Original Article

Effect of vitamin C and hawthorn beverage formula on blood pressure and oxidative stress in heat-exposed workers: a cluster-randomized controlled trial

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Background and Objectives: There is no evidence on antioxidant-rich diets in preventing hypertension in heat-exposed workers. We aimed to evaluate the effects of formula supplemented with vitamin C (Vit C) and hawthorn beverage on reducing blood pressure (BP) and oxidative stress levels in heat-exposed workers. **Methods and Study Design:** In the 40-day cluster-randomized controlled trial, four heat-exposed shift-teams were enrolled and randomly assigned to the intervention and control groups. The intervention group was given one Vit C tablet (130 mg) and a 500 mL hawthorn beverage containing 278.7 mg flavonoids daily whereas the control group was given 500 mL of slightly salted water daily; both groups were provided education on a healthy diet. BP and creatinine-corrected urinary 8-isoprostane-prostaglandin F2α (8-iso-PGF2α/Cr) concentrations were assessed at baseline, Day 17 (only BP) and Day 41, respectively. **Results:** Compared with the control group, the systolic BP (SBP), diastolic BP (DBP), and log10-transformed 8-iso-PGF2α/Cr in the intervention group decreased by 7.41 mmHg, 7.93 mmHg and 0.232, respectively, from baseline to day 41 (all p<0.05). When comparing BP levels at baseline, DBP in the intervention group was reduced by 5.46 mmHg when compared to control (p<0.05) among participants with lower baseline BP; SBP and DBP experienced reductions of 9.74 and 9.22 mmHg among participants with higher baseline BP (both p<0.05). **Conclusions:** Supplementation of Vit C and flavonoids rich hawthorn beverage to heat-exposed workers prevented elevated BP caused by heat exposure which may be attributed to its oxidative stress inhibition effects.

Key Words: vitamin C, hawthorn flavonoids, blood pressure, 8-iso-PGF2α, heat exposure

INTRODUCTION

Hypertension is a key risk factor for cardiovascular diseases and is responsible for one-fifth of the total mortality (approximately 10.8 million) worldwide in 2019.[1] In China, the prevalence of hypertension among adults has steadily increased in the past three decades, reaching 27.5% (approximately 300 million people) in 2018.[2] As a severe global public health concern, preventing hypertension has become an important task. From the perspective of prevention strategies and measures for cardiovascular disease, high-risk prevention strategies are more effective for people at high risk.[3] Heat-exposed workers are prone to hypertension, which is associated with vitamin C (Vit C) deficiency.[4,5] The increased metabolic rate and oxidation reactions caused by heat exposure, along with the excessive loss of water-soluble antioxidants through sweat, can disrupt the balance between oxidation and antioxidation, directly impacting cardiac systolic function.[6] Increasing foods (drinks) rich in antioxidants is a feasible solution for preventing hypertension caused by heat exposure.

Oxidative stress, due to the excessive production of oxygen free radicals and a decrease in antioxidant capacity, is linked to the development of cardiovascular damage.[7] A case–control study indicated that natural antioxidants found in fruits, vegetables, and drinks (tea and coffee) could reduce the incidence of hypertension.[8] Employing whole foods instead of isolated components as supplements in interventions is more reasonable and feasible. Therefore, high-quality vegetables and fruits or diets fortified with nutrients are typically used in intervention trials.[9,10] A RCT reported that an 8-week high-vegetable and fruit juices intervention decreased the concentration of urine 8-iso-PGF2α, which is a biomarker of lipid peroxidation.[11] These beneficial effects are attributed to Vit C and flavonoids, which are abundant in vegetables and fruits and act as ideal antioxidants, playing an important

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role in maintaining intracellular redox homeostasis.[12] Recent RCTs have shown that diets naturally rich in antioxidants, such as orange juice rich in Vit C or diets rich in polyphenols, could reduce oxidative stress and improve elevated BP.[13,14] However, there is insufficient evidence that foods (drinks) rich in antioxidants can prevent elevated BP in high-risk populations.

Previous studies have shown that Vit C could induce transcription factor Nrf2 activity in rats, whereby Nrf2 is involved in the antioxidant protection effects against oxidative damage.[15] However, Vit C supplementation could not completely inhibit the oxidative stress caused by heat exposure and prevent BP levels from increasing in rats; instead, the combination of Vit C with flavonoids supplements from hawthorn extract could reduce BP levels.[16] There is a growing interest in the effects of consuming dark-coloured fruits on oxidative stress.[17-20] Hawthorn, which is rich in flavonoids compared with other drupes, has a greater oxygen radical absorbance capacity[21] and can reduce BP levels.[22] Since 2000, heatstroke prevention in steel workers by providing them with ice lollies or dried hawthorn soaked in drinking water has been common among Chinese steel enterprises. Soaking dried hawthorn in drinking water is not convenient for workers; a more suitable measure for heat-exposed workers experiencing oxidative stress may be to use hawthorn juice.

Therefore, a cluster-RCT design was applied to evaluate the effects of a daily formula supplemented with Vit C and hawthorn beverage rich in flavonoids to prevent an increase in BP in heat-exposed workers, giving a 5-shift-work-cycle (40-day) intervention during the summer of the year. The inhibitory effect on oxidative stress was also evaluated by urinary isoprostane levels. Slightly salted carbonated water, a common drink in heat-exposed workers, was given to the control group. To date, no study has evaluated the effect of a high-antioxidant drink supplement on BP levels of heat-exposed workers.

METHODS

Study design

This study was a cluster-RCT at a continuous casting workshop of a steel company in Hebei Province, North China, from July to August 2023. The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of North China University of Science and Technology (approval no. 2023064). This trial was registered with the Chinese Clinical Trial Registry (No. ChiCTR2400080611), and all participants provided written informed consent before the start of the trial.

Study participants

All four shift teams from the workshop were selected, each consisting of 40 to 50 steel workers. Steel workers exposed to heat (wet bulb globe temperature: 28.5-35.5 °C) were invited to participate in the trial; they were exposed to heat at work and lived in dormitories during workdays. The inclusion criteria were as follows: (1) male, 22-55 years old steelworkers; (2) service length ≥1 year. The exclusion criteria were as follows: (1) participated in other intervention trials in the past 3 months; (2) took anti-hypertensive drugs; (3) consumed dietary supplements; (4) had prediabetes or diabetes; (5) had other cardiovascular diseases; (6) had gastrointestinal disease in the past 1 month; (7) planned to take a vacation; (8) refused to participate in the trial.

