Different cardiorespiratory effects of indoor air pollution intervention with ionization air purifier: Findings from a randomized, double-blind crossover study among school children in Beijing

Different cardiorespiratory effects of indoor air pollution intervention with ionization air purifier: findings from a randomized, double-blind crossover study among school children in Beijing

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Declarations of interest

None.

Abstract

Indoor air pollution is associated with numerous adverse health outcomes. Air purifiers are widely used to reduce indoor air pollutants. Ionization air purifiers are becoming increasingly popular for their low power consumption and noise, yet its health effects remain unclear. This randomized, double-blind crossover study is conducted to explore the cardiorespiratory effects of ionization air purification among 44 children in Beijing. Real or sham purification was performed in classrooms for 5 weekdays. Size-fractionated particulate matter (PM), black carbon (BC), ozone (O_3), and negative air ions (NAI) were monitored, and cardiorespiratory functions were measured. Mixed-effect models were used to establish associations between exposures and health parameters. Real purification significantly decreased PM and BC, e.g. $PM_{0.5}$, $PM_{2.5}$, PM_{10} and BC were dereased by 48%, 44%, 34% and 50% respectively. O_3 levels were unchanged, while NAI was increased from 12 to 12,997 cm^{-3}. Real purification was associated with a 4.4% increase in forced exhaled volume in 1 second (FEV_1) and a 14.7% decrease in exhaled nitrogen oxide (FeNO). However, heart rate variability (HRV) was altered negatively. Interaction effects of NAI and PM were observed only on HRV, and alterations in HRV were greater with high NAI. Ionization air purifier could bring substantial respiratory benefits, however, the potential negative effects on HRV need further investigation.

Keywords: ionization air purifier; size-fractionated PM; children; lung function; cardiac autonomic function.

Capsule: This study suggested that ionization air purification could bring substantial respiratory benefits while potential negative effects on cardiac autonomic function.

1.Introduction

Numerous studies have reported associations between air pollution and adverse health outcomes among different populations. On average, people spend >80% of their time within indoor environments(Almeida-Silva et al., 2014; Klepeis et al., 2001; Zhao et al., 2018), and it has been indicated that indoor air pollution could pose an equal, or even higher, risk to morbidity and mortality compared to ambient air pollution(Karottki et al., 2014; Karottki et al., 2015). Indeed, World Health Organization (WHO) reported that 4.2 million and 3 million premature deaths were attributable to household and ambient air pollution, respectively, in 2012(WHO, 2014, 2016). At present, indoor PM is still a severe environmental problem in both developed and developing countries. For instance, in China, some researchers reported that the average fine particulate matter ($PM_{2.5}$) concentration reached about 60 $\mu g/m^3$ within residences in urban Beijing(Pan et al., 2018), largely higher than the WHO Interim Target 1 (35 $\mu g/m^3$) for outdoor pollution. Furthermore, it was observed that adverse health effects are associated with indoor PM exposure in countries with relatively low pollution levels (<20 $\mu g/m^3$)(Allen et al., 2011; Karottki et al., 2013).

Air purifiers have been widely used as an effective measure to reduce indoor particulate matter (PM) pollution. Previous studies have investigated different kinds of air purifiers and their health effects. The mechanic filters, such as high-efficiency air particulate (HEPA) filtration purifiers, could lower indoor pollution and have

cardiorespiratory benefits in human subjects(Huichu Li et al., 2017; Luo et al., 2018; Liu et al., 2018; Butz et al., 2011; Kajbafzadeh et al., 2015) while other studies demonstrated that HEPA air purifiers could not significantly improve cardiorespiratory function in adults(Cui et al., 2018; Day et al., 2017a). Also, some researchers paid attention to other types of purifiers, such as electrostatic precipitator purifiers (ESP)(Day et al., 2017a; Skulberg et al., 2005). Association between the use of ESP and improved lung function was found among office workers(Skulberg et al., 2005). However, another study showed that the operation of ESP could generate incidental ozone (O_3)(Day et al., 2017b), which is recognized as a potential health hazard to people(Day et al., 2017b; Hongyu Li et al., 2017). It is reported that ESP could even increase some cardiovascular risks (Day et al., 2017a). Besides, associations between the use of electret air filters and improved cardiorespiratory function were found among adults (Chen R et al., 2015; Chuang et al., 2017). While to the best of our knowledge, the ionization air purifier and its health effects have not been widely explored.

Currently, due to the low power consumption and noise, ionization air purifiers are manufactured for use in buildings such as homes and industrial environments in different countries(Berry et al., 2007; Grinshpun et al., 2005; Shiue and Hu, 2011). Nowadays more and more primary and middle schools have installed ionization air purifier for indoor intervention in Beijing, China. Although given evidences have shown high purification efficiencies of ionization air purifiers on air pollutants

(Grabarczyk, 2001; Krueger and Reed, 1976), it remains unknown related to its cardiorespiratory effects. Moreover, some studies showed that some ionization air purifiers could generate O_3 in a similar manner to ESP(Niu et al., 2001). This also presents an initial route of concern that ionization air purifiers may have unforeseen effects on health.

Children are considered as a potentially susceptible population to air pollution since their organ systems are developing rapidly(Dietert et al., 2000; Hoek et al., 2012; Morgenstern et al., 2008; Weinmayr et al., 2010). Previous evidences have showed that exposure to PM was associated with adverse cardiorespiratory effects among children(Hoek et al., 2012; Calderón-Garcidueñas et al., 2007). School children spend most of their daytime in classrooms, where indoor PM could be an underlying health risk factor. Air purifiers have been installed in schools to protect children from air pollution in cities such as Beijing(Mo, 2017), thus it is necessary to explore the potential effects of purifiers that have been put into use. Therefore, we conducted a randomized, double-blind crossover study using a commercially available ionization air purifier among a group of school children to: 1) examine the purification efficiency of the purifier in reducing size-fractionated PM and black carbon (BC); 2) evaluate O_3 and negative air ions (NAI) emissions from purifiers; 3) explore the cardiorespiratory effects of ionization air purification; 4) establish associations between size-fractionated PM, BC, NAI and health parameters. The findings will provide evidence-based guidance on the application of ionization air

purifiers and could bring new insight in protecting children health from indoor air pollution.

