Official Title: The Health Benefits of Indoor Air Filtration Among Children

NCT Number: NCT04835337

Document Date: 2024-09-12

Protocol Synopsis

Title	The Health Benefits of Indoor Air Filtration Among Children
Intervention	Classroom and household air purifiers
Study Objectives	This study aims to explore the health benefits of air purifiers on children's health.
Study Design	The study is a randomized, controlled, double-blind, crossover trial of a multi-setting air purification intervention.
Primary Endpoint(s)	The primary outcomes are cardio-respiratory function including lung function, airway inflammation, blood pressure, heart rate variability, electrocardiograph, academic performances including standardized scores and relative ranking of scores.
Secondary Endpoint(s)	The secondary outcomes are metabolites in exhaled breath condensate, serum protein, cognitive function measured by Wisconsin Card Sorting Test, Attention Network Test, and N-BACK Test, other omics and targeted biomarkers of interest (e.g., CRP, 8-OHdG, etc).
Accrual Objective	105
Study Duration	9 months (from April 2021 to December 2021)
Treatment Description	Participants are divided into an intervention group and a control group according to the principle of cluster randomization. The intervention group is equipped with true-particulate air purifiers and the control group is equipped with sham-purification devices in households and school classrooms.
Inclusion Criteria	(i) Fourth-grade students (10–12 years old) in primary school; (ii) no plans to change schools during the current school year; (iii) those who participate voluntarily and are able to undergo questionnaires and health checks; and (iv) those who have good compliance and accept the installation of an air purifier and $PM_{2.5}$ monitoring equipment at home.
Exclusion Criteria for Individual	(i) transferring schools expected during the study period; (ii) having a chronic disease diagnosed by a doctor within the past year.

Glossary of Abbreviations

FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
PEF	Peak expiratory flow
$FEF_{25-75\%}$	Forced expiratory flow at 25–75% of FVC
$MEF_{75\%}$	Maximal expiratory flow at 75% of FVC
$MEF_{50\%}$	Maximal expiratory flow at 50% of FVC
$MEF_{25\%}$	Maximal expiratory flow at 25% of FVC
FeNO	Fractional exhaled nitric oxide
FeCO	Fractional exhaled carbon monoxide
COHb	Carboxyhemoglobin
TC	Total correct
%TC	Percentage total correct
TE	Total errors
%TE	Percentage total errors
PR	Perseverative responses
%PR	Percentage perseverative responses
PE	Perseverative errors
%PE	Percentage perseverative errors
NPE	Nonperseverative errors
%NPE	Percentage nonperseverative errors
CLR	Conceptual level responses
%CLR	Percentage conceptual level responses
CC	Categories completed
FM	Failure to maintain set
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
PP	Pulse pressure
SDNN	Standard deviation of all normal-to-normal intervals
rMSSD	Root mean square of successive differences between adjacent normal cycles
pNN50	Percentage of adjacent NN interval differences greater than 50 ms
VLF	Very low frequency
LF	Low frequency
HF	High frequency
LF/HF	Ratio of LF to HF
PR interval	The interval of the beginning of the P wave to the beginning of the QRS complex
QRS duration	The interval of the beginning of Q wave to the end of the S wave
QT interval	The interval from the onset of the QRS complex to the end of the T wave
QTc interval	The QT correction for rate
RV5	Amplitude of the R wave in lead V5
SV1	S-wave depth in lead V1
RV5+SV1	The sum of the R-wave amplitude in lead V5 and the S-wave amplitude in lead V1

1. Background and Rationale

Previous studies have suggested that fine particulate matter ($PM_{2.5}$) has adverse effects on children's respiratory, cardiovascular, and cognitive health. However, it is not clear whether reduced $PM_{2.5}$ concentration by indoor air purifiers is beneficial for the multi-system health of school-age children.

2. Study Objectives

This study aims to explore the health benefits of air purifiers on children's health.