The sample size was estimated using the formula for a cluster-RCT. Based on data from a previous study targeting cardiovascular health following Vit C supplementation,[23] assuming a standard deviation (SD) of systolic BP (SBP) of 10 mmHg, with an intraclass correlation coefficient of 0.01, we estimated that a sample size of 124 participants would provide 80% power (with a two-sided alpha=0.05) to detect a difference in mean SBP ≥5 mmHg between the intervention and control groups, allowing for a 10% loss-to-follow-up rate of participants. Eligible participants completed and met all the investigations within the study period, and a total of 132 qualified data were included in the analysis. A summary of the study process based on the CONSORT flow diagram (2010) is presented in Figure 1.

Randomization

Participants were provided with a 500 mL bottle of slightly salted carbonated water during an 8-day run-in period. After that, the four eligible shift teams (clusters) were randomly assigned to the intervention and control groups by a random numbers table in a 1:1 ratio. Due to the nature of the intervention, blinding of the participants was infeasible.

Intervention programs

In the antioxidant formula supplement intervention group, each participant was given 1 Vit C tablet and 2 cans of hawthorn beverage per workday in a 5-shift work cycles (2-day shifts + 2-night shifts + 4-rest days/cycle, total of 40 days). The Vit C chew tablet was manufactured by By-health Co., Ltd., Zhuhai, China; each tablet contained 130 mg of Vit C. The Boiled Hawthorn Drink was manufactured by Liyuan Food Co., Ltd., Tangshan, China; volume of each can were 250 mL that contained less than 1 mg of Vit C and 139.4 mg of flavonoids (Supplementary Table 1). It was requested that the workers chew the Vit C tablet before their shifts and drink the hawthorn beverage during work breaks.

In the control group, each participant was given a bottle of slightly salted carbonated water daily during the workdays. The slightly salted carbonated water is a common heatstroke prevention drink at the worksite manufactured by Beishuang Drink Water Co., Ltd., Tangshan, China. Each bottle had 500 mL and contained 0.5 g of salt. Reason for using the slightly salted carbonated water as a control was based on the requirement for on-site heatstroke prevention drinks. In addition, loss of salt via sweat among heat-exposed workers (sweat excretion during work was 3.18 L, and the sodium concentration in sweat is 1173.1 mg/L) was also considered.[5] The total daily sodium intake of the control group was 5811 mg/d (182 mg from slightly salted carbonated water and 5629 mg from diet), accounting for 89.4% of the maximum intake (6500 mg/d) recommended for heat-exposed workers.[24] Total daily sodium intake of control group was also not significantly different from that of the intervention group (5212 mg/d) (p=0.058).

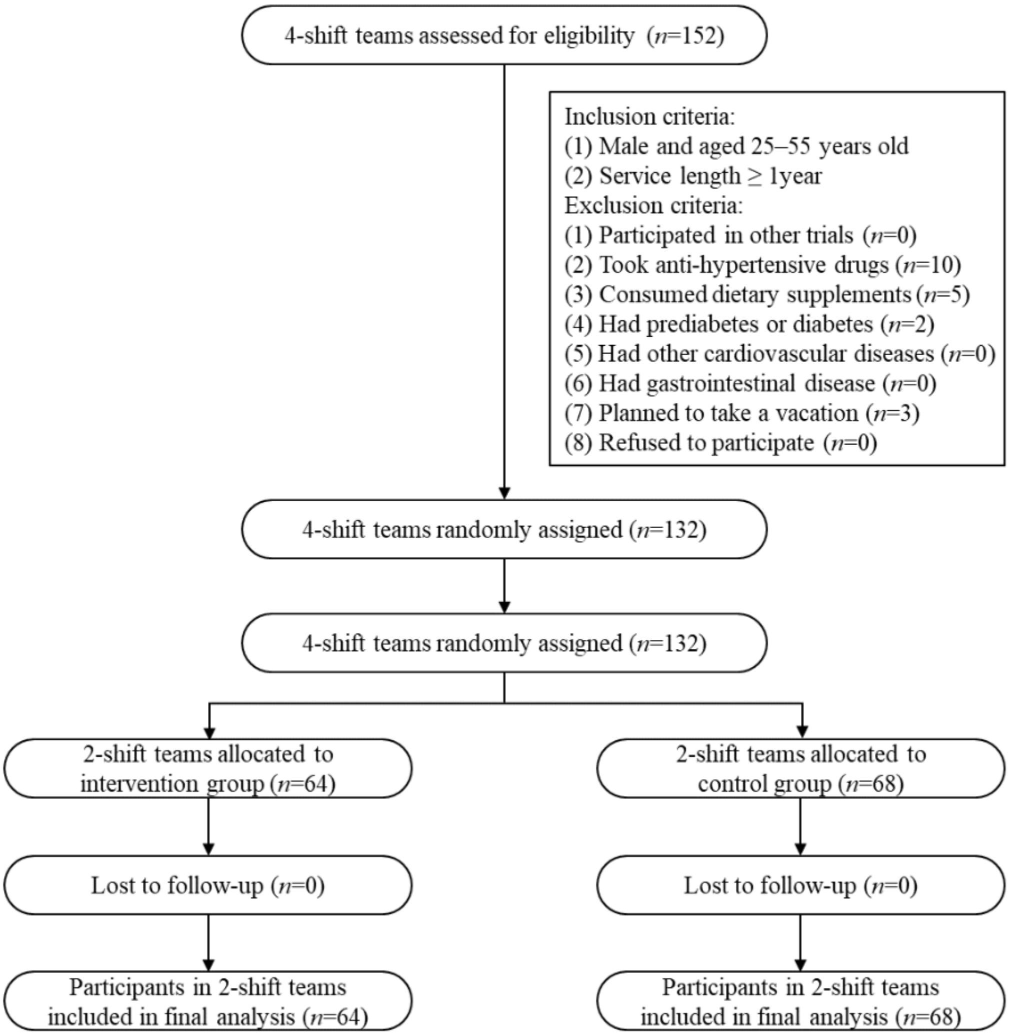

Figure 1. Flow diagram of the recruitment and follow-up of study participants

Each beverage bottle was marked with a different number. A trained doctoral candidate, who collaborated with shift team leaders, was responsible for distributing the Vit C tablet and hawthorn beverage or slightly salted carbonated water to the participants daily. Participants were requested to upload photos of used tablets, empty cans or bottles to an online document; the trained candidate will then record the daily consumption of each participant based on the information above. In order to enhance the compliance of individuals, a brief guidance on healthy drinking habit was provided to all participants in both groups on the first day of each work cycle via cell phone messages. Guidance content included the appropriate drinking frequency, quantity and beverage temperature for heat-exposed workers, and the advantage of drinking hawthorn beverage (sent to participants in the intervention group) or slightly salted carbonated water (sent to participants in the control group). The participants were asked to report any side effects of the supplements on the last day of each shift cycle.

