Letter

Effects of Ozone Exposure on Cardiopulmonary Function and Adaptive Responses in Han and Tibetan Children during Physical Activity at High Altitudes

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The cardiopulmonary health of children may be affected by acute ozone (O_3) exposure during physical activity[1]; however, its effects in high-altitude regions such as the Xizang Plateau remain uncertain. In high-altitude areas, lower oxygen levels may cause children to experience shortness of breath or require increased respiratory effort during vigorous activities such as running. This could lead to increased pollutant inhalation, potentially elevating the burden on the cardiovascular system and triggering adverse reactions such as increased heart rate and elevated blood pressure. Furthermore, differences in physiological adaptation between Han children who have migrated to Xizang and Tibetan children who are native to the region may contribute to different reactions to environmental exposure[2].

This study aimed to explore the health impacts of O_3 exposure during physical activity in children residing in the Xizang Plateau and to investigate the influence of adaptive responses.

The experiment was conducted in Lhasa, Xizang Plateau, where the O_3 concentration is sustained at high levels partly due to strong ultraviolet radiation during summer afternoons, while fine particulate matter ($PM_{2.5}$) concentration is extremely low. The typical daily maximum 8-h average O_3 concentrations is 124 $\mu g/m^3$, exceeding the air World Health Organization (WHO) guideline of 100 $\mu g/m^3$. The typical daily mean $PM_{2.5}$ concentration is 8 $\mu g/m^3$, well below the WHO guideline of 15 $\mu g/m^3$. Therefore, we attributed the observed adverse effects of O_3 exposure.

Based on the preliminary studies, a total of 60 children were included (28 Han and 32 Tibetan students). Participants were divided into five groups, ensuring equal distribution of boys, girls, Tibetans,

and Han in each group. The experiment were conducted across five afternoons during the week under consistent experimental conditions.

This study aimed to analyze the health effects of O_3 exposure through multiple experiments. Upon arrival at the study center, participants rested and underwent baseline health measurements. From 15:00 to 15:30 pm, participants completed a 2-km run at maximal effort. Following the run, they rested and were re-assessed for the same health measurements. Blood pressure and lung function were measured before and after exposure. The study protocol was approved by the institutional ethics review committee, and written informed consent was obtained from all participants and their guardians. Environmental monitoring included measurement of O_3, PM_1, $PM_{2.5}$, PM_{10}, carbon monoxide (CO), nitrogen dioxide (NO_2), and light intensity using a Personal Exposure Kit (PEK) with a 60-s resolution. Real-time ambient temperature and relative humidity were recorded using a Hobo data logger. All instruments were calibrated before use. Outdoor pollutant levels were measured within 3 m of the exercising area, and indoor pollutant concentrations were also documented as potential confounders because the students spent approximately 12 h indoors. Outdoor pollutant data were aggregated into 30 min intervals, while indoor daily averages were calculated based on 12-h measurements. Trained technicians conducted the lung function and blood pressure measurements at the clinical center. Lung function was measured using a calibrated spirometer according to ATS/ERS recommendations, and included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), and mean forced expiratory

flow between 25% and 75% of FVC (FEF$_{2575}$). Three to four maneuvers were performed by each participant. Blood pressure was measured using an Omron HEM-7211 sphygmomanometer which is produced by Omron Corporation in Kyoto, Japan, with three readings averaged for systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP).

A detailed questionnaire was designed for all three parties—households, students, and parents—to better understand and control for potential confounding factors that may influence the results of the study. This information was used to enhance the accuracy and reliability of the findings.

We assessed the differences in lung function and blood pressure from baseline to post-exposure in children following running exercise, identifying the main pollutant as O$_3$. A generalized linear model (GLM) was used to explore the effects of O$_3$ exposure on lung function and blood pressure. In this model, the O$_3$ concentration served as the independent variable, while lung function indices and blood pressure measurements served as dependent variables. We incorporated various potential confounding factors, including age, sex, body mass index (BMI), and ethnicity, as covariates in the GLM. Additional adjustments were made for other covariates such as temperature, humidity, concentrations of other pollutants, indoor O$_3$ concentrations, and questionnaire results. Stratified regression analyses were performed according to ethnicity and sex to explore the effects of O$_3$ on different populations. All statistical analyses were performed using IBM SPSS Statistics V22. Two-tailed P-values < 0.05 were considered statistically significant.

Our findings revealed that local Tibetan students had higher blood pressure than Han students who migrated to the plateau. Additionally, lung function was better among Tibetans than in Han individuals. The mean and peak values of O$_3$ were 63.06 ± 18.33 μg/m^3 and 84.44 ± 18.00 μg/m^3, respectively, and the mean concentrations of PM$_1$, PM$_{2.5}$, and PM$_{10}$ were substantially lower: 1.14 ± 0.61 μg/m^3, 1.21 ± 0.56 μg/m^3 and 1.44 ± 0.53 μg/m^3, respectively.

