and the BCP group had significant changes in albumin ($P = 0.049$) at week 8 and urine pH ($P = 0.003$) at week 12. Overall, no particular trend was observed. In the between-group comparison, the change in urine pH at week 12 was significantly greater in the BCP

group (P = 0.026), but no significant differences were found between the two study groups in all other variables. Overall, a distinct effect of BCP inhalation on any of the test items was not confirmed.

Table S17. Summary statistics of baPWV measurements on day 0 and at weeks 4, 8, and 12 by study group

		Initial baPWV < 1400 cm/s		Initial baPWV ≥ 1400 cm/s	
		Placebo group	BCP group	Placebo group	BCP group
Day 0	n	9	14	24	22
	Mean ± SD	1327.9 ± 53.8	1294.6 ± 71.2	1501.5 ± 79.9	1555.2 ± 133.3
	Range	1199–1376	1151–1366	1412–1729	1417–1856
Week 4	n	9	14	24	21
	Mean ± SD	1406.4 ± 117.7	1335.8 ± 117.3	1517.3 ± 119.1	1484.6 ± 149.9
	Range	1285–1686	1201–1560	1345–1881	1199–1779
Week 8	n	9	13	23	20
	Mean ± SD	1377.4 ± 117.7	1337.6 ± 111.7	1481.2 ± 158.3	1470.3 ± 113.1
	Range	1184–1694	1115–1576	1222–1805	1276–1746
Week 12	n	9	13	23	21
	Mean ± SD	1380.6 ± 155.9	1354.4 ± 94.3	1495.4 ± 138.7	1501.7 ± 146.9
	Range	1184–1694	1175–1515	1260–1816	1232–1832

Table S18. Results of the repeated measures mixed model for the analysis stratified by baPWV < 1400 and ≥ 1400 cm/s on day 0

Initial baPWV < 1400 cm/s		**Placebo group**			**BCP group**			**Difference between BCP and placebo groups**		
		Mean	**95% CI**	**P-value (vs. day 0)**	**Mean**	**95% CI**	**P-value (vs. day 0)**	**Mean**	**95% CI**	**P-value (vs. placebo)**
Day 0	Absolute	1310.3	1230.9, 1389.7	-	1299.4	1228.7, 1370.1	-	-	-	-
Week 4	Absolute	1407.9	1328.5, 1487.2	-	1362.8	1292.1, 1433.4	-	-	-	-
	Difference	97.6	10.5, 184.7	0.058	63.3	-3.2, 129.9	0.123	-34.2	-143.8, 75.4	>0.999
Week 8	Absolute	1354.6	1275.2, 1433.9	-	1356.9	1283.7, 1430.1	-	-	-	-
	Difference	44.3	-42.8, 131.4	0.624	57.5	-11.0, 126.0	0.196	13.2	-97.6, 124.0	>0.999
Week 12	Absolute	1335.2	1255.8, 1414.5	-	1372.1	1298.9, 1445.3	-	-	-	-
	Difference	24.9	-62.2, 112.0	0.569	72.7	4.2, 141.2	0.038	47.8	-63.0, 158.6	0.39
Initial baPWV ≥ 1400 cm/s		**Placebo group**			**BCP group**			**Difference between BCP and placebo groups**		
		Mean	**95% CI**	**P-value (vs. day 0)**	**Mean**	**95% CI**	**P-value (vs. day 0)**	**Mean**	**95% CI**	**P-value (vs. placebo)**
Day 0	Absolute	1535.7	1469.8, 1601.6	-	1543.1	1488.7, 1597.5	-	-	-	-
Week 4	Absolute	1544.9	1479.0, 1610.8	-	1447.7	1393.3, 1502.1	-	-	-	-
	Difference	9.2	-57.8, 76.1	>0.999	-95.4	-152.7, -38.1	0.003	-104.6	-192.7, -16.4	0.041
Week 8	Absolute	1472.6	1406.7, 1538.5	-	1472.4	1417.4, 1527.4	-	-	-	-
	Difference	-63.1	-130.1, 3.9	0.129	-70.7	-129.4, -12.0	0.038	-7.6	-96.6, 81.4	>0.999
Week 12	Absolute	1523.6	1457.7, 1589.5	-	1489.7	1434.7, 1544.7	-	-	-	-
	Difference	-12.1	-79.0, 54.9	0.72	-53.4	-112.1, 5.2	0.074	-41.3	-130.4, 47.7	0.358