Outcomes

Our primary outcome was the difference in net changes in SBP or diastolic BP (DBP) between the intervention and control groups from baseline to the end of the 5-shift-work-cycle intervention period. The secondary outcome was the net change in the urine 8-iso-PGF2α concentration.

Data collection and follow-up

BP measurement and fasting urine sample collection were carried out on the first day of the intervention (baseline), on the day after the 2-shift-work-cycle intervention (day 17) (BP measurement only), and on the day after the 5-shift-work-cycle intervention (day 41). These were done in the morning before the start of the shift, using the exact method by trained researchers.

Before randomization, the characteristics of each participant, such as age, length of service, type of work, smoking status, alcohol drinking status, tea drinking status, physical activity, sleeping time, and personal and family history of illness, were collected via face-to-face interviews using structured questionnaires. Body height and weight were also measured, and the participants' general dietary intake was assessed before randomization.

BP measurements

The SBP and DBP of the right upper arm were measured three times using a fully automatic electronic sphygmomanometer (HEM-7301-IT, Omron Healthcare Co., Ltd., Kyoto, Japan) with an interval of 1 to 2 min after the participants had been quietly sitting in an upright position for 5 min. The first reading was taken but discarded. If the difference between the last two readings was >5 mmHg, the measurements were taken again and the mean of the last two recorded values was used for analysis. In addition, BP were measured in participants that had left their work environment more than 12 h.

Urine collection and 8-iso-PGF2α concentration assessment

Midstream urine samples (15 mL) were collected from the participants in the morning following an 8-h period without drinking or intake. The study participants were adequately trained on proper collection and storage procedures. The urine samples were placed in a foam box with ice packs and transported to the laboratory at North China University of Science and Technology. Urine samples were separated at a low temperature, fractionated into aliquots, and stored at -80°C.

For the analysis of 8-iso-PGF2α, aliquots were thawed on ice immediately before the assay, centrifuged, and the resulting supernatant were diluted 20 times. The concentrations of 8-iso-PGF2α were measured using an 8-isoprostane enzyme immunoassay kit (Cayman Chemicals Co., Ann Arbor, MI, USA). The assay was conducted manually and ran through a spectrophotometer thrice. Creatinine concentration was measured using a sarcosine oxidase kit (Jiancheng Bio. Co., Nanjing, China). The concentration of creatinine-corrected 8-isoprostane-prostaglandin F2α (8-iso-PGF2α/Cr) in urine was expressed as μg/mol.

Anthropometric examinations

The body height and weight of each participant were assessed using a height measuring scale (C200, Shunjia Liming Medical Technology Co., Ltd., Jiangsu Changzhou, China) and an electronic weight scale (EB5636H, Senssun Weighing Apparatus Group Ltd., Guangdong Zhongshan, China). The precision of body height was 0.1 cm, and the body weight was 0.01 kg, whereby the participants wore light clothing (work clothes were required to be removed) and bare foot.

Assessments of workday dietary intake

Workday dietary intake was assessed using a combination of 24-h dietary recall over a 2-day period (including one day shift and one night shift). Models and photographs of food portions were provided to assist in estimating food intake. Participants' food intake during the day shift was recorded by face-to-face inquiry, and the intake during the night shift was recorded by participants using an online questionnaire designed and distributed by the researcher. After the dietary data were classified and sorted, the Vit C contents in various foods were converted and manually calculated by the researcher according to the China Food Composition,[25] and the flavonoid contents were converted based on the corresponding literature.[26-31] The workday dietary intakes were calculated as the average values of the 2-day food records.

Statistical analysis

The main analysis of intervention effect evaluation followed the intention-to-treat analysis (ITT). All the subjects completed our trial, and no missing value imputation was applied. Continuous variables were presented as the mean ± SD or as median (P_{25}, P_{75}), and categorical variables were expressed as numbers (percentages). Baseline characteristics were compared between the intervention and control groups to evaluate their comparability using Student's t-test for normally distributed data, the Mann–Whitney U test for skewed distributed or ordinal categorical data, and Pearson chi–square tests for unordered categorical variables.

Linear mixed model (LMM) analysis with a random intercept at the participant level was used to examine the effectiveness of the antioxidant formula intervention on BP levels and 8-iso-PGF2α/Cr concentrations between groups, time and their interactions. The shift team level cluster was not included in the model because the intraclass correlation coefficient was less than 5%. The model was adjusted for age, body mass index (BMI), service length, type of work, etc. The environmental temperature on the day of BP measurement was further adjusted when comparing the differences in SBP and DBP. Mean estimation was conducted with a 95% confidence interval (CI). The models utilized a variance component model to account for repeated measures within subjects. Comparisons between the intervention and control groups were conducted at all three time points (baseline, day 17and day 41) for SBP and DBP and at two time points (baseline and day 41) for 8-iso-PGF2α/Cr. A Bonferroni adjustment was used to correct for multiple comparisons. For 8-iso-PGF2α/Cr with a skewed distribution, a log10 transformation was conducted to achieve a normal distribution before analysis. In addition, we conducted post hoc subgroup analyses considering baseline BP status. Participants were stratified into a lower BP group if their baseline SBP was <130 mmHg and DBP was <85 mmHg and a higher BP group if their baseline SBP was ≥130 mmHg or DBP was ≥85 mmHg.

The analyses were performed using SPSS software version 23.0 (IBM Corp: Armonk, NY, USA). The statistical significance level was defined as $p<0.05$.

RESULTS

Characteristics of participant and intervention adherence

Among the 132 workers who participated in the trial, no one voluntarily withdrew during the study period (Figure 1). The average ages of the participants in the intervention and control groups were 39.4±5.2 years and 40.4±6.1 years, respectively. The baseline characteristics were not significantly different ($p>0.05$) between the intervention and control groups (Table 1). The overall compliance in the intervention group was 93.6% (Supplementary Table 2).