3. Study Design

3.1 Description of Study Design

A cluster-randomized, double-blind, crossover trial of a multi-setting (classroom and bedroom) air purification intervention is conducted in Mengzhou City, Henan Province, China, from April 2021 to December 2021. Children aged 10–12 years old (fourth grade) are recruited as subjects. Participants are divided into an intervention group and a control group according to the principle of cluster randomization. The intervention group is equipped with true-particulate air purifiers and the control group is equipped with sham-purification devices both in bedrooms and school classrooms. The two groups receive alternating treatments of true or sham purification in a random order, with each study period separated by a washout period of over two months. A linear mixed-effects model is used to explore the effects of purification intervention. Ambient $PM_{2.5}$ and indoor $PM_{2.5}$ exposure concentrations are monitored in the study.

3.2 Primary and Secondary Outcomes

The primary outcomes for respiratory health are lung function indicators, including forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow (PEF), forced expiratory flow at 25–75% of FVC ($FEF_{25-75\%}$), maximal expiratory flow at 75% of FVC ($MEF_{75\%}$), maximal expiratory flow at 50% of FVC ($MEF_{50\%}$), and maximal expiratory flow at 25% of FVC ($MEF_{25\%}$); changes of FeNO; Changes of FeCO. The primary outcomes for cardiovascular health are blood pressure indicators, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse pressure (PP); heart rate variability indicators, including standard deviation of all normal-to-normal intervals (SDNN), the root mean square of successive differences between adjacent normal cycles (rMSSD), the percentage of adjacent NN interval differences greater than 50 ms (pNN50), very low frequency (VLF), low frequency (LF), high frequency (HF), the ratio of LF to HF (LF/HF); and electrocardiograph parameters, including the interval of the beginning of the P wave to the beginning of the QRS complex (PR interval), the interval of the beginning of Q wave to the end of the S wave (QRS duration) , the interval from the onset of the QRS complex to the end of the T wave (QT interval), the QT correction for rate (QTc interval), amplitude of the R wave in lead V5 (RV5), S-wave depth in lead V1 (SV1) and the sum of the R-wave amplitude in lead V5 and the S-wave amplitude in lead V1 (RV5+SV1). The primary outcomes for cognitive health are academic performances, including standardized scores and relative ranking of scores.

The secondary outcomes include the metabolites in exhaled breath condensate, serum protein, the indicators measured by the Wisconsin Card Sorting Test, Attention Network Test, and N-BACK Test. Furthermore, other omics and targeted biomarkers of interest (e.g., CRP, 8-OHdG, etc) are also considered.

3.3 Stratification, Randomization, and Blinding

Students are allocated by class cluster randomization to the intervention group or the control group. The intervention assignment is handed over to independent trained professionals, who do not participate in

any other processes of the trial. Confidentiality of the intervention is maintained for the researcher and participants to achieve double blindness.

4. Participants and Sites

4.1 Inclusion Criteria

Inclusion rules for the study participants are:

1. Fourth-grade students (10–12 years old) in primary school
2. No plans to change schools during the current school year
3. Those who participate voluntarily and are able to undergo questionnaires and health checks
4. Those who have good compliance and accept the installation of air purifiers and $PM_{2.5}$ monitoring equipment at home

4.2 Exclusion Criteria for Participant

The exclusion criteria are as follows:

1. Expecting to transfer schools during the study period
2. Having a chronic disease (including asthma, childhood diabetes, childhood hypertension, behavior-related diseases, etc.) diagnosed by a doctor within the past year.

4.3 Sites

In 2020, the average annual $PM_{2.5}$ concentration of 56 μg/m^3 in Jiaozuo City still exceed the annual average $PM_{2.5}$ limit of 35 μg/m^3 [1]. In addition, there are various sources of air pollution in Jiaozuo, including agricultural, industrial and transportation sources. Therefore, Jiaozuo City, Henan Province is selected as the study area.

5. Known and Potential Risks and Benefits to Participants

The medical examination is carried out by professional staff and is demonstrated and explained before the measurements, which does not cause health risks and discomfort. All information and the samples tested about the subject are kept strictly confidential and are only used for this project. Participation in the survey is voluntary, and the rights of respondents who do not agree to participate in this survey, or withdraw at any time after the start of the survey, are not affected in any way.