2.Methods and Materials

2.1.Study design and participants

A randomized, double-blind crossover study was conducted from December, 2017 to March 2018 in a middle school in Daxing District, a suburban area with relatively high air pollution, in the south of Beijing, China. The school was basically constructed in cement structure. The surfaces of walls and floors had been slightly damaged, which could generate cement dust, one of the important sources for PM(Tian et al., 2015). We calculated the sample size based on the formula $N = \frac{(z_\alpha+z_\beta)^2\sigma^2}{d^2}$. Specifically, α =0.05, β =0.10, d = 0.037 L and σ = 0.083 L, the latter two parameters were based on the lung function parameter, forced exhaled volume in 1 second (FEV_1) from a previous study (Gao et al., 2013). The sample size we calculated was 40. Taking into account the 20% rate of loss to follow-up, the final sample size was determined to be 48. As there are only 6 classes of grade one in this junior high school, we randomly recruited 8 children per classroom for a total of 48 participants with the following certain criteria:1) aging from 11 to 14; 2) living in Beijing for more than two consecutive years; 3) not suffering any health conditions; 4) having no asthma and thoracic surgery history; 5) living in school dormitories from Monday to Friday.

Before the study, six ionization air purifiers were installed about 1.2 meters below the ceilings, in an identical position in each classroom. As the ceilings were 4.5 meters high in every classroom, the purifiers were 3.3 meters from the floor vertically. Two different treatments were employed, "real" (machine turned on) and "sham" (machine turned off) purification, in a random order with a 2-month washout period. We considered that exams and other school events might influence the health outcomes of the participants (e.g. heart rate), so those time periods were avoided. Besides, after winter holiday, it was after two weeks that we began the second period of the study in order that the participants got used to the school environment. The treatments were randomized by classrooms as is shown in the flow chart (**Figure 1**), and **Table S1** in supplemental material presents the details for each classroom including the date of treatment and the number of participants. Since the operation of the purifiers was silent and the indication lights were removed, both the participants and field investigators could not distinguish the operation statuses. Each treatment lasted five weekdays (Monday to Friday) starting at 7:00 and ending at 17:00 according to the school schedule. The study was conducted in the winter heating season in Beijing, thus all windows and doors were kept closed except two small ventilation openings with an area of 0.09 m^2. The participants were instructed to stay within the classrooms as much as possible. A self-administered activity questionnaire was given to each participant during the treatments. They were told to record the time and place when they went outside, such as lunch break and toilet visit.

Before the study began, the study protocol was approved by the Review Board of Peking University Health Science Center, which conforms to Declaration of Helsinki. Before inclusion, written informed consents were provided by all participants and their guardians, who could withdraw from the study at any time.

2.2.Exposure Measurements

All exposure measurement devices were installed at the height of breathing zone (about 1.2 m high from the floor) at the same position of each classroom. Measurements started at 7:00 am and ended at 17:00 pm from Monday to Friday. Exposure measurements included size-fractionated PM, BC, O_3, NAI, carbon dioxide (CO_2), noise, temperature and relative humidity (RH). Machines used for measurements were as follows: size-fractionated PM (Model Handheld PC3016; GrayWolf Inc., USA), BC (microAeth Model AE51; Magee Scientific, Berkeley, CA, USA), O_3 (Aeroqual Series 500; Aeroqual, New Zealand), CO_2 (Model HCZY-1; Tianjianhuayi Inc., Beijing, CHINA), noise (Model ASV5910; Hangzhouaihua Inc., Hangzhou, CHINA), NAI (COM-3200 Pro II; Com System.Inc, Japan), real-time temperature and RH (Model WSZY-1B; Tianjianhuayi Inc., Beijing, CHINA). All exposure measurements were recorded as 5-min segments in line with heart rate variability (HRV) indices, and calculated as 1-h averages for ST-segment elevation and 8-h (08:00-16:00) averages for the other health measurements.

2.3.Health measurements

Health parameters were measured by trained investigators on Monday, Wednesday and Friday of each treatment period. Pulmonary tests, blood pressure (BP) tests and exhaled breath condensate (EBC) collections were conducted at 7:00-9:00 am and 15:00-17:00 pm. Ambulatory electrocardiogram (ECG) monitoring, including HRV, heart rate (HR) and ST-segment elevation, began at 8:00 am, and ended at 15:00-16:00 pm. To avoid possible variation arising between different investigators, the same investigator ran the same tests throughout the study wherever possible.

2.3.1. Pulmonary tests

FeNO was measured by the NIOX VERO® machine (Aerocrine AB, Solna, Sweden) following standardized procedures(Peltier, 2005). Participants were asked to refrain from exercise, food and beverage 1 hour before. After the FeNO tests, a portable PEF meter (Model 2110; Vitalograph Ltd., UK) was used to measured FEV_1 and peak expiratory flow (PEF) simultaneously following American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations(Miller et al., 2005). For FEV_1 and PEF, each measurement included two blows, and two to five measurements were conducted in each participant for each time. Once relative difference of two measurements was less than 10%, the better result of two blows was recorded for final analysis.

2.3.2. Blood pressure tests

Following at least 10 minutes of rest, upper arm blood pressure was measured using an automated oscillometric monitor (HEM-7052; Omron Healthcare Co. Ltd., Japan) at three times with a minimum 3-minute interval. We calculated the averages of the blood pressure values (from the second to the last measurement) within a 5-mmHg range of difference and recorded them as the final outcomes.

2.3.3. Ambulatory electrocardiogram (ECG) monitoring

ECG monitoring were conducted using a 12-channel Holter monitor (model MGY-H12; DM Software Inc., USA), which was positioned on the participants using a standard protocol. The participants were instructed not to take any designated food or drink (e.g. coffee, wine, tea) that may affect HRV and avoid high intensity exercise on the day of, and the day before, the health measurements. Participants were instructed to wear the Holter monitors for 7-8 hours, during which they were told to stay indoor as much as possible and record their activities in the formatted diaries. Further details and data processing procedure have been documented in our previous work(Pan et al., 2018).

2.3.4. Sample collection and biomarker assay

EBC was collected using a designated device (Dingblue Tech., Ltd, China) that have been used in a previous study(Zheng et al., 2017), and according to ATS/ERS recommendation(Horváth et al., 2005). All samples were immediately stored at -80℃. Malondialdehyde (MDA) were measured as an indicator of oxidative stress in EBC.

The method of high-performance liquid chromatography (HPLC) with fluorescence detection was used according to previous study(Lärstad et al., 2002).