Table S19. Results of the correlation analysis between the initial baPWV value and baPWV changes at weeks 4, 8, and 12

	Placebo group		BCP group		Difference in correlation coefficient between BCP and placebo groups
	Correlation coefficient	P-value	Correlation coefficient	P-value	P-value
Week 4	-0.216	0.228	-0.502	0.002	0.191
Week 8	-0.193	0.274	-0.615	<0.001	0.193
Week 12	-0.238	0.190	-0.513	0.002	0.209

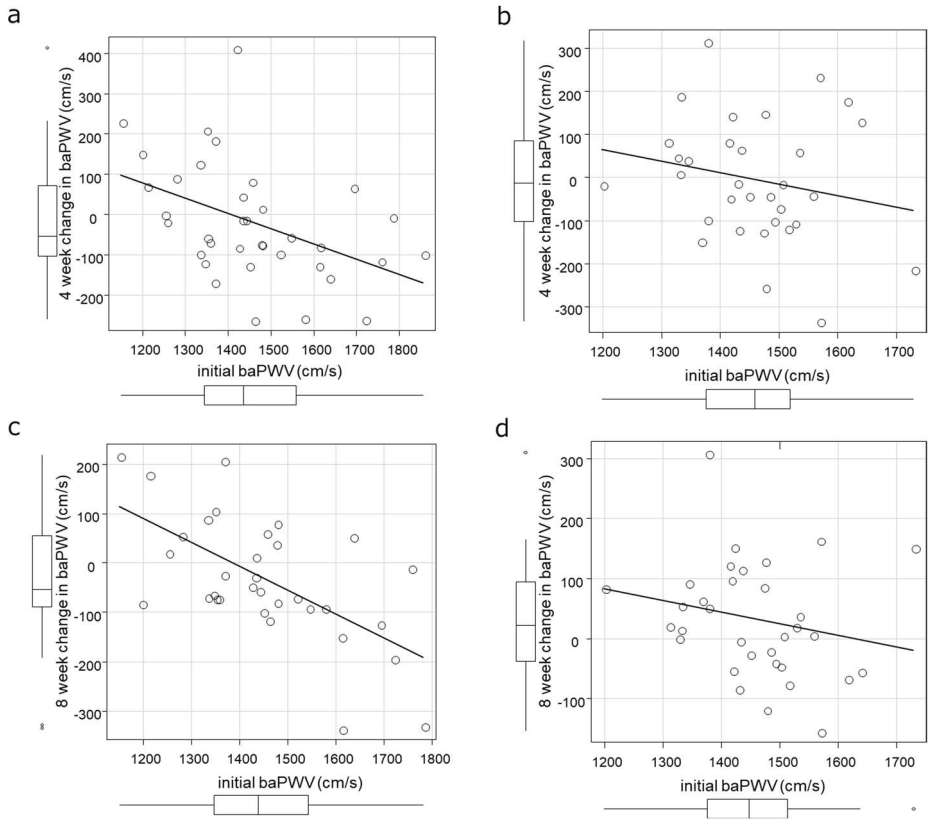

Figure S2. Results of the correlation analyses. (a) Correlation between baPWV on the start date (day 0) and 4-week change in baPWV in the BCP group. (b) Correlation between baPWV on day 0 and 4-week change in baPWV in the placebo group. (c) Correlation between baPWV on day 0 and 8-week change in baPWV in the BCP group. (d) Correlation between baPWV on day 0 and 8-week change in baPWV in the placebo group.

Table S20. Adverse events and their occurrence rates in the placebo group

Adverse event	Onset rate
COVID-19	7.7% (3/39)
Acute post-COVID-19 syndrome	5.1% (2/39)
Sudden deafness	2.6% (1/39)
Fever	2.6% (1/39)
Influenza	2.6% (1/39)
Nasopharyngitis	2.6% (1/39)
Ankle fracture	2.6% (1/39)
Avulsion fracture	2.6% (1/39)
Increased sputum production	2.6% (1/39)

Table S21. Adverse events and their occurrence rates in the BCP group

Adverse event	Onset rate
Nasopharyngitis	5.6% (2/36)
Back pain	2.8% (1/36)
Headache	2.8% (1/36)
Increased sputum production	2.8% (1/36)
Oropharyngeal discomfort	2.8% (1/36)