Respondents receive a feedback report on the results of the medical examination, an air pollution exposure monitoring report, personalized protection advice, and a small gift to thank for participating.

6. Intervention

6.1 Intervention

The intervention group is equipped with purifiers with true-purification (i.e., with high-efficiency particulate air (HEPA) filter), and the control group with sham-purification purifiers (without HEPA filter), which are installed in the classrooms and households of both groups. In the school environment, an air purification efficiency of 850 m^3/h (LEXY, KJ901) and a fresh air ventilation with the purification efficiency of 320 m^3/h (AIRTAO, AT320) are placed in the front of the classroom and the air purification equipment is the same as the back of classroom. In the home environment, one air purifier with the purification efficiency of 220 m^3/h (Haier, KJ210F- A180A) is installed in each of the children's bedroom. Two different treatments are employed, including true-purification and sham-purification, in random order with a washout period of over 2 months. The air purification intervention is performed by trained professionals on and off at regular intervals each day to ensure that the air purification unit is on during the time the children are in the indoor environment. In the event of offline situations such as those caused by poor internet access, the survey respondents are contacted and communicated with promptly. A health examination is conducted at the beginning and end of each study period, and a questionnaire is used to collect basic information about the respondents. We also measured the environmental factors including

$PM_{2.5}$ concentration, temperature, and relative humidity. 24 time-weighted mean $PM_{2.5}$ concentrations are calculated as personal daily exposures for further analysis.

6.2 Washout Period

A total of four surveys are conducted during the study, and the two sets of purifiers are swapped before the third survey to achieve the purpose of elution.

6.3 Biological sample collection and testing

The trained medical staff collect exhaled breath condensate (EBC) before and at the end of each intervention period. EBC samples are stored in a -80°C refrigerator before metabolomics analysis. After the cardiovascular indicator measurements, medical staff collect 6 ml peripheral venous blood. Children are instructed to fast before the blood collection. The blood samples are heated in a water bath and centrifuged, after which the upper serum is extracted in EP tubes and stored in the -80°C freezer before proteomics testing and analysis. Urine, saliva, oral cells, oral swabs, nasal swabs, skin swabs, nails and feces samples are collected during each visit and stored in the -80°C refrigerator before laboratory testing.

6.4 Criteria for discontinuing or modifying

1. The intervention is ended if it is disruptive to the classroom.
2. The participation is voluntary and participants can be withdrawn at any time. Their rights are not affected in any way.

6.5 Strategies for adherence

During the investigation, all tests are conducted by professionally trained medical personnel and all computer-based tests are conducted for children of that age and do not cause any adverse effects.

The physical examination report and environmental test report are returned timely so that the survey subjects can better understand their own health status and environmental exposure, deepen their understanding of the test and better cooperate.

6.6 Permitted or prohibited interventions

During the intervention study period, it is recommended to have less window opening ventilation to ensure the effectiveness of the air purification intervention. If the subject takes medication regularly, it can be carried out normally according to the doctor's instructions.

7. Study Procedures

7.1 Enrollment

The research subjects are surveyed through the screening questionnaire, combined with the above inclusion and exclusion criteria, and the research subjects with good compliance and willingness to complete the study according to the requirements of the project are selected.

7.2 Randomization

Students are allocated by class cluster randomization to the intervention group or the control group. The intervention assignment is handed over to independent trained professional, who does not participate in any other processes of the trial. Confidentiality of the intervention is maintained for the researcher and the survey participants to achieve double blindness.

7.3 Environmental exposure measurement

Exposure assessment of $PM_{2.5}$ is measured based on the daily activity pattern of students, including indoor measurement (residence and classroom) and ambient measurement during their commute to school. Indoor $PM_{2.5}$ exposure data is collected by installing Hike B3-L2 (Beijing Haike Zhidong Technology Development Co. LTD, China) in the study children's bedrooms and classrooms. The monitors are installed on a platform at least 1m from the purifier and approximately 1.5m above the floor. The monitors collect ambient $PM_{2.5}$ concentrations every five minutes, and we collect real-time $PM_{2.5}$