2.4. Statistics Analysis

We used paired t-tests to compare exposure levels (8-h averages) and health measurements between two periods. Mixed-effect models were conducted to examine the effects of real purification and different exposures on the health parameters, and explore the possible interaction effects between different exposures and between gender and indoor air pollutants. Health measurements were log_{10}-transformed to improve the normality and stabilize the variance due to skewed distribution, except ST-segments elevation, among which there were zero values. We controlled for personal characteristics, including age, gender and BMI, classroom and long-term time trend, including day-of-measurement and squared day-of-measurement, as fixed-effect terms. Day-of-measurement means the count of the day that the measurement was conducted over the whole study course. In addition, other potential confounders were included as fixed-effect terms such as hour of day, day of week, noise, temperature, RH and CO_2.[9]

To investigate the effect of purification and exposures, mixed-effect models were fit, in which real purification was coded as “1” and sham purification as “0”:

$$Y_{it}=b_0+u_i+b_1x_1+\ldots+b_px_p+\beta\ (\text{treatment or exposure})+\varepsilon_{it}$$

where Y_{it} is the logarithm of health measurement in subject i at time t, b_0 is the overall intercept, u_i is the specific random intercept for the subject i, x_1-x_p are covariates, b_1-

b_p are regression coefficients for x_1-x_p, β is the regression coefficient for treatment or exposure, and ε_{it} is the error for subject *i* at time *t*.

We estimated percent change with 95% confidence intervals (CI) in $\log_{10}$-transformed health measurements, and value changes of ST-segment elevation per interquartile range (IQR) increase in moving average of each exposure measurements with 95% confidence intervals. Percent changes were calculated as $[10^{(\beta\times IQR)}-1]\times100\%$, with 95% CI $\{10^{[IQR\times(\beta\pm1.96\times SE)]}-1\}\times100\%$, where β and SE were the estimated regression coefficients and its standard error, respectively(Wu et al., 2010). All data were analyzed using the "nlme (version 3.1-128)" package for R software (version 3.3.2; R project for Statistical Computing).

3. Results

3.1. Participants characteristics

Forty-four participants completed the whole study (see **Table 1**). There were 24 (55%) boys and 20 (45%) girls, and the ages ranged from 11 to 14 years old, with an average of 12.4 (±0.8). The average of body mass index (BMI) was 18.7±3.3 among the participants. The variance homogeneity test showed that there was no significant difference among the participant groups from different classes. According to the self-reported activity diaries, all participants spent more than 80% of their time in classroom during the exposure monitoring period (data not shown).

3.2. Exposure measurements statistics

Table 2 presents the comparisons of indoor exposure measurements. Size-fractionated PM and BC were significantly lower during real purification ($P<0.05$). The purification efficiency for BC was the highest with a reduction rate of 50%. For size-fractionated PM, higher purification efficiency was shown in smaller PM ($PM_{0.5}$ VS $PM_{2.5}$ VS PM_{10}: 48% VS 44% VS 34%). NAI was markedly higher during real purification (12997 cm^{-3} VS 12 cm^{-3}, $P<0.001$). No significant difference was observed in O_3, RH, temperature and noise between two scenarios.

3.3. Health measurements statistics

Table 2 also gives the comparison for health measurements among the participants between two periods. FEV_1 and PEF were higher during real purification, however, only the difference in FEV_1 was statistically significant (2.34 L VS 2.19 L, $P<0.01$). FeNO was found significantly lower during real purification (15 ppb VS 17 ppb, $P<0.01$). MDA in EBC tended to be lower after real purification compared to sham purification (0.20 μmol/L VS 0.24 μmol/L, $P=0.06$). Blood pressure indices showed no significant differences between the two periods. Interestingly, we observed marked significant differences in HRV indices. Power in high frequency (HF), power in low frequency (LF), and standard deviation of all NN intervals (SDNN) were significantly lower during real purification, while heart rate (HR) and LF to HF ratio (LF/HF) were significantly higher. II_ST, V2_ST and V5_ST are three representative leads in ST-segment analysis as an indicator for ischemic burden(Langrish et al., 2012). Slight decreases in ST-segment elevation were observed in the three leads,

among which that in V5_ST showed statistical significance (P<0.01). Additional testing confirmed that the Holter monitors were not directly disturbed by the operation of ionization air purifiers (see Supplementary Material, Supplemental Test and **Table S2**).

In addition, we compared the health measurement of Monday morning (before treatment) and Friday afternoon (after treatment) between real and sham purification periods (**Table 3**). The results are in lines with the averages of three days shown in **Table 2**, which supports that the health changes were attributed to the indoor air purification rather than the different time periods.

3.4. Estimated effect of air purification

To explore estimate effects of purification on the health measurements, we conducted mixed-effect models after adjusting potential confounders (see **Figure 2**). As **Figure 2** shows real purification was associated with 4.4% increase in FEV_1 and 14.7% decrease in FeNO compared to sham purification among all the participants. Blood pressure results did not show significant differences. Significant alterations were observed among all HRV indices. HF, LF and SDNN were decreased by 18.8%, 13.4% and 5.4%, respectively, and HR and LF/HF was increased by 3.1% and 14.2%, respectively. Elevations in II_ST and V5_ST were decreased by 0.008mV and 0.019mV, respectively.

3.5. Estimated effect of PM and BC

As the ionization air purification could significantly reduce the indoor levels of PM and BC, we analyzed the estimated effects of those pollutants on health parameters using mixed-effect models.

Figure 3A shows the estimated percent changes in respiratory measurements per IQR increases in size-fractionated PM and BC. The greatest decrease of FEV_1 was 6.5% per IQR increase in $PM_{0.5}$ (17.9 $\mu g/m^3$), and the greatest increase of FeNO was 23.5% per IQR increase in $PM_{1.0}$ (22.2 $\mu g/m^3$). BC was associated with 7.0% decrease in FEV_1 and 22.1% increase in FeNO per IQR increase in BC (3.6 $\mu g/m^3$). Increases in MDA in EBC were associated with levels of PM and BC, but these effects were not statistically significant.

Figure 3B shows percent changes in HRV indices per IQR increases in size-fractionated PM and BC over different moving averages. The greatest decrease in HF was 16.1% per IQR increase in $PM_{0.5}$ (17.9 $\mu g/m^3$) at 5-min moving average. The smaller PM was, the stronger the effect observed. The greatest decreases were observed at 5-min moving averages for $PM_{0.5}$ and $PM_{1.0}$, but 2-h moving averages for $PM_{2.5}$, PM_5 and PM_{10}. For BC, greatest decrease in HF was 18.8% per IQR increase (3.6 $\mu g/m^3$) at 3-h moving average. The association patterns of other indices were similar to HF (see **Figure 3B** and Supplementary Material, **Figure S1**). **Figure 3C** shows estimated changes in ST-segment elevation per IQR increase in size-fractionated PM and BC. We observed significant increases in V5_ST elevation

associated with $PM_{0.5}$ and $PM_{1.0}$. The greatest increase in V5_ST elevation was 0.022 mV per IQR increase in $PM_{1.0}$ (22.2 μg/m^3).