Our study found that children exercising under these pollution-exposed high-altitude conditions had decreased lung function and blood pressure. FVC, FEV$_1$, PEF, and FEF$_{25-75}$ decreased by 4.99% (95% confidence interval [CI]: −12.20 to 2.22%), 4.70% (95% CI: −11.81% to 2.40%), 2.38% (95% CI: −11.55% to 6.78%), and 6.13% (95% CI: −15.90% to 3.65%) per 1 μg/m^3 increase in O$_3$ exposure, respectively, indicating that the adverse effect of O$_3$ on lung function exceeded the benefits from physical activity overall (Figure 1). O$_3$ exposure during physical activities decreased SBP, DBP, and MAP by 0.85% (95% CI: −5.05% to 3.36%), 3.67% (95% CI: −10.40% to 3.06%), and 2.19% (95% CI: −7.02% to 2.64%) per 1 μg/m^3 increased in O$_3$ concentration, respectively (Figure 2). These findings are consistent with previous studies. For instance, a strictly controlled
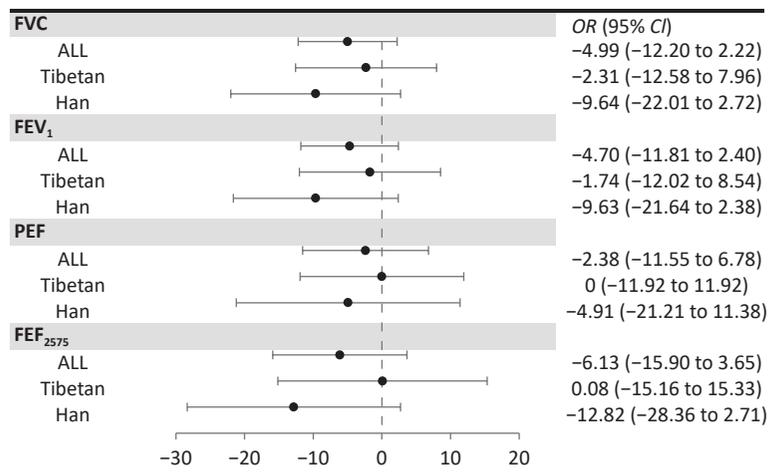

	OR (95% CI)
FVC	
ALL	−4.99 (−12.20 to 2.22)
Tibetan	−2.31 (−12.58 to 7.96)
Han	−9.64 (−22.01 to 2.72)
FEV$_1$	
ALL	−4.70 (−11.81 to 2.40)
Tibetan	−1.74 (−12.02 to 8.54)
Han	−9.63 (−21.64 to 2.38)
PEF	
ALL	−2.38 (−11.55 to 6.78)
Tibetan	0 (−11.92 to 11.92)
Han	−4.91 (−21.21 to 11.38)
FEF$_{2575}$	
ALL	−6.13 (−15.90 to 3.65)
Tibetan	0.08 (−15.16 to 15.33)
Han	−12.82 (−28.36 to 2.71)

Figure 1. Percent change in lung function change per 1 μg/m^3 increase in Ozone (O$_3$) concentration, stratified by Tibetan and Han groups. The model is adjusted for age, body mass index (BMI), sex, temperature, humidity, indoor O$_3$ concentration, other air pollutants, exercise habits, and household habits. Estimates and 95% confidence intervals (*CIs*) for percent change in lung function are shown. FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; PEF, peak expiratory flow; FEF$_{2575}$, forced expiratory flow between 25% and 75% of vital capacity.

laboratory study showed that after 3 h of exercise, FEV_1 and FVC were lower in the 70 ppb (P_{FEV1} = 0.116 and P_{FVC} = 0.115) and 120 ppb O_3 exposure groups (P_{FEV1} = 0.001 and P_{FVC} = 0.003, respectively) than in those without O_3 exposure (0 ppb)[1]. The mean O_3 concentration during the 30-min running period in this experiment (approximately 30 ppb) was much lower than in the above study, indicating that even low O_3 levels (below the WHO guidelines) can degrade lung function. A mechanistic study showed that O_3 exposure increased the permeability of epithelial cells, facilitating the entry of inhaled allergens and toxins and triggering the release of inflammatory cytokines (interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor [TNF]) [3,4]. Other studies also support our results regarding blood pressure. Pun et al.[5] reported that after a 30-min run along a polluted route with an O_3 concentration of 73.5 ppb, SBP and DBP decreased by 6.6 mmHg (95% CI: −13.2 to −0.06 mmHg) and 5.8 mmHg (95% CI: −11.0 to −0.70 mmHg), respectively.