exposure levels in bedrooms and classrooms for the duration of the study. Secondly, real-time outdoor $PM_{2.5}$ data is collected by installing a micro atmospheric environment monitoring station (Capri Environmental Technology Ltd., Shenzhen, Guangzhou) on the roof of the school. Meanwhile, this micro atmospheric environment monitoring station also monitors and collects outdoor concentrations of PM_{10} ($\mu g/m^3$), NO_2 ($\mu g/m^3$), SO_2 ($\mu g/m^3$), CO (mg/m^3), and O_3 ($\mu g/m^3$). Finally, twenty-four-hour time-weighted mean $PM_{2.5}$ concentrations are calculated as personal daily exposures based on $PM_{2.5}$ concentrations in different environments and twenty-four-hour time-activity patterns of survey respondents. The monitoring particle concentration data has undergone quality control and calibration following the previous approach [2]. Temperature and relative humidity are collected via the HOBO® MX Temp/RH Data Logger MX1101 (Onset, USA).

7.4 Questionnaire

The questionnaire is in the form of an electronic questionnaire (questionnaire.com). Professional staff train and qualify classroom teachers to supervise parents and students to complete the parent questionnaire, student questionnaire and the 24h time-activity questionnaire. Information collected during the baseline survey does not have to be collected for the other surveys if there is no significant change during the other surveys.

The parent questionnaires are conducted on the parents of the students, and the survey included basic family information, living environment, risk perception, and child evaluation scale (parent volume). The children's questionnaires are conducted on students, and the survey included risk perceptions and the Children's Evaluation Scale (Children's Volume). The 24h time-activity questionnaires are conducted on students, documenting their activity patterns and diet behaviors.

7.5 Physical Examination

7.5.1 Height measurement

Height measurement is conducted by using a tape measure fixed on the wall. Before the measurement, the subjects are required to take off their shoes, hats and outerwear, stand on the pedal and maintain an upright posture. After the measurement is completed, the accurate measurement results are filled into the physical examination form.

7.5.2 Weight measurement

Weight measurement is performed using an electronic weight scale. Measurements are taken in a quiet, spacious environment with a level and firm floor. After the measurement is completed, the results are entered into the medical examination form in a timely manner.

7.5.3 Waist circumference measurement

Waist circumference is measured using a waist tape. The subject stands upright, with the abdomen relaxed, arms hanging down naturally, feet combined and weighted evenly, exposing the abdominal skin. After completing the measurement, the results are entered into the physical examination form.

7.5.4 Hip circumference measurement

Hip circumference measurement is performed using a waist circumference tape. The soft ruler is lightly pressed against the skin, passing through the highest point of the buttocks and circling around the body. Measurements are carried out twice, with a difference of no more than 1 cm, and the average value should be recorded in the physical examination form.

7.6 Respiratory health measurements

Pulmonary function measures are performed by a professional medical device. Before the pulmonary function test, subjects practiced several times with the guidance of professional staff. During the examination, each subject is in a sitting position clamp the nose clip, and repeat the test, with the best

result as the criterion. The indicators include FEV_1, FVC, FEV_1/FVC, PEF, $FEF_{25-75\%}$, $MEF_{75\%}$, $MEF_{50\%}$, $MEF_{25\%}$. A NIOX VERO Sensor is used to measure fractional exhaled nitric oxide (FeNO) as a biomarker for airway inflammation. After deep breathing, the subjects gently inhaled into the device. The instrument shows the FeNO level of the subjects. Use PICO to measure fractional exhaled carbon monoxide (FeCO) as a biomarker. After deep breathing and holding the breath for 15 seconds, the subjects gently inhaled into the device. The instrument shows the FeCO and COHb level of the subjects.

7.7 Blood pressure measurement

After a 5-minute rest in a quiet environment, the child-appropriate BP cuff is wrapped around the left upper arm of the children to measure BP using the Omron electronic sphygmomanometers (OMROM, J751). BP is measured at 2-minute intervals, with a total of three measurements taken. If the difference in BP values between the last two measurements exceeds 5 mmHg, additional measurements are performed. Each child is allowed to measure BP at least three times and up to five times. The SBP, DBP and heart rate are recorded; the mean arterial pressure (MAP) and pulse pressure (PP) are calculated. The HOBO thermo-hygrometer is set up in the medical examination room to monitor the temperature and relative humidity.