3.6. The interaction of NAI with PM and BC

Significance was observed in the interaction effects of NAI with PM and BC on HRV but not on pulmonary function. Therefore, we analyzed the effect on HRV in real and sham purification separately (see **Figure 4**). In general, the effects of $PM_{2.5}$, $PM_{5.0}$ and PM_{10} were close at different moving averages between two periods. However, the effects of $PM_{0.5}$, $PM_{1.0}$ and BC appeared greater during real purification. A reduction of 35.1% in HF was observed per IQR increase in $PM_{1.0}$ (22.2 μg/m^3) at 5-min moving average during real purification, but only 25.2% during sham purification. The results were similar for LF and SDNN during the two periods (see Supplementary Material **Figure S3**). Besides, no significant interaction effects of gender and indoor air pollutants was found on cardiorespiratory function (**Table S3**).

4. Discussion

To date, this is the first study to investigate the health effects of ionization air purification on cardiorespiratory parameters among children. The purifier used in this study had a high efficiency for reducing size-fractionated PM and BC. Consequently, we found improved lung function, reduced airway inflammation, less oxidative stress and a lowered potential myocardial ischemia risk after purification. However, potentially negative changes were observed in HRV indices. Further analysis showed that increases in PM and BC were associated with decrements in all health

parameters, indicating that reduction of the pollution might bring improvements in all measured cardiorespiratory parameters. However, heterogeneity was observed related to the effect of NAI. Our findings suggested exposure to high NAI might have adverse effect on cardiac autonomic function while other parameters were positively affected. To conclude, adverse respiratory effects of PM and BC were substantially ameliorated by using ionization air purification, however, the benefits in cardiac autonomic function of the reduction in particulate pollution appeared to be lost due to the high levels of NAI emitted by air purifiers.

Previous studies have examined the efficiencies of ionization purifiers, but not to the depth of the current study that examined reduction efficiency on size-fractionated PM and BC. Higher purification efficiencies were found for BC and smaller PM (i.e. $PM_{0.5}$, $PM_{1.0}$ and $PM_{2.5}$) compared to $PM_{2.5-10}$. The reduction rate for BC and $PM_{0.5}$ were about 50% while that was about 30% for PM_{10}. Previous studies have demonstrated health benefits from lowering indoor pollution with filtration air purifiers among different populations(Brown et al., 2014; Huichu Li et al., 2017). In our study, different cardiorespiratory effects were found among the children after ionization air purification. Compared to filtration air purifiers, the essential feature of ionization air purifier is to emit NAI, which could enhance the gravitational settlement of airborne particles(Grinshpun et al., 2005). Therefore, we conducted further analysis to explore the associations between PM, BC and NAI with different health parameters.

As is implied in **Figure 3**, decreases in size-fractionated PM and BC were associated with improvements of those health outcomes. Several previous studies investigating the potential respiratory improvements brought by indoor air purification found similar results with our present study (Skulberg et al., 2005; Weichenthal et al., 2013), whereas others did not. It is reported that no significant changes of lung function were found with 50% purification efficiency of $PM_{2.5}$ from 8μg/m^3 to 4μg/m^3 among the elderly (Karottki et al., 2013). Another study conducted among young, healthy adults demonstrated that the beneficial impacts on lung function were not statistically significant with 57% reduction in $PM_{2.5}$ concentration from 96.2 to 41.3 μg/m^3 (Chen R et al., 2015). Compared with adults, children are believed to be especially susceptible to the adverse effects of air pollution (Dietert et al., 2000; Hoek et al., 2012; Morgenstern et al., 2008; Weinmayr et al., 2010), thus our study may find some potential respiratory benefits in such vulnerable population. Furthermore, our present study explored the improvements of lung function with decreases in size-fractioned PM, not just $PM_{2.5}$ and found higher purification efficiencies for smaller PM compared to $PM_{2.5}$. Some studies indicated that smaller particles have larger surface areas for a given mass, might contain more toxic substances and elicit greater health effects on people (Chen W et al., 2015; Lin et al., 2016), which suggested the decreases in smaller PM may have greater improvements of lung function. Although the purification efficiency of $PM_{2.5}$ in this study was less than those mentioned above (Karottki et al., 2013; Chen R et al., 2015), we found

greater purification efficiencies of smaller PM than $PM_{2.5}$ while those studies did not explore other sizes of PM other than $PM_{2.5}$. In previous studies, inflammation and oxidative stress have been considered plausibly as the main mechanism through which air pollution affects human health(Gehring et al., 2013). Besides potential benefits of reduced PM, NAI might also contribute to the decreases in airway inflammation and oxidative stress, which might be due to the ability of NAI in inhibiting growth of airborne microorganism(Krueger and Reed, 1976). Nevertheless, the underlying mechanism still remains unidentified. Therefore, it should be further explored considering the respiratory health effect of short-term air purification, whether ionization purifier or other types, especially for children, a susceptible population to particulate air pollution.

In addition, we observed higher ST-segment elevation associated with increases in PM, which is similar to previous findings(Hanna and Glancy, 2015). However, the association between ST-segment elevation and NAI was not found. Our results could be an indication that reduction in PM pollution through air purification might lead to lower ischemic risks among children. However, the results were different for cardiac autonomic function. It was observed that increases in PM and BC were associated with decreases in HF, LF and SDNN, similar to previous findings among young adults and the elderly(Chen et al., 2007; Dong et al., 2018; Pan et al., 2018). Yet the potential benefits from reduced particulate pollution might be overcast by increased NAI. The possible biological and psychological effects of NAI have been previously

discussed(Iwama, 2004; Nakane et al., 2002; Nimmerichter et al., 2014; Ryushi et al., 1998; Sirota et al., 2008). For instance, exposure to NAI might improve erythrocyte deformability and aerobic metabolism(Iwama, 2004). However, the potential impact of NAI on cardiac autonomic function has not been investigated among humans. As our experimental test excluded the possibility that Holter monitoring was disturbed by NAI, the results could indicate that NAI might exert negative impact on cardiac autonomic function, which could result from unknown charge-related response occurred in human body(Krueger and Reed, 1976).

Attention has been paid to the interaction effects of PM and other environmental factors, such as temperature and noise(Huang et al., 2013; S. Wu et al., 2015). Therefore, we hypothesized that NAI could interact with PM and BC and subsequently pose health impacts on people. The results exhibited significant interaction effects of NAI with PM and BC on HRV but not on pulmonary functions, no significant interaction effects of gender and indoor air pollutants on cardiorespiratory function were observed. Then we analyzed the alterations of HRV associated with PM and BC in sham and real purification, respectively. Greater changes were found in HF, LF and SDNN with IQR increase in PM and BC during real purification period with high NAI. Forest environment was considered high in NAI(Ling et al., 2010; Tammet et al., 2006). A field experiment claimed increased HF and SDNN among women after exposure to forest environment(Lanki et al., 2017). However, our findings implied potential negative effect of NAI on cardiac

autonomic function. The difference might be because that the forest environment was more natural and complicated, thus the health benefits were resulted from multiple factors. In addition, the concentration of NAI was much higher than that in forest environment in this study. Therefore, it could provide implications for future development of ionization air purifiers. On the one hand, ionization air purifiers might not be used in high PM indoor environment like the classrooms in this study. On the other hand, the emission of NAI should be controlled not only for purification efficiency but also for avoiding potential negative health effect.

