University of British Columbia

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SUBJECT INFORMATION AND CONSENT FORM

Examining the Effect of Salbutamol Use in Asthma and/or EIB Whilst Exercising in Ozone Air Pollution

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Sponsors: UBC Faculty of Education
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1. INVITATION

You are being invited to take part in this research study because you have asthma and or exercise induced bronchoconstriction (EIB) and are between 19 and 50 years of age. If you are allergic to salbutamol (also known as Ventolin), pregnant, have a history of smoking, use inhaled corticosteroid medication, had an upper respiratory tract infection in the last four weeks, or have a chronic respiratory disease other than asthma or EIB you are not eligible for this investigation.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation in this study is completely voluntary. You have the right to refuse participation in this study. Should you choose to participate, you may choose to withdraw from the study at any time without penalty. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts.

If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

If you do not wish to participate, you do not have to provide any reason for your decision not to participate nor will you lose the benefit of any medical care to which you are entitled or are presently receiving.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. WHO IS CONDUCTING THIS STUDY?

This study is funded by the UBC Faculty of Education and the Natural Sciences and Engineering Research Council of Canada (NSERC).

4. BACKGROUND

Physical activity has been recognized as an important component of a healthy lifestyle. This is especially true in developed regions of the world where sedentary behaviour has been associated with health conditions such as type 2 diabetes, hypertension, mood disorders, and certain types of cancer. As the world's population continues to become more developed, more people are living in areas with increased ambient air pollution. Exposure to air pollutants, such as ozone

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gas, have been associated with increased mortality and hospitalization due to heart and lung disease. This presents a potential issue because increased breathing rates during exercise result in an increased amount of inhaled air pollution. This issue is particularly relevant for individuals with asthma and/or exercise induced bronchoconstriction (EIB) who are more sensitive to respiratory irritants such as ozone. Salbutamol is a medication commonly prescribed to this population and its use is increased in regions with higher levels of ozone pollution. However, rodent studies have indicated a potential for negative consequences of salbutamol use in ozone air pollution including increased protein leakage and lung inflammation.

5. WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to investigate the influence of salbutamol use on lung function and inflammation in people with asthma and/or EIB when exercising in ozone air pollution.

6. WHO CAN PARTICIPATE IN THIS STUDY?

You may be able to participate if you:

- Are between 18 and 50 years of age
- Have asthma and/or EIB related airway narrowing during exercise (this will be confirmed on the first lab visit)
- Are able to perform maximal exercise
- Are able to communicate sufficiently using the English language

In total a minimum of 24 participants will be recruited.

7. WHO SHOULD NOT PARTICIPATE IN THIS STUDY?

You should not participate if you:

- Are allergic to salbutamol (also known as Ventolin)
- Are pregnant or potentially pregnant
- Have a history of smoking
- Had an upper respiratory tract infection within the last 4 weeks
- Have a chronic respiratory disease other than asthma or EIB

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8. WHAT DOES THIS STUDY INVOLVE?

This is a maximal exercise study design where you will complete both room air and ozone conditions after taking either a placebo or an asthma medication. This design has two independent variables (air quality and medication) and two dependent variables (lung function and lung inflammation). The two levels of the air quality variable are room air and ozone containing air. The air quality variable will be double blinded. The two levels of the medication variable will be salbutamol and placebo medication. The medication variable will be double blinded. This study will involve five visits to the lab separated by a minimum of 48 hours. There are pre-lab visit restrictions described below in section 9 related to food to avoid 12 hours before, medication, supplements and exercise. After providing informed written consent, we will ask you to complete a questionnaire regarding your medical history and physical activity levels (PAR-Q+) to ensure it is safe for you to exercise. The first visit will be a screening day where you will do test breathing test (EVH test) and a maximal exercise (VO_{2max} test). The EVH test will determine the degree of airway narrowing that occurs during exercise. The VO_{2max} test is a maximal exercise test that will be used to standardize exercise intensity in subsequent visits. Days 2-5 will be experimental days involving lung function (spirometry), lung inflammation (FeNO) measurement, blood pressure measurement, and symptom rating (breathlessness, cough, sore throat, headache, chest pain, and chest tightness) before and after doing moderate intensity exercise for 30 minutes. Before exercise you will inhale either placebo or real salbutamol. During exercise you will be breathing air from a tube connected to a sealed chamber that will contain room air or air with ozone. Over the course of the four experimental days you will exercise under four different conditions: (salbutamol + ozone), (salbutamol + room air), (placebo + ozone), and (placebo + room air). The order of these conditions over the four experimental days will be determined by a random number generator in an Excel spreadsheet. The testing will take place in Room 118 of the Medical Sciences Block C building located at 2176 Health Sciences Mall. The first day should take about 2 hours and days 2-5 should take about 2.5 hours each for a total of 12 hours.