7.8 Heart rate variability measurements

A 3-minute comprehensive assessment is conducted to measure HRV using the handheld electrocardiographic recorder-CarePatch (ECG-H01, Hangzhou Proton Technology Co., Ltd., China). The participants are required to rest quietly for 2 minutes before the measurement. The professional staff activate the Bluetooth on the terminal device (Thinkpad) and enter the “CarePatch” (a WeChat Mini Program), then guide the children to hold the electrodes with their thumbs at moderate pressure for a “3-minute comprehensive examination”. During this process, children are prohibited from speaking or physical activity. 3 time-domain indicators, including standard deviation of all normal-to-normal intervals (SDNN), the root mean square of successive differences between adjacent normal cycles (rMSSD), the percentage of adjacent NN interval differences greater than 50 ms (pNN50); and 4 frequency-domain indicators, including very low frequency (VLF), low frequency (LF), high frequency (HF), the ratio of LF to HF (LF/HF) are selected.

7.9 Electrocardiograph measurements

The staff use a 12-lead electrocardiogram (ECG) to record the values of PR interval (the interval of the beginning of the P wave to the beginning of the QRS complex), QRS duration (the interval of the beginning of Q wave to the end of the S wave), QT interval (the interval from the onset of the QRS complex to the end of the T wave), QTc interval (the QT correction for rate), RV5 (amplitude of the R wave in lead V5), SV1 (S-wave depth in lead V1), and RV5+SV1 (the sum of the R-wave amplitude in lead V5 and the S-wave amplitude in lead V1).

7.10 Academic achievement measurements

Academic achievement is collected at the beginning and end of each study period. The evaluation of academic performance consisted of standardized scores (maths, chinese and total) and the relative ranking of the scores within the grade. Standardized grades are converted from raw grades by z-scores according to the number of exams and class in order to eliminate differences due to different exams; rankings are converted from place rankings of raw grades, reflecting the relative value of grades.

7.11 Cognitive executive function measurements

7.11.1 The Attention Network Test

The Attention Network Test (ANT) is used to measure an individual's ability to acquire and maintain a state of alertness to a certain type of information or target, selective attention to externally useful

information, and processing of conflicting information. The ANT is a computer-based, annotated test that is typically used to measure different behavioral aspects of attention, and it is based on the Attention Network Theory.

The ANT is divided into two phases: a practice and a formal game. The practice phase consists of 10 questions that are used to familiarize with the operation. After completing the exercise, the system prompts the start of the formal game. The formal game is divided into three parts, with the option of resting or continuing directly between each part. In this test, the subject's task is to feed a hungry little fish located right in the middle by judging the direction of its mouth. When the mouth of the small fish is facing left, press the left button; when the mouth of the small fish is facing right, press the right button. During the test, the subject is asked to look intently at the gaze point (+) on the screen as it will indicate where the minnow is likely to appear. Also, watch out for the left and right buttons to show clear positions on the screen.

7.11.2 The Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) is used to measure children's cognitive executive function. WCST is a widely used executive function task proposed by Berg (1948) to assess abstract reasoning and cognitive change in the context of changing environmental contingencies and the ability to cope with changing environmental contingencies[3-5].

The study uses computerized WCST software (Kunming Quanlu Technology Co., Ltd) and is administered to children by professional investigators in a quiet classroom to minimize external distractions. WCST consist of four key cards and one hundred and twenty-eight stimulus cards which depicted four shapes, four colors and four numbers in response. The 4 key cards with the upper features are placed in front of the subject in order from left to right. The stimulus cards are then presented to the subject one at a time and the subject is instructed to match the stimulus card with one of the key cards using either the pictorial, color, or number consistency rules. Subjects are only told whether each response is correct or incorrect. The matching rule is changed once the subject has successfully matched the stimulus card to the key card in succession using the matching rule. The WCST underwent extensive set transfer (i.e., matching rule) across the three categories (color, pictorial and numerical).