Dietary intake assessment

Supplementary Table 3 and 4 displayed the general mean or median daily intakes of food groups and Vit C and flavonoids from their workday diet in both intervention and control groups. There were no significant differences in the dietary intake of major food groups (e.g., cereals, soybeans, animal foods, vegetables, fruits, nuts, drinks), Vit C or flavonoids from each relevant source food between the intervention and control groups (all $p>0.05$). In

Table 1. Baseline characteristics of the study participants†

Variables	Overall (n = 132)	Intervention group (n = 64)	Control group (n = 68)	*p* value
Age (years)				
25-34	19 (14.4)	11 (17.2)	8 (11.8)	0.189
35-44	87 (65.9)	43 (67.2)	44 (64.7)	
45-54	26 (19.7)	10 (15.6)	16 (23.5)	
Service length (years)				
5-14	17 (12.9)	8 (12.5)	9 (13.2)	0.480
15-24	104 (78.8)	49 (76.6)	55 (80.9)	
25-35	11 (8.30)	7 (10.9)	4 (5.90)	
Work types				
Captain	13 (9.80)	6 (9.40)	7 (10.3)	0.916
Large ladle operator	28 (21.2)	13 (20.3)	15 (22.1)	
Steel caster operator	10 (7.50)	4 (6.30)	6 (8.80)	
Second operator	81 (61.5)	41 (64.0)	40 (58.8)	
BMI (kg/m^2)				
Underweight (<18.5)	2 (1.50)	1 (1.60)	1 (1.50)	0.582
Normal (18.5-23.9)	45 (34.1)	23 (35.9)	22 (32.4)	
Overweight (24.0-27.9)	60 (45.5)	29 (45.3)	31 (45.6)	
Obesity (≥ 28.0)	25 (18.9)	11 (17.2)	14 (20.5)	
Current smoker (Yes)	76 (57.6)	39 (60.9)	37 (54.4)	0.084
Current alcohol drinker (Yes)	69 (52.3)	34 (53.1)	35 (51.5)	0.385
Current tea drinker (Yes)	49 (37.1)	29 (45.3)	20 (29.4)	0.059
Regular exercise (Yes)	15 (11.4)	7 (10.9)	8 (11.8)	0.881
Sleeping time ≥6 (h/d)	88 (66.7)	43 (67.2)	45 (66.2)	0.902
SBP (mmHg)	128±14.2	128±14.4	128±14.0	0.884
DBP (mmHg)	85.7±11.4	86.8±11.5	84.6±11.2	0.277
8-iso-PGF2α/Cr(μg/mol)	87.9 (62.9, 123)	91.7 (74.9, 123)	85.1 (50.9, 135)	0.203

BMI: body mass index.
†Continuous data with a normal distribution are expressed as mean ± SD, other continuous variables with a skewed distribution are shown as median (P_{25}, P_{75}), and ordinal and unordered categorical data are expressed as n (%).

addition, the total energy intake in the intervention and control group were 2269±570 kcal/d and 2398±659 kcal/d, respectively; there was no significant difference between the two groups (p=0.231).

During the study period, as shown in Table 2, the intervention group had significantly greater median daily total intake of Vit C (181 mg vs. 77.9mg) and flavonoids (382 mg vs. 129 mg) compared with the control group due to supplementation (both p<0.001).

Effects of Vit C and hawthorn beverage intervention on BP

Figure 2 showed the mean SBP and DBP changes in the intervention and control groups at three time points. There was no significant difference between the intervention and control groups in terms of SBP or DBP at baseline (both p>0.05). Apart for SBP from baseline to day 17 (p=0.155), there was a significant decrease in SBP and DBP from baseline to day 17 and from day 17 to day 41 (all p<0.05) in the intervention group. In the control group, there was a significant increase in SBP from baseline to day 41 (p=0.023), but a significant change was not observed in SBP or DBP at other time points (all p>0.05). After examining the effect of the intervention using LMM controlled for covariates, the mean difference between the intervention group and the control group from baseline to day 41 was -7.41 (-11.0 to -3.86) mmHg for SBP and -7.93 (-10.9 to -4.96) mmHg for DBP (Table 3).

The study participants in the two groups were further categorized into lower and higher BP subgroups based on

Table 2. The average daily Vit C and flavonoids intake during the intervention†

Nutrients	Intervention group (n = 64)	Control group (n = 68)	*p* value
Vit C (mg/d)			
Hawthorn beverage (Supp.)	<2.0	—	—
Vit C tablet (Supp.)	117 (117, 124)	—	—
Dietary intake	56.5 (35.9, 87.5)	77.9 (45.0, 98.9)	0.076
Total	181 (157, 208)	77.9 (45.0, 98.9)	<0.001
Flavonoids (mg/d)			
Hawthorn beverage (Supp.)	251 (251, 265)	—	—
Dietary intake	125 (98.4, 167)	138 (99.9, 262)	0.246
Total	385 (362, 421)	138 (99.9, 262)	<0.001

Supp.: supplement.
†All continuous data with skewed distributions are expressed as median (P_{25}, P_{75}), and the Mann–Whitney *U* test was applied to compare the differences between groups.