We note three main strengths in this study. Firstly, it is the first study to investigate the health effects of using ionization air purifiers. To note, we found disparate effects between respiratory functions and cardiac autonomic function, which could be an important indication for the application of those purifiers in the future. Secondly, we chose children, one of the most susceptible population to air pollution, as participants to explore the health effects of ionization purification. Thirdly, this study compared the purification efficiencies on indoor PM of different sizes and BC for the first time.

Nonetheless, this study also has certain limitations listed as follows. Firstly, air purification and environmental measurement could not be measured during the night time. However, the primary aim of this study was to explore the short-term effect of purification, and the repeated measurements could address the potential long-lasting action of the intervention, albeit in the presence of other periods of pollution

exposure. Secondly, we did not measure gaseous pollutants other than ozone. However, in the inhabited environments such as school, gaseous pollutants are known to be very low and would not alter the substantial results(Chen et al., 2017). Thirdly, due to the poor operability of sampling blood from children, we did not collect blood samples yet other studies did (Huichu Li et al., 2017), so we may not obtain more biomarkers to some extent.

5. Conclusion

This study demonstrates that ionization air purification can reduce indoor PM with high purification efficiency in school classrooms. To date, our study is firstly to investigate the health effects of ionization air purification. We observed that ionization air purification could elicit significant benefits to respiratory system, however, these benefits were seemingly off-set by apparently negative effects on cardiac autonomic function. The negative effects on HRV may be attributed to the very high levels of NAI from these purifiers and further studies are urgently needed to confirm if NAI is the underlying mechanism, and whether it could also have other unrecognized effects on the body. These results are important for the use of this type of air purifier, and due consideration is needed for the balance of potentially beneficial versus negative effects of this technology, and its future development.

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Table 1 Demographic characteristics for the study participants

Characteristics	
Number	44
Male (%)	24（55）
Female (%)	20（45）
Age, years	
Mean ±SD	12.4 ±0.8
Median	12
Range	11-14
BMI, kg/m^2	
Mean ±SD	18.7 ±3.3
Median	18.1
Range	14.2-33.5

Abbreviation: SD, standard deviation; BMI, body mass index.

Table 2 Comparison of indoor exposure measurements and health measurements between sham purification and real purification

Variables	N[a]	Sham-purification (Mean ± SD)	Real-purification (Mean ± SD)	P value
Exposure measurements				
$PM_{0.5}$, μg/m^3	3097	18.8 ± 13.9	9.8 ± 8.9	<0.05*
$PM_{1.0}$, μg/m^3	3097	36.4 ± 21.1	19.2 ± 10.2	<0.05*
$PM_{2.5}$, μg/m^3	3097	72.5 ± 30.3	40.8 ± 13.3	<0.05*
$PM_{5.0}$, μg/m^3	3097	375.2 ± 180.3	242.8 ± 160.2	<0.01**
PM_{10}, μg/m^3	3097	923.6 ± 360.8	608.9 ± 280.6	<0.01**
BC, μg/m^3	3097	4.4 ± 2.1	2.2 ± 1.3	<0.01***
O_3, μg/m^3	3097	21 ± 6	19 ± 5	0.28
NAI, cm^{-3}	3097	12 ± 10	12997 ± 3814	<0.001***
RH, %	3127	53.3 ± 8.5	54.4 ± 8.2	0.70
Temperature, ℃	3127	16.7 ± 4.4	15.2 ± 4.3	0.36
Noise, dB	3127	69.3 ± 2.6	70.1 ± 2.5	0.23
CO_2, μg/m^3	3127	2410 ± 1027	2865 ± 1044	0.29
Health measurements				
FEV_1, L	257	2.19 ± 0.50	2.34 ± 0.45	<0.01**
PEF, L/min	257	343 ± 80	346 ± 85	0.41
FeNO, ppb	257	17 ±7	15 ± 8	<0.01**
MDA, μmol/L	257	0.24 ± 0.15	0.20 ± 0.14	0.06
SBP, mmHg	257	106 ± 7	105 ± 8	0.76
DBP, mmHg	257	64 ± 6	64 ± 6	0.96
PP, mmHg	257	40 ± 5	41 ± 6	0.86
HF, ms^2	9100	381.4 ± 346.9	349.6 ± 338.7	<0.001***
LF, ms^2	9100	982.8 ± 656.9	950.8 ± 619.3	<0.001***
SDNN, ms	9100	65 ± 23	64 ± 22	<0.001***
LF/HF	9100	4.0 ± 3.3	4.3 ± 3.2	<0.001***
HR, min^{-1}	9100	91 ± 13	92 ± 12	<0.001***
II_ST, mV	825	0.13 ± 0.10	0.12 ± 0.11	0.49
V2_ST, mV	825	0.28 ± 0.16	0.27 ± 0.15	0.57
V5_ST, mV	825	0.10 ± 0.11	0.09 ± 0.10	<0.01**

Abbreviation: SD, standard deviation, PM, particulate matter; BC, black carbon; O_3, ozone; NAI, negative air ion; RH, relative humidity; CO2, carbon dioxide; FEV_1, forced expiratory volume in the first second; PEF, peak expiratory flow; FeNO, fractional exhaled nitrogen oxide; MDA, Malondialdehyde; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HF, power in high frequency; LF, power in low frequency; SDNN, standard deviation of all NN intervals; LF/HF, LF to HF ratio; HR, heart rate.

[a]Observation after excluding all missing values and abnormities.