7.11.3 The N-BACK Test

The N-back test is a classic working memory task used to assess an individual's working memory capacity and attentional control. The N-back test consists of a 1-back and a 2-back, and each level of the test includes three tests: a colour contrast, a shape contrast, and a position contrast, so there are a total of six tests, namely the 1-back colour test, the 1-back shape test, the 1- back position test, 2-back colour test, 2-back colour test, and 2-back colour test. In this test, the subject's task is to compare the position, colour, or shape of the currently displayed stimulus card with that of a stimulus card in a previous or alternate position. If they are consistent, click the "Confirm" button on the right side of the interface; if they are not consistent, do not click any button. Subjects are asked to focus their attention, constantly update and maintain the stimulus information, and make accurate judgments within a short period of time, this task is designed to examine the short-term memory ability of the subjects as well as their ability to update and maintain the information.

8. Statistical Considerations and Analytical Plan

8.1 Sample size calculation

In this randomized, double-blind crossover study, the sample size is determined according to the relative literature on respiratory outcome[6-8], cardiovascular outcome[9-10], and cognitive function outcome[11] and confirmed in PASS15.0 software with the statistical significance of 0.05. Combined with the supporting

evidence and the requirement of sample size calculated in PASS15.0, and considering the typical number of students in each class and the possible withdrawal, we ultimately plan to recruit 100 children for this study.

8.2 Analytical models

We use a linear mixed-effects model to estimate the effects of air purification intervention or per interquartile range (IQR) decrease in personal $PM_{2.5}$ exposure on several functional indicators and targeted biomarkers of children's health. To account for the impact of varied outcome levels at baseline, the absolute or relative change in outcome level is calculated as the difference between post-intervention and pre-intervention, comparing the change in health outcomes between the intervention and control groups after the intervention. We further adjusted for the confounders including sex, age, body mass index (BMI, kg/m^2), temperature (℃), relative humidity (%), etc. A random intercept for each participant is included in the models to account for the repeated measurements.

In addition, we plan to perform metabolomics analysis of EBC samples using ultra-high performance liquid chromatography-tandem mass spectrometry and proteomic analysis of serum samples with 4D-label free technology. Besides, other omics analyses and targeted biomarkers of interest are planned to further explore the potential biological mechanisms.

8.3 Analytical tools

All statistical analyses are carried out in R software. Statistical tests are two-sided, and $p < 0.05$ is considered statistically significant.

9. Criteria for Participant and Study Completion and Premature Study Termination

9.1 Participant Completion

Study participants who meet the inclusion-exclusion criteria and complete all interventions during the study.

9.2 Participant Stopping Rules and Withdrawal Criteria

Subjects may terminate the study early for the following reasons:

1. Study participants may voluntarily withdraw at any point in the course of the study.
2. Subject "lost to follow-up"
3. Participant died.
4. If any clinical adverse events, other medical conditions, or circumstances occur that make it not in the best interest of the subject to continue participating in the study, the study subject will discontinue further study intervention.
5. The intervention is determined to be too disruptive in the classroom or school, and the school or classroom staff requested to withdraw from the study.

10. Protocol Deviations

The investigator conducts the study in strict accordance with the protocol and does not allow deviations from the protocol. In the event of any changes, disagreements, or deviations during the course of the study, corrective actions are developed by the site and implemented immediately.

11. Ethical Considerations

Participation in the trial is voluntary and the subject may withdraw from the study at any time for any reason. Subjects (or their legal representatives) participating in the trial are issued and read an informed consent form, signed and dated informed consent form prior to any study procedures, and the informed consent materials are presented in the participant's primary language.

12. Quality Control and Quality Assurance

12.1 Quality control during site surveys

Before the on-site investigation, each technical person responsible for exposure monitoring, questionnaire survey and computer testing should participate in technical training and pass the training assessment. Each technical person should be familiar with the division of labor and tasks and responsibilities. During the on-site investigation, all technical personnel should carry out various tasks in strict accordance with the investigation process and operating procedures. When encounter a problem, one should report it to the relevant person in charge and ask for help as soon as possible. The replacement of research subjects and monitoring instruments should be recorded, and the monitoring data obtained should be handed in a timely manner, and the data collector should check the quality of the monitoring data in a timely manner, and feedback to the investigator for correction if necessary.