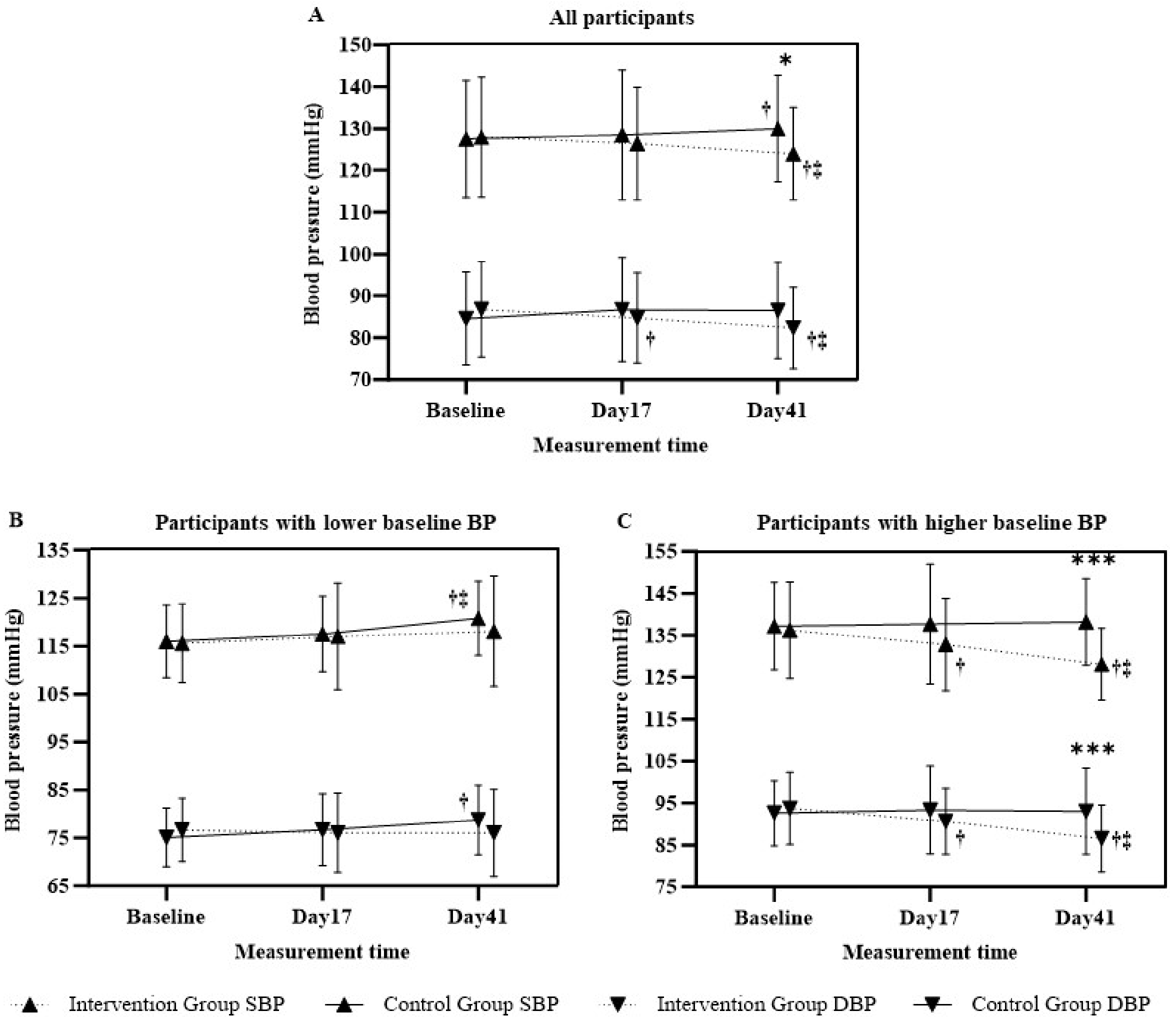

Figure 2. Mean blood pressure during the intervention according to assigned group. (A) In all participants. (B) Participants with lower baseline BP levels (SBP <130 and DBP <85 mmHg). (C) Participants with higher baseline BP levels (SBP ≥130 or DBP ≥85 mmHg). The error bars represent the standard error of the means. Baseline: on the first day before the intervention started; Day 17: after the 2-shift-work-cycle intervention; Day 41: after the 5-shift-work-cycle intervention; SBP: systolic blood pressure; DBP: diastolic blood pressure. [†]*p*<0.05 compared to baseline using paired sample *t*-test; [‡]*p*<0.05 compared to day 17 using paired sample *t*-test; **p*<0.05, ****p*<0.001 compared between groups using independent sample *t*-test.

Table 3. Effects of supplementation with Vit C and hawthorn beverage rich in flavonoids on blood pressure[†]

Outcome	Intervention group		Control group		Intervention versus control group	
	n	Mean differences[‡] (95% CI)	n	Mean differences[‡] (95% CI)	Mean differences[§] (95% CI)	*p* value
SBP (mmHg)						
All	64	-4.55 (-7.91, -1.19)**	68	2.86 (0.296, 5.42)*	-7.41 (-11.0, -3.86)	<0.001
Lower BP	26	1.80 (-2.60, 6.19)	31	4.89 (1.52, 8.27)**	-3.10 (-7.74, 1.55)	0.190
Higher BP	38	-8.62 (-13.1, -4.18)***	37	1.13 (-2.20, 4.45)	-9.74 (-14.4, -5.10)	<0.001
DBP (mmHg)						
All	64	-5.89 (-8.69, -3.08)***	68	2.04 (-0.110, 4.19)	-7.93 (-10.9, -4.96)	<0.001
Lower BP	26	-1.65 (-5.17, 1.87)	31	3.861 (1.20, 6.42)**	-5.46 (-9.16, -1.77)	0.004
Higher BP	38	-8.69 (-12.6, -4.78)***	37	0.529 (-2.21, 3.26)	-9.22 (-13.4, -5.07)	<0.001
lg 8-iso-PGF2α/Cr	64	0.051 (-0.031, 0.133)	68	0.283 (0.204, 0.362)	-0.232 (-0.346, -0.118)	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; Lower BP: SBP <130 and DBP <85 mmHg; Higher BP: SBP ≥130 or DBP ≥85 mmHg; CI: confidence interval.

[†]All comparisons were analysed separately using linear mixed models, and *p* values were adjusted for age, body mass index, service length, type of work, smoking status, alcohol consumption, tea drinking habit, intake days of the slightly salted carbonated water or antioxidant intervention ingredients and environmental temperature on the day of BP measurement.

[‡]Comparison of changes from the first day before the intervention started (baseline) to the day after the 5-shift-work-cycle intervention (day 41) within the group.

[‡]Comparison of changes from the first day before the intervention started (baseline) to the day after the 5-shift-work-cycle intervention (day 41) between the intervention and control groups; negative values support the effect of the intervention on lowering BP or 8-iso-PGF2α/Cr.

**p*<0.05, ***p*<0.01, ****p*<0.001 compared within groups using paired sample *t*-test.

baseline BP levels (SBP/DBP < or ≥130/85 mmHg). The response of participants to intervention in each subgroup was assessed using the LMM adjusted for baseline values of confounding factors. A drastic difference in response was observed depending on the baseline BP levels analysed. Interestingly, participants in the control group with a lower baseline BP showed a significant increase in the mean level of SBP and DBP on day 41 compared to baseline (both $p<0.05$); however, there was no significant change in SBP or DBP in the intervention group on day 41 compared to baseline (both $p>0.05$). In participants with higher baseline BP levels, the mean SBP significantly decreased on day 41 in the intervention group compared to that at baseline and day 17 (both $p<0.05$); conversely, no significant change was observed in the control group (both $p>0.05$). Mean DBP significantly decreased on day 41 compared to that at baseline and day 17 in the intervention group (both $p<0.05$), whilst no significant change was found in the control group (both $p>0.05$). In regards to the effects of the antioxidant formula on BP levels from baseline to day 41, although no significant effect was observed on SBP ($p=0.190$), a restrained increase in DBP was noted among the participants with lower baseline BP levels ($p=0.004$). In contrast, a more substantial reduction was observed in both SBP and DBP in participants with higher baseline BP levels (both $p<0.01$) (Table 3).