If you decide to join this study:

Specific procedures day 1

On day 1 you will re-read and sign this consent form in addition to a PAR-Q+ questionnaire. You will then do a EVH test which simulates breathing during exercise. After the EVH test you will take 200µg (two puffs) of salbutamol, wait 15 minutes, do a self-selected warm up on a stationary bike, and then complete a maximal exercise test (VO_{2max} test). Overall this day may last up to 2 hours.

Lung Function Measurement (Spirometry):
Lung function will be measured as per the guidelines of the American Thoracic Society (ATS). The baseline measurements involve using a machine (called a spirometer) to measure your breathing function (spirometry). This will involve taking a series of breaths (at rest) as instructed

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by the investigators. You will exhale into a machine that measures the amount of air that you breathe out. Standard measures of pulmonary function will be measured.

Eucapnic Voluntary Hyperpnea Test (EVH test):
The EVH test is the most commonly used test to assess exercise-induced airway narrowing in athletes. After three lung function tests (see above), you will breathe a dry gas mixture (5% CO_2, 21% O_2, balanced with N_2) for 6 min. During those 6 min you will be asked to increase your breathing rate and volume, similar to how you breathe during intense exercise. The purpose is to simulate the breathing pattern you would use while training or competing at a high intensity. Following this 6 min period, you will repeat the lung function testing that you already performed at the beginning of the test. This test will indicate if you have asthma related airway narrowing during exercise. -

Maximal Exercise Test (VO_{2max} test):
We will ask you wear appropriate exercise attire for the cycling exercise. Before the cycling test begins, you will perform a 5-minute self-selected warm up on a stationary bike. Following the warm up, you will start the exercise test at 75 or 100 Watts, with the workload increasing in a step-wise fashion by 10 or 20 Watts every two-minutes until you feel you can no longer continue or until you can no longer maintain a cadence of 60 rpm. We will ask you to perform a large breath in until your lungs are completely full at the end of each stage of exercise. This allows us to assess your lung volumes. During all exercise bouts, you will be breathing on a standard mouthpiece while wearing a nose clip to monitor breathing.

Specific procedures days 2-5

Days 2-5 will involve taking either placebo medication or salbutamol, waiting 15 minutes and then doing pre-exercise measures. Pre-exercise measures include spirometry, lung inflammation (FeNO) measurement, blood pressure measurement, and rating of breathlessness. You will then exercise for 30 minutes at 60% of your VO_{2max} while breathing in room air or air that contains ozone. During all exercise bouts, you will be breathing from a standard mouthpiece while wearing a nose clip to monitor breathing. We will ask you to perform a large breath in until your lungs are completely full periodically during exercise. This allows us to assess your operating lung volumes. Immediately after exercise, blood pressure, symptoms, FeNO, and spirometry will be measured. These measures will be repeated again after 30 minutes and 1 hour after exercise. These 4 days will be separated by a minimum of 48 hours. Each visit should take roughly 2.5 hours.

Lung Function Measurement (Spirometry):
Same at day 1 described above.

Lung Inflammation Measurement (FeNO):
Nitic oxide (NO) is produced by the epithelial cells lining your airway and is related to the level of airway inflammation. When there is a larger amount of airway inflammation more NO is

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produced and there is a larger amount of NO in the air you breath out. Measuring the fraction of exhaled NO (FeNO) is a common technique used to measure airway inflammation in people with asthma. To do this you will take a big breath in and then exhale slowly into a FeNO monitor for 10 seconds. During these 10 seconds the FeNO monitor will guide you on how fast you should exhale.

Blood Pressure Measurement
We will wrap a blood pressure cuff around your upper arm. A machine will then briefly inflate and then deflate this cuff.

Rating of breathlessness (dyspnea) measurement
We will show you a rating scale from one to ten and ask you how severe your feeling of breathlessness is.

9. WHAT ARE MY RESPONSIBILITIES?

Avoid alcohol consumption 24 hours before each visit

Avoid eating or drinking 1 hour before each visit

Foods to avoid 12 hours before each visit:
-Rocket, Spinach, Lettuce, Radish, Beetroot, Chinese cabbage, Turnips, Cabbage, Green beans, Leeks, Spring onion, Cucumber, Carrot, Potato, Garlic, Sweet pepper, Green pepper.

Medication:
-No leukotriene modifier medication (such as montelukast or Singulair) 24 hours before each visit.
-No short-acting beta agonists (such as salbutamol or Ventolin) 8 hours before each visit.
-No long-acting beta agonists (such as salmeterol or Serevent) 48 hours before each visit.
-No anti-histamines 72 hours before each visit.