Table 3 Comparisons of health measurements on Monday mornings and Friday afternoons between sham and real purification

Variables	N[a]	Sham-purification (Mean ± SD)	Real-purification (Mean ± SD)	Difference	P value
FEV_1, L					
Monday morning	42	2.23 ± 0.51	2.25 ± 0.44	0.02	0.48
Friday afternoon	40	2.22 ± 0.52	2.38 ± 0.48	0.16	<0.05*
PEF, L/min					
Monday morning	42	317 ± 73	321 ± 76	4	0.68
Friday afternoon	40	353 ± 89	356 ± 95	3	0.53
FeNO, ppb					
Monday morning	42	19 ± 10	18 ± 11	-1	0.71
Friday afternoon	40	18 ± 8	14 ± 7	-4	<0.01**
SBP, mmHg					
Monday morning	42	108 ± 10	107 ± 9	-1	0.30
Friday afternoon	40	106 ± 7	105 ± 7	-1	0.12
DBP, mmHg					
Monday morning	42	68 ± 8	66 ± 7	-2	0.25
Friday afternoon	40	65 ± 6	63 ± 6	-2	<0.05*
PP, mmHg					
Monday morning	42	41 ± 7	41 ± 5	1	0.82
Friday afternoon	40	41 ± 6	41 ± 5	1	0.59

Abbreviation: SD, standard deviation; FEV_1, forced expiratory volume in the first second; PEF, peak expiratory flow; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

[a]Observation after excluding all missing values and abnormities.

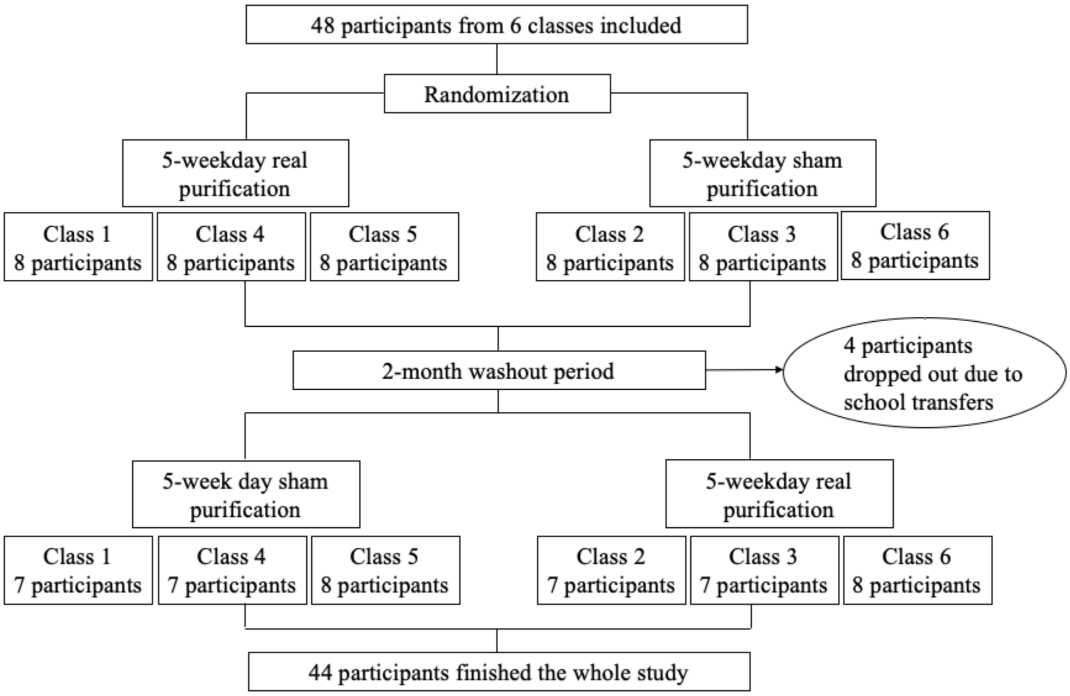


Figure 1 Flow chart of the study.

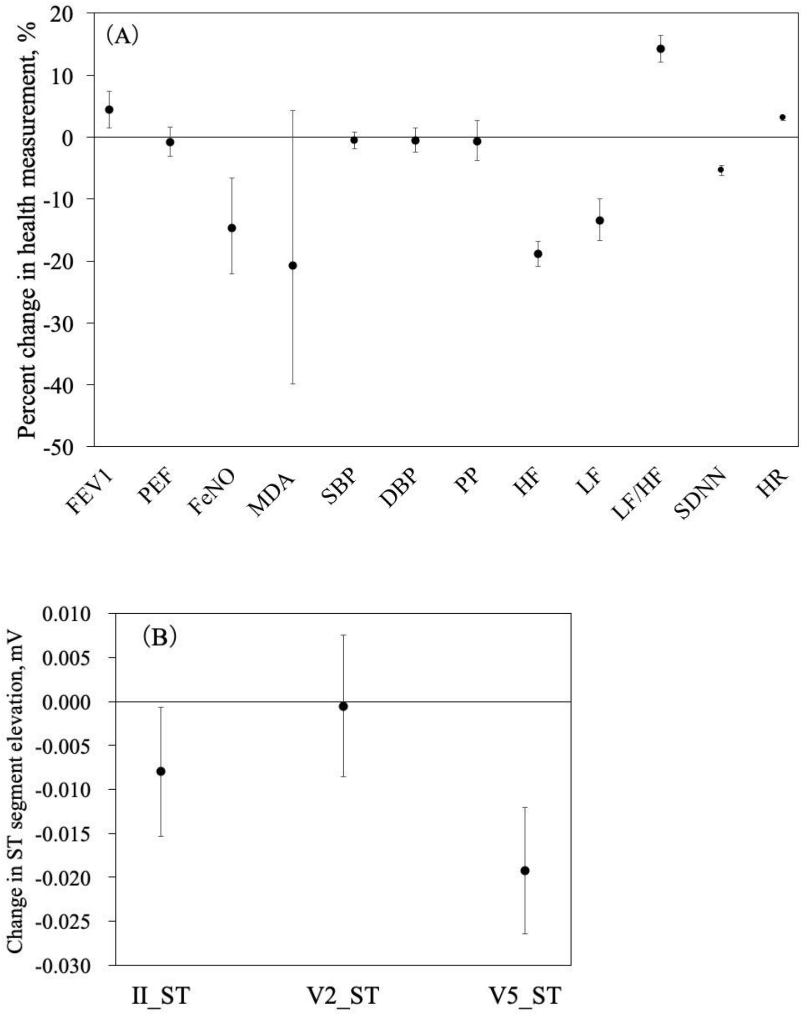
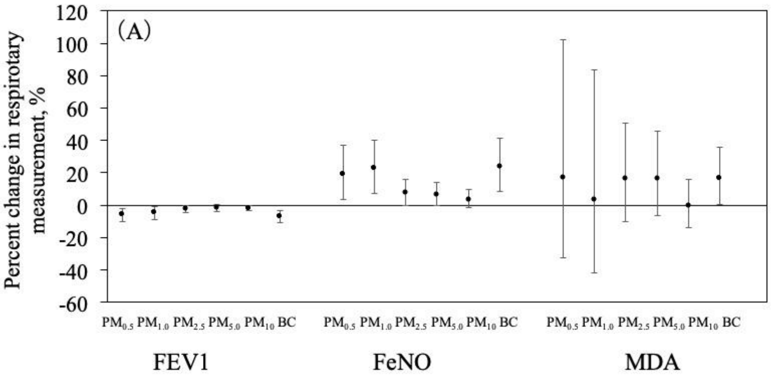