Among local Tibetan students, lung function showed marginal changes after physical activity, with FEF_{2575} increasing slightly by 0.08% (95% CI: −15.16% to 15.33%), possibly due to the beneficial effects of physical activity offsetting the harmful effects of high O_3 levels. In contrast, Han group children experienced greater declines in lung function indicators, with FVC, FEV_1, PEF, and FEF_{25-75} decreasing by 9.64% (95% CI: −22.01% to 2.72%), 9.63% (95% CI: −21.64% to 2.38%), 4.91% (95% CI: −21.21% to 11.38%), and 12.82% (95% CI: −28.36% to 2.71%) per 1 μg/m³ increase in O_3 exposure, respectively, suggesting that the harmful effects of

O_3 exposure exceeded the benefits of physical activity.

Blood pressure showed similar results. O_3 exposure showed a positive effect on SBP among Tibetan students but a negative effect among Han students. DBP decreased by 1.74% (95% CI: −11.18% to 7.70%) for Tibetans and 2.73% (95% CI: −14.77% to 9.31%) for Han per 1 μg/m³ increase in O_3. Physical activity under high-O_3 conditions in the highlands also showed unfavorable effects on MAP for both Tibetans and Han, with greater effects observed in the Han Chinese students.

We also discussed the different outcomes for Tibetan girls, Han girls, Tibetan boys, and Han boys and found that for different sexes, there was a more pronounced effect among Han students compared to Tibetan students (Table 1).

Our study showed that exercise in a plateau environment had a greater effect on lung function and blood pressure in Han children than in Tibetan children. This may be due to differences in adaptation to plateau environments. The cardiorespiratory function of the Tibetan population is usually stronger because of their long-term residence in highland areas. They have larger chest circumference and total lung capacity, higher resting ventilation per minute, higher aerobic capacity, and a sensitive hypoxic ventilatory response[6], resulting in more efficient gas exchange in the low-oxygen environment of the plateau. This adaptation allows Tibetan students to exchange gases more efficiently in the low-oxygen environment of the plateau using a step-by-step load cycling test; they showed higher minute ventilation ($P < 0.05$), oxygen uptake ($P < 0.05$), stroke volume ($P < 0.05$), and cardiac output ($P
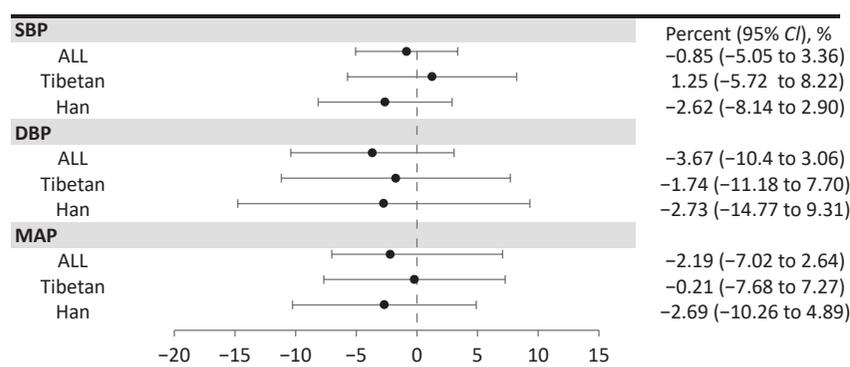

Figure 2. Percent change in blood pressure change per 1 μg/m³ increase in O_3 concentration, stratified by Tibetan and Han groups. The model is adjusted for age, BMI, sex, temperature, humidity, indoor O_3 concentration, other air pollutants, exercise habits, and household habits. Estimates and 95% confidence intervals (CIs) for percent change in blood pressure are shown. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Table 1. Lung function and blood pressure change (%) per 1 μg/m^3 O$_3$ increase and grouped according to sex and Tibetan-Han group