12.2 Quality control of questionnaires

First of all, make sure that the questionnaire is filled in on the day of the physical examination, and the questionnaire quality review should be completed on the day of the questionnaire survey. Each technical person shall review whether the questionnaire filled in by the respondent assigned to him is complete and correct, ensure that the completion date is correct, and exchange the audit with other technical personnel after completing the audit within the group, and the specific audit content includes, whether the information of the respondent is complete, whether there are outliers, the unit is not uniform, the logic is wrong, and the phenomenon of blind filling and filling in is random. If the subjects find a problem, they should promptly report to the school teacher, ask them to verify and correct the information, or contact the parents to make corrections. Research group sent technical personnel to supervise and provide technical support for the investigation site.

12.3 Quality control of physical examinations and on-site laboratory tests

Laboratory tests use blank samples for quality control.

References

1. www.henan.gov.cn

2. Wang Y, Du Y, Wang J, Li T. Calibration of a low-cost $PM_{2.5}$ monitor using a random forest model. Environ Int. Dec 2019;133(Pt A):105161. doi:10.1016/j.envint.2019.105161

3. Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G. Wisconsin Card Sorting Test Manual. Education, Medicine. 1993;

4. Tien AY, Spevack TV, Jones DW, Pearlson GD, Schlaepfer TE, Strauss ME. Computerized Wisconsin Card Sorting Test: comparison with manual administration. Kaohsiung J Med Sci. Aug 1996;12(8):479-85.

5. K.Rao A, AlbertEinstein. Chapter 6 - Cognition and Motor Skills. Hand Function in the Child (Second Edition); 2006.

6. Cui, X.; Li, Z.; Teng, Y.; Barkjohn, K. K.; Norris, C. L.; Fang, L.; Daniel, G. N.; He, L.; Lin, L.; Wang, Q.; Day, D. B.; Zhou, X.; Hong, J.; Gong, J.; Li, F.; Mo, J.; Zhang, Y.; Schauer, J. J.; Black, M. S.; Bergin, M. H.; Zhang, J., Association Between Bedroom Particulate Matter Filtration and Changes in Airway Pathophysiology in Children With Asthma. JAMA Pediatr 2020, 174 (6), 533-542.

7. Liu, S.; Huang, Q.; Wu, Y.; Song, Y.; Dong, W.; Chu, M.; Yang, D.; Zhang, X.; Zhang, J.; Chen, C.; Zhao, B.; Shen, H.; Guo, X.; Deng, F., Metabolic linkages between indoor negative air ions, particulate matter and cardiorespiratory function: A randomized, double-blind crossover study among children. Environ Int 2020, 138, 105663.

8. Wang, Y.; Zhao, Y.; Xue, L.; Wu, S.; Wang, B.; Li, G.; Huang, J.; Guo, X., Effects of air purification of indoor PM(2.5) on the cardiorespiratory biomarkers in young healthy adults. Indoor Air 2021, 31 (4), 1125-1133.

9. Cui, X.; Li, F.; Xiang, J.; Fang, L.; Chung, M. K.; Day, D. B.; Mo, J.; Weschler, C. J.; Gong, J.; He, L.; Zhu, D.; Lu, C.; Han, H.; Zhang, Y.; Zhang, J. J., Cardiopulmonary effects of overnight indoor air filtration in healthy non-smoking adults: A double-blind randomized crossover study. Environ Int 2018, 114, 27-36.

10. Li, H.; Chen, R.; Cai, J.; Cui, X.; Huang, N.; Kan, H., Short-term exposure to fine particulate air pollution and genome-wide DNA methylation: A randomized, double-blind, crossover trial. Environ Int 2018, 120, 130-136.

11. Pan, C. Y.; Tsai, C. L.; Chu, C. H.; Sung, M. C.; Huang, C. Y.; Ma, W. Y., Effects of Physical Exercise Intervention on Motor Skills and Executive Functions in Children With ADHD: A Pilot Study. J Atten Disord 2019, 23 (4), 384-397.