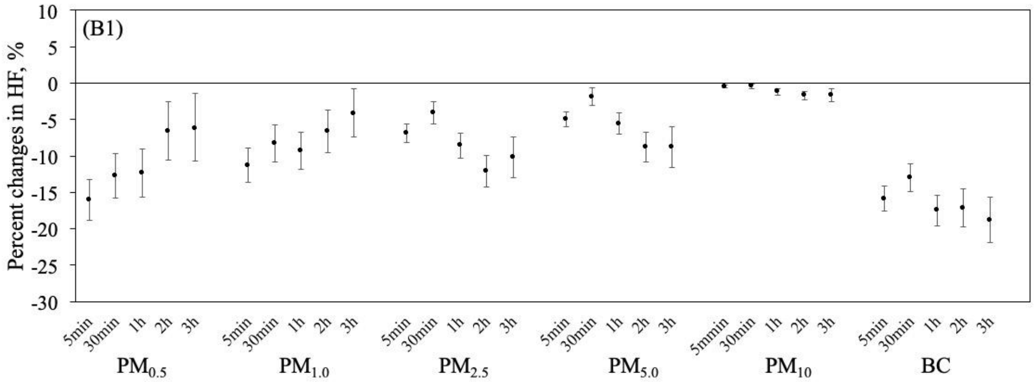
Figure 2 (A) Estimated percent changes with 95% confidence intervals in health measurements (except ST segments) with real purification; (B) Estimated changes with 95% confidence intervals in ST segments elevation with real purification.

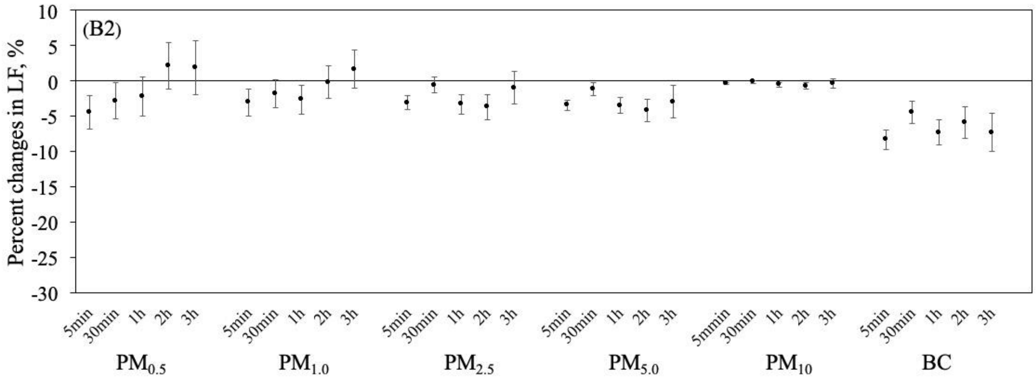
[a.] Abbreviations: FEV_1 (N=257), forced expiratory volume in the first second; PEF (N=257), peak expiratory flow; FeNO (N=257), fractional exhaled nitrogen oxide; MDA (N=257), Malondialdehyde; SBP (n=257), systolic blood pressure; DBP (N=257), diastolic blood pressure; PP (N=257), pulse pressure; HF (N=9100), power in high frequency; LF (N=9100), power in low frequency; SDNN, standard deviation of all NN intervals; LF/HF (N=9100), LF to HF ratio; HR (N=9100), heart rate.

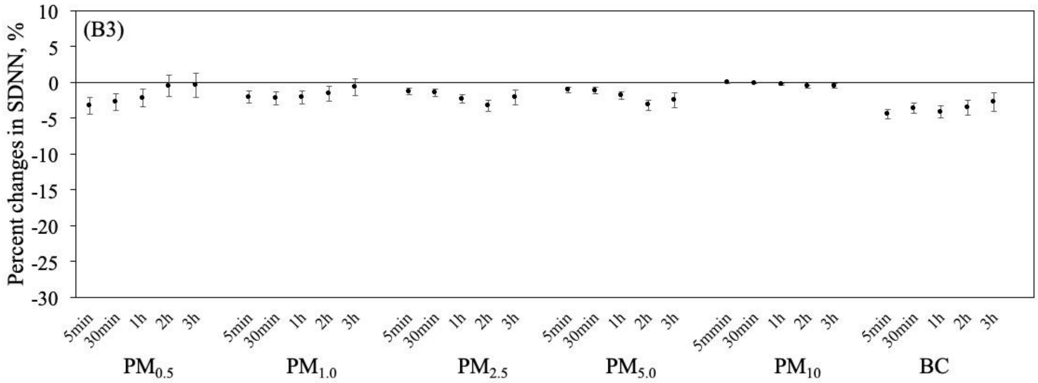
[b.] II_ST (N=825); V2_ST (N=825); V5_ST (N=825).

[c.] N: number of observation.


(A)
Percent change in respirotary measurement, %
120
100
80
60
40
20
0
-20
-40
-60
PM0.5 PM1.0 PM2.5 PM5.0 PM10 BC
FEV1
FeNO
MDA


(B1)
Percent changes in HF, %
10
5
0
-5
-10
-15
-20
-25
-30
5min 30min 1h 2h 3h
5mmin
PM0.5
PM1.0
PM2.5
PM5.0
PM10
BC


(B2)
Percent changes in LF, %
10
5
0
-5
-10
-15
-20
-25
-30
5min 30min 1h 2h 3h
5mmin
PM0.5
PM1.0
PM2.5
PM5.0
PM10
BC


(B3)
Percent changes in SDNN, %
10
5
0
-5
-10
-15
-20
-25
-30
5min 30min 1h 2h 3h
5mmin
PM0.5
PM1.0
PM2.5
PM5.0
PM10
BC

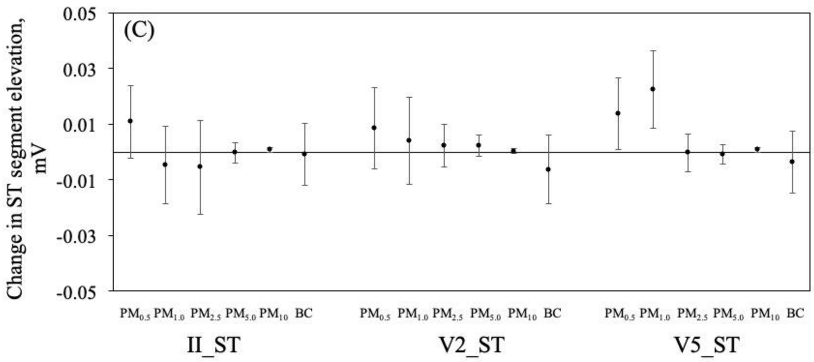


Figure 3 (A) Estimated percent changes with 95% confidence intervals in respiratory measurements per IQR increases in size-fractionated PM and BC; (B) Estimated percent changes with 95% confidence intervals in HRV indices per IQR increases in size-fractionated PM and BC over different moving averages. (B1) HF; (B2) LF; (B3) SDNN (C) Estimated changes with 95% confidence intervals in ST segment elevation per IQR increases in size-fractionated PM and BC.