Effects of Vit C and hawthorn beverage intervention on oxidative stress biomarkers

The raw Cr-corrected urine 8-iso-PGF2α concentrations of the intervention group and control group at baseline and day 41 were 91.7 (74.9, 122.6), 85.1 (50.9, 134.6), 94.7 (72.6, 139.0) and 152.4 (106.7, 215.0), respectively. After log10 transformation, there was no significant difference in the urine 8-iso-PGF2α/Cr concentration between the intervention and control groups at baseline ($p=0.095$). There was no significant change in the urine 8-iso-PGF2α/Cr concentration observed in the intervention group ($p=0.221$), while a significant increase was noted in the control group ($p<0.001$) from baseline to day 41. After adjustment for confounders, the mean difference between the intervention and control groups was -0.232 (-0.346 to -0.118) (Figure 3 and Table 3).

DISCUSSION

Principal findings

The results of this study indicated that supplementation with a formula of 130 mg/d Vit C plus 500 mL/d hawthorn beverage (containing 279 mg flavonoids) over 5 shift work cycles during the hottest period in summer significantly prevented BP increase in heat-exposed workers. In addition, it significantly decreased urine 8-iso-PGF2α concentration, which might be the beneficial effects of this antioxidant formula. There were no side effects reported.

Formula of Vit C and hawthorn beverage improved BP

The findings on BP improvement are in disagreement with most non-acute antioxidation interventions.[8] Although BP is commonly decreased in high-risk cardiovascular health interventions, studies exploring the preventive functions of Vit C and flavonoids (dietary) in BP elevation in populations experiencing a high oxidative stress state need more evidence.[13,14] A trend of magnitude in BP levels was observed following the antioxidant formula interventions in the current study. Particularly, compared with heat-exposed workers in the control group who experienced elevated BP levels (although the change in DBP was not significant), BP levels in the intervention group were significantly decreased. This finding was also partly supported by a previous antioxidant intervention

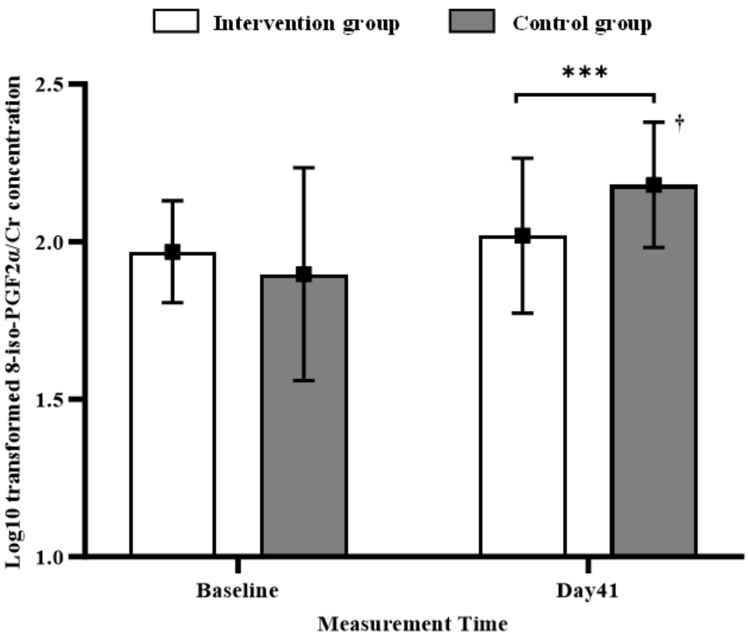

Figure 3. Mean urinary 8-iso-PGF2α/Cr concentration during the intervention according to the assigned groups. The 8-iso-PGF2α/Cr concentration was log10 transformed. The error bars represent the standard error of the means. Baseline: on the first day before the intervention started; Day 41: after the 5-shift-work-cycle intervention; 8-iso-PGF2α/Cr: creatinine-corrected 8-isoprostane-prostaglandin F2α. † $p<0.05$ compared to baseline within group using paired sample *t*-test; *** $p<0.001$ compared between groups using independent sample *t*-test.

trial whereby prophylactically ingested Vit C (2 g/day) effectively abrogated peripheral vascular dysfunction following exposure to 60% O_2 in divers.[32] The intervention dosages and total daily intakes of Vit C (130 mg & 186.5 mg) and hawthorn beverage flavonoids (278.7 mg & 403.7 mg) were more similar to the diets naturally rich in antioxidants for this special population. Thus, these findings support the beneficial effect of Vit C combined with flavonoid supplementation on BP control in heat-exposed workers.

In addition, since it was reported that middle-aged Chinese with BP levels above 130/85 mmHg had a greater risk of hypertension after 10 years than those with lower BP levels,[33] we conducted a post-hoc subgroup analyses considering baseline BP status. Among participants with lower baseline BP levels (SBP <130 and DBP <85 mmHg), BP levels in the intervention group did not change from baseline, whereas those in the control group increased. Conversely, among participants with higher baseline BP levels (SBP ≥130 or DBP ≥85 mmHg), BP levels in the control group did not change from baseline, whereas those in the intervention group decreased. It was speculated that the ventricular adjustments of participants with higher BP may not be easily affected by heat exposure (e.g., cardiovascular adaptations to temperature-sensitive mechanisms), resulting in only a small change in BP.[34] These results indicated that nutritional formula supplementation of Vit C and hawthorn beverage for heat-exposed workers had a positive influence on preventing a normal increase in BP or reducing higher BP. Currently, there are limited data on the antioxidant/dietary preventative interventions for BP. A recent crossover RCT evaluating the impact of blueberry consumption showed no effect on SBP or DBP in healthy adults.[35] This suggested that antioxidant supplements do not affect normal BP in the absence of risk factors that would elevate BP. Our study was consistent with a RCT in healthy adults undergoing intense physical training which compared participants consuming a carbohydrate-based control beverage and those receiving 10 mL/kg/day purple grape juice supplementation (phenolics content 1821 mg/L) for 28 days, whereby those in the latter group experienced a decrease in SBP.[18] This difference in preventing the increase in DBP found in this study may be associated with the lower baseline BP in some participants. Intervention with Vit C and hawthorn beverage rich in flavonoids targeting populations with higher BP levels resulted in a reduction in BP. This finding was consistent with other reports indicating that hawthorn extract had a significant effect in decreasing BP in patients with stage I hypertension.[36] Previous interventions had shown that consuming Vit C or juice rich in flavonoids/polyphenols can reduce hypertension in individuals with other CVD risk factors, and these effects may be attributed to the potent antioxidant properties of hawthorn flavonoids or the synergistic effects of Vit C at a safe dose[37]. Our findings highlighted the importance of sufficient Vit C intake combined with hawthorn beverage consumption in heat-exposed workers who had limited access to antioxidant-rich foods or who were at high CVD risk.