Group		β	95% CI	
			Lower	Upper
FVC				
Girls	Tibetans	4.68	−17.05	26.41
	Han Group*	−22.9	−32.21	−13.58
Boys	Tibetans	−4.55	−17.08	7.97
	Han Group	16.34	−1.79	34.47
FEV$_1$				
Girls	Tibetans	3.81	−17.58	25.20
	Han Group*	−22.05	−32.97	−11.14
Boys	Tibetans	−3.67	−16.98	9.64
	Han Group	15.46	−4.48	35.39
PEF				
Girls	Tibetans	−0.59	−21.75	20.57
	Han Group	−10.78	−50.07	28.50
Boys	Tibetans	2.92	−16.63	22.48
	Han Group	−10.4	−44.90	24.1
FEF$_{2575}$				
Girls	Tibetans	−5.51	−21.81	10.80
	Han Group	−12.49	−35.79	10.80
Boys	Tibetans	2.95	−26.74	32.63
	Han Group	−10.07	−42.34	22.20
SBP				
Girls	Tibetans	1.59	−11.05	14.24
	Han Group	−5.32	−15.45	4.80
Boys	Tibetans	2.15	−6.59	10.89
	Han Group	−4.87	−15.99	6.25
DBP				
Girls	Tibetans	−3.12	−23.77	17.53
	Han Group	−10.33	−50.08	29.43
Boys	Tibetans	0.66	−11.43	12.75
	Han Group	0.72	−22.01	23.44
MAP				
Girls	Tibetans	−0.69	−16.30	14.93
	Han Group	−7.83	−28.07	12.41
Boys	Tibetans	1.36	−7.90	10.63
	Han Group	−1.85	−18.88	15.18

Note. The model was adjusted for age, body mass index (BMI), temperature, humidity, indoor O$_3$ concentration, other air pollutants and exercise habits, household habits. Estimates and 95% confidence intervals (*CIs*) for percent change in blood pressure are shown. *$P < 0.05$. FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; PEF, peak expiratory flow; FEF$_{2575}$, forced expiratory flow between 25% and 75% of vital capacity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

< 0.01) at maximal effort[7]. In contrast, Han students may be more susceptible to poor cardiorespiratory fitness in the same plateau environment because they have not yet developed such adaptations. Due to their stronger cardiorespiratory function, Tibetans may be able to cope better with the physiological stress brought about by the low-oxygen environment of the plateau, thus keeping their blood pressure stable. In contrast, the Han students, due to their relatively weaker cardiorespiratory fitness, experience more pronounced blood pressure fluctuations when exercising in a plateau environment. DNA methylation is linked to lifelong high-altitude adaptation. For instance, Quechua populations in Peru exhibit plateau-adapted phenotypes associated with epigenetic modifications. Local genetic variations influence DNA methylation levels, with methylation-related single nucleotide polymorphisms offering a potential avenue for studying genetic adaptations to hypoxia[8]. Similarly, plateau-dwelling Tibetan populations may exhibit such phenotypes. According to the research from the Su Bing laboratory, a series of candidate genes related to Tibetan high-altitude adaptation have been identified, including EPAS1 and EGLN1, and further functional omics analysis has confirmed the involvement of these genes in the adaptation to hypoxic environments[9].

Although this study yielded certain findings, it also exhibited several limitations that are crucial for a comprehensive understanding and application of its conclusions. We did not find a significant correlation between air pollution and blood pressure or lung function parameters; however, the consistent trends observed in our results suggest potential physiological relevance and warrant further investigation. The specific mechanisms underlying these trends require further investigation to confirm their universality and reliability. Additionally, the small sample size (n = 60) may limit the generalizability of the findings; however, these preliminary results provide screening and guidance values for subsequent studies. Considering that the study was conducted in a highland area to compare Han and Tibetan children, this complex environmental and demographic context posed several challenges. However, in this study, we included as many participants as possible. Finally, as an experimental study, this research primarily focused on children with long-term exercise habits who were exposed to relatively high O_3 concentrations in the highlands, relying solely on self-controlled experiments to draw epidemiological conclusions. Therefore, the underlying mechanisms and scope of their application must be further explored and validated.

Our study shows that Han children have a greater decrease in lung function and blood pressure under O_3 exposure compared to Tibetan children. These results have important implications for public health strategies and policy development in plateau regions. Schools should develop personalized physical education programs for Tibetan and Han children. Medical institutions and public health departments should enhance health monitoring and early screening for children living in plateau regions, with early intervention and treatment for those with altitude sickness or cardiopulmonary abnormalities. Families and society should increase awareness of children's health issues in a plateau environment, with parents guiding their children to understand and protect themselves from adverse effects. Society should work together to create healthier and safer living environments for children in plateau regions. Further research on the mechanisms and factors influencing children's health in plateau environments, as well as the health effects of O_3 pollution, is needed to provide a scientific basis for more effective health policies and public health interventions.

Competing Interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics The Ethics Review Committee of the University of Science and Technology Beijing approved the study (Reference No.: 2021-1-103). All participants have signed the informed consent.

Authors' Contributions Investigation, Data Curation, Formal analysis, Writing - original draft, Visualization: Mengyao Bian; Conceptualization, Supervision, Project administration, Funding acquisition: Xiaoli Duan; Writing review & editing: Ling Qi, Xiaoli Duan; Methodology: Mengyao Bian, Ling Qi, Qian Guo, Yuchen Zhao, Xiaoli Duan.

Data Sharing No additional data available.

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