[a.] Abbreviations: FEV_1 (N=257), forced expiratory volume in the first second; PEF (N=257), peak expiratory flow; FeNO (N=257), fractional exhaled nitrogen oxide; MDA (N=257), Malondialdehyde; SBP (n=257), systolic blood pressure; DBP (N=257), diastolic blood pressure; PP (N=257), pulse pressure; HF (N=9100), power in high frequency; LF (N=9100), power in low frequency; SDNN, standard deviation of all NN intervals.

[b.] II_ST (N=825); V2_ST (N=825); V5_ST (N=825).

[c.] N: number of observation.

[d.] IQR increases: $PM_{0.5}$, 17.9 μg/m^3; $PM_{1.0}$, 22.2 μg/m^3; $PM_{2.5}$, 26.7 μg/m^3; $PM_{5.0}$, 170.0 μg/m^3; PM_{10}, 331.7 μg/m^3; BC, 3.6 μg/m^3

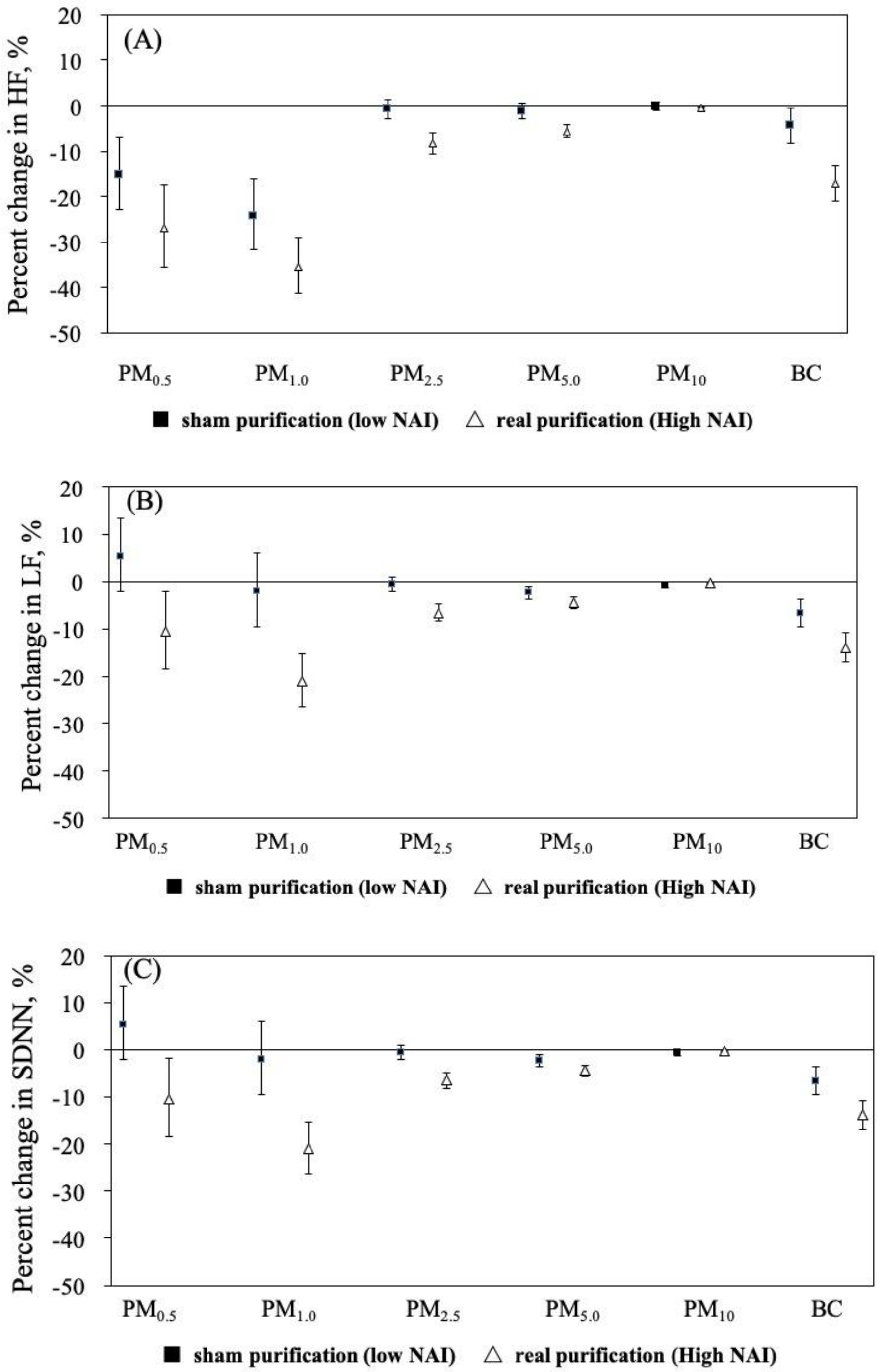


Figure 4 Estimated percent change in HRV indices per IQR increase in size-fractionated PM and BC at 5min moving average in sham-purification group and real-purification group, respectively. **Solid squares**: effect estimated in sham purification (low NAI) scenario; **open triangles**: effect estimated in real purification (high NAI) scenario. (A) HF; (B) LF; (C) SDNN.

[a.] Abbreviations: HF (N=4523 for sham purification; N=4577 for real purification), power in high frequency; LF (N=4523 for sham purification; N=4577 for real purification), power in low frequency; SDNN (N=4523 for sham purification; N=4577 for real purification), standard deviation of all NN intervals.

[b] N: number of observation.

[c] IQR increases: $PM_{0.5}$, 17.9 μg/m^3; $PM_{1.0}$, 22.2 μg/m^3; $PM_{2.5}$, 26.7 μg/m^3; $PM_{5.0}$, 170.0 μg/m^3; PM_{10}, 331.7 μg/m^3; BC, 3.6 μg/m^3