Vit C and hawthorn beverage reduced oxidative stress

The beneficial effects of Vit C and hawthorn beverage/flavonoid intervention on oxidative stress were supported by membrane lipid peroxidation-related biomarkers such as decreased urinary isoprostane excretion. This was also observed in a previous study where peroxide product concentration decreased after healthy subjects with habitually low intake of fruits and vegetables consumed antioxidant and polyphenol-rich blackcurrant juice.[17] The results indicated that supplemental Vit C and hawthorn beverage/flavonoids led to apparent changes in oxidation resistance and biomarker formation. The antioxidant intervention group showed significantly lower BP levels than the control group, which was consistent with the improvement in BP observed. Previous studies have shown the beneficial effects of Vit C or flavonoid-rich food on oxidative stress and oxidative lipid damage markers in individuals at high risk for cardiovascular health issues. For example, chronic Vit C treatment can prevent oxidative stress-induced dysregulation of BP by reducing serum 8-iso-PGF,[38] and 4 weeks of red wine consumption might decrease urine 8-iso-PGF2α concentrations in healthy men with a high risk of obesity (indicated by a high BMI).[39]

8-iso-PGF2α is considered to be a biomarker of lipid peroxidation that represents an end product of peroxide derived from free radicals attacking arachidonic acid on the cell membrane.[40] It is commonly used to reflect the overall level of oxidative stress in the body and to evaluate the impact of intervention measures on oxidative damage. 8-iso-PGF2α is present in the plasma at low concentrations and rapidly excreted; it is accumulated in urine without the influence of other factors.[41] In addition, the method used for collecting urine samples is easily accepted and can be carried out on site; this can address the limitations of using blood samples. Lower 8-iso-PGF2α excretion in urine was consistent with a decreased peroxide products indicated by a significant reduction in serum malondialdehyde concentrations in high-risk cardiovascular populations following a heart-healthy diet.[42]

Oxidative stress interference (OSI) aims to regulate oxidative stress effectively during critical periods, preventing the body from undergoing pathological changes.[43] Previous experimental studies have shown that the effect of antioxidants in the treatment of cardiovascular diseases was not ideal.[44] It is necessary to explore a more suitable antioxidant formula for reducing the oxidative stress caused by external factors. In our current trial, we observed that the formula of Vit C and hawthorn beverage rich in flavonoids could effectively inhibit oxidative stress in heat-exposed workers. This was supported by the significant decrease in the urine 8-iso-PGF2α concentration in the antioxidant formula group compared to the control group. A RCT demonstrated that compared to a high-vitamin diet, the combination of antioxidant supplements could significantly reduce oxidative stress in patients with cardiometabolic risk.[45] Therefore, daily supplementation of 130 mg of Vit C and 278.7 mg flavonoids in hawthorn beverage may be sufficient to prevent oxidative stress in heat-exposed workers during the hottest period in summer, thus helping to maintain BP levels.

Nutritional factors in the Vit C and hawthorn beverage formula and antioxidation effects

Previous RCTs have shown that dietary supplementation is the most natural method for intervention in preventing and improving hypertension in high-risk populations.[46] The effects of the Vit C tablet and hawthorn beverage may be attributed to the active nutritional ingredients contained in the formula.[47,48] Water-soluble Vit C and flavonoids have superior antioxidant properties. They can penetrate cell membranes and reach mitochondria to inhibit peroxidation reactions, thereby reducing the formation of peroxide products and protecting the lipid membrane of vascular cells from damage.[49] The remarkable improvement in SBP and DBP in the antioxidant formula intervention group indicated that by drinking a beverage rich in flavonoids and taking Vit C tablets (diet + additional supplement), an adequate Vit C intake of 186.5 mg/d, accounting for 103.6% of heat-exposed workers' RNI of 180 mg/d, along with a flavonoid intake of 403.7 mg/d, which is within the range from the general population's SPL of 200 mg/d to UL of 800 mg/d, could meet the requirements for optimal antioxidant ability to combat oxidative stress induced by heat-exposure. This highlights the importance of adequate antioxidant supplementation and a well-functioning antioxidant network among heat-exposed workers. In addition, hawthorn in beverage provides a relatively rich source of high-quality flavonoids, similar to those found in blueberries, which could help improve cardiovascular health.[41] This supplement drink was favoured amongst heat-exposed workers because of the need for plenty of water and the appetite for a strong fruit acid taste. Moreover, considering the challenge to achieve optimal nutrient intake from fruits and vegetables due to unrestricted cooking methods as indicated in a randomized trial,[50] we added Vit C chewable tablets in the formula to fortify the low Vit C content in hawthorn beverage. Together with flavonoids, the formula in this study met the levels needed for anti-peroxidation and cardiovascular health protection. In addition, the hawthorn beverage was shown to be a relatively low source of potassium (4.3% of the recommended intake), in which sufficient potassium intake could help improve cardiovascular health.[51]

Strengths and limitations of this study

This study has several strengths. Participants in two groups from four shift work groups were selected through cluster randomization to balance potential confounding bias and enhance the statistical power of this trial. The study was conducted on healthy participants who had an increased risk of high BP due to oxidative stress induced by heat exposure. This is a key priority in CVD prevention. Next, the high adherence (100.0%) to the formula of Vit C tablet and hawthorn beverage supplementation in the intervention group and slightly salted carbonated water in the control group reduced the likelihood of false negatives for the primary study outcome. Finally, intervention products were distributed daily only to the shift group on duty to prevent contamination.

Some limitations should be noted. Participant recruitment was conducted at a single site, which might introduce bias due to demographic characteristics and could limit the generalizability of the results. However, this study laid the groundwork for future research on the preventive effects of antioxidant supplementation on BP increase in a larger sample of heat-exposed populations at various sites. Also, we could not provide beverages with the same salt and sugar content for both groups or let participants opt for sugar-free drinks due to the varying ingredients in packaged foods. Slightly salted carbonated water was utilized as a control based on heat-exposed workers' daily requirements, taking into account their sweat loss. There was no significant difference in the total sodium intake between the two groups; the total sodium intake was also below the maximum recommended intake. The dietary intake during workday was only assessed once at baseline, and no assessment was performed after the intervention. However, the participants were shift workers living in dormitories during workdays and most of the time ate at factory canteens. Their dietary habits were unlikely to change during the 40-day intervention.

Conclusions

In conclusion, this study showed that daily supplementation with Vit C and hawthorn beverage decreased BP and urine 8-iso-PGF2α concentrations in heat-exposed workers, suggesting the positive effects on preventing BP increase and inhibiting oxidative stress via lipid peroxidation inhibition. Our findings highlight the importance of consuming adequate amounts of ideal antioxidants, such as Vit C and flavonoids, especially in populations exposed to intense heat. It is suggested that the hypertension-protective effects of the antioxidant formula during the hottest period in summer was achieved via the control of BP increase. Further replication in long-term intervention studies is needed.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflicts of interest.

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Supplementary Tables

Supplementary Table 1. Main nutrient compositions of the intervention and control groups

Components of foods	Intervention group		Control group
	Vit C chew tablet (per 1 tablet/1 g)	Hawthorn (dried) beverage (per 2 cans/500 ml)	Slightly salted carbonated water (per 1 bottle/500 ml)
Vit C (mg)	130.0[†]	<2.00[‡]	–
Flavonoids(mg)	–	278.7[§]	–
Sodium (mg)	–	0.00[¶]	200.0[¶]
Potassium (mg)	–	137.3[††]	–
Total Carbohydrates (g)	–	57.2[¶]	12.5[¶]
From Hawthorn (g)	–	23.5[††]	–
From Sugars (g)	–	33.7[††]	12.5[¶]

[†]Vit C Chew Tablet information from By-health Co., Ltd.
[‡]Analysed by the researcher at North China University of Science and Technology, applying the 2,6-dichlorphenol indophenol method.
[§]Analysed by the Beijing Nutrition Analysis Centre, applying the spectrophotography method (UV-1780 spectrophotometer; Shimadzu, Japan), using rutin as a standard sample.
[¶]From nutrition label information on food package.
[††] Converted by the researcher with China Food Composition information.

Supplementary Table 2. Intervention adherence of participants†

	Overall (n = 132)	Intervention group (n = 64)	Control group (n = 68)
Participants who adhered 90%~94% of the study period	69 (52.3)	33 (51.6)	36 (52.9)
Participants who adhered 95%~99% of the study period	19 (14.4)	16 (25.0)	3 (4.40)
Participants who adhered 100% of the study period	44 (33.3)	15 (23.5)	29 (42.7)
Overall compliance (%)	94.1	93.6	94.6

Overall compliance: The ratio of the total number of adherence days to the total number of intervention days.
†Values are n (%), unless otherwise indicated.

Supplementary Table 3. Baseline workday food groups intake of participants†

Food groups	Intervention group (n = 64)	Control group (n = 68)	*p* value
Cereals (g/d)			
Rice/Wheat	331±81.7	361±111	0.076
Coarse cereals/beans	0.00 (0.00, 11.9)	0.00 (0.00, 23.1)	0.393
Starch product	0.00 (0.00, 10.0)	0.00 (0.00, 0.00)	0.210
Total	347±81.0	379±116	0.069
Soybean (g/d)	12.5 (0.00, 20.0)	10.0 (0.00, 12.5)	0.055
Animal foods (g/d)			
Livestock	75.0 (37.5, 113)	75.0 (50.0, 122)	0.341
Poultry	25.0 (0.00, 50.0)	0.00 (0.00, 50.0)	0.106
Eggs	76.3 (50.0, 97.5)	65.0 (21.3, 110)	0.281
Aquaculture	0.00 (0.00, 5.00)	0.00 (0.00, 50.0)	0.115
Dairy	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.976
Total	225±103	229±100	0.816
Vegetables (g/d)			
Leafy vegetables	50.0 (0.00, 100)	75.0 (0.00, 125)	0.115
Dark root/stem	62.5 (25.0, 150)	62.5 (25.0, 150)	0.921
Others	100 (75.0, 186)	125 (75.0, 200)	0.250
Total	288 (216, 400)	333 (250, 400)	0.241
Edible Fungus	12.5 (0.00, 28.8)	3.80 (0.00, 25.0)	0.325
Fruits (g/d)	0.00 (0.00, 100)	25.0 (0.00, 100)	0.165
Nuts (g/d)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.586
Drinks (ml/d)			
Pure water	2500 (1410, 2750)	2500 (1880, 2750)	0.625
Tea water	250 (0.00, 1230)	0.00 (0.00, 930)	0.247
Fruit beverage	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.710
Carbonate beverage	0.00 (0.00, 200)	0.00 (0.00, 0.00)	0.091
Total	2800 (2500, 3200)	2800 (2300, 3300)	0.516
Ice lolly (g/d)	0.00 (0.00, 90.0)	0.00 (0.00, 60.0)	0.283
Oil (g)	33.2±11.8	33.4±10.8	0.924
Salt (g)	13.0±4.10	14.1±4.80	0.185
Sugar (g)	0.00 (0.00, 3.00)	0.00 (0.00, 4.50)	0.785

†Continuous data with a normal distribution are expressed as the mean ± SD, and two independent *t*-test was applied to compare the two groups. Other continuous variables with a skewed distribution are shown as median (P_{25}, P_{75}), and the Mann–Whitney U test was used to compare the differences.

Supplementary Table 4. Baseline workday Vit C and flavonoids intake of participants†

Nutrients	Intervention group (n = 64)	Control group (n = 68)	*p* value
Vit C (mg/d)			
Vegetables	50.0 (31.4, 81.2)	67.1 (43.8, 89.9)	0.056
Fruits	0.00 (0.00, 12.0)	1.50 (0.00, 12.0)	0.151
Other beverage	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.393
Total	56.5 (35.9, 87.5)	77.9 (45.0, 98.9)	0.076
Flavonoids (mg/d)	12.5 (0.00, 20.0)		
Vegetables	21.9 (11.4, 26.6)	18.8 (13.4, 26.2)	0.827
Fruits	0.00 (0.00, 8.80)	3.0 (0.00, 8.80)	0.130
Cereals	50.8 (37.9, 72.5)	58.5 (44.6, 97.7)	0.054
Soybean	25.6 (0.00, 41.0)	20.5 (0.00, 25.6)	0.055
Nuts	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.524
Teas	12.0 (0.00, 16.1)	0.00 (0.00, 17.3)	0.523
Total	125 (98.4, 167)	138 (99.9, 262)	0.246

†All continuous data with skewed distributions are expressed as median (P_{25}, P_{75}), and the Mann–Whitney *U* test was applied to compare the differences between groups.