If you need to take one of these medications within the time limit before your visit please do not hesitate. You can always reschedule your visit to a later date.

Vitamins:
-No vitamin E supplements for the duration of the study
-No vitamin C supplements for the duration of the study
-No multivitamin supplements for the duration of the study

Exercise:
-Avoid exercising 24 hours before each visit

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10. WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

Risks related to maximal exercise:
Some rare risks related to maximal exercise include: vomiting (2%), abnormal blood pressure, (less than 1%), disorders of heartbeat, or arrhythmia (0.1%), and very rare instances of heart attack (less than 0.001%). The percentage of risk of heart attack based on males and females who have been given these tests is very small (less than 0.0001%).

Risks related to EVH test:
Performing spirometry and EVH test involves exhaling forcefully into the mouthpiece of the spirometer and may cause some light-headedness, chest discomfort and coughing immediately after the procedure.
Risks related to ozone exposure:
Some uncommon side effect to this level of ozone exposure include: cough, throat irritation, pain, burning, or discomfort in the chest when taking a deep breath, chest tightness, wheezing a shortness of breath.

Risk related to salbutamol side effects:
Some less common side effects of salbutamol use include throat iteration (10%), and viral respiratory infection (7%). Some uncommon symptoms include upper respiratory tract infection (5%), cough (5%), and musculoskeletal pain (5%).

How risks will be mitigated?
Risk related to maximal exercise will be minimized by fill out the PAR-Q+ questionnaire which is designed to screen for individuals that are at higher risk of experiencing complications from exercise. Risks related to ozone exposure will be minimized by using a 170ppb ozone concentration. This concentration is much lower than in studies done on ozone previously and is representative of what one might find on a polluted summer day in certain cities in the real world. For example, ozone concentrations can reach 200ppb at 3pm in Mexico City during September. Risk related to salbutamol will be minimized by excluding people who are allergic to salbutamol and by using a dose of 200µg. This is a lower dose of salbutamol that is typically used for preventing exercise related asthma attacks. In the event of an emergency at least one of the researchers present will be trained in standard first aid and an AED will be present on site. The nearest emergency room is also located approximately 250 metres away at UBC hospital.

11. WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

As part of your participation, you will undergo a maximal oxygen consumption measure (VO2max test). The results will give individuals a direct measure of cardiorespiratory fitness likely unavailable to them otherwise. The results of the EVH test may also provide insight into the current severity of the participants asthma. The results of the exercise trials in ozone may also provide insight into your susceptibility to ozone pollution. Other than that, there are no

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known direct benefits from taking part in this study. We hope that the information learned from this study can be used in the future to benefit individuals who are repeatedly training and competing in areas of increased air pollution levels to better manage any asthma-symptoms, cardiorespiratory risks and complications associated with exercising in polluted conditions.

12. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw later, you have the right to request the withdrawal of your information collected during the study. This request will be respected to the extent possible. Please note however that there may be exceptions where the data will not be able to be withdrawn for example when it is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data, please let your study investigator know.

13. CAN I BE ASKED TO LEAVE THE STUDY?

You may be asked to leave the study if it is not in your best interest to continue, if you are unable to fulfill the requirements for the study, or for any other reason. If you are asked to leave the study, the reasons for this will be explained to you and you will have the opportunity to ask questions about this decision. The study may also be stopped at any time by the sponsor to the Research Ethics Board if new information rises about the safety of the study treatment. The reasons for study stoppage will be explained to you.

14. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of UBC Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

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Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected and also give you the right of access to the information about you, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

15. WHAT HAPPENS IF SOMETHING GOES WRONG?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

16. WHAT WILL THE STUDY COST ME?

There will be no cost to the participant to partake in this study. However, you will be expected to arrange your own transportation to and from the laboratory for each visit.
Remuneration: You will be paid $150 (Canadian dollars) for your participation in the study. Payments will be pro-rated ($30 for each day) if the participant withdraws from the study. No receipts are required to receive payment.

17. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Ben Stothers at ben.stothers@ubc.ca or (604) 240-7188. You may also contact the Principal Investigator, Dr. Michael Koehle, at (604) 788 7268.

18. WHOM DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT?

If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics at 1-877-822-8598 (toll free); or by email at RSIL@ors.ubc.ca. Please reference the study number [H21-01080] when calling so the Complaint Line staff can better assist you.

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Notice of COVID-Related Risks during Research | Version A

Please read this form before you consent to participate in a research study. Please also talk to the researcher about any concerns you have before signing the consent form or agreeing to participate. Remember that research participants may withdraw from a study at any time, without giving a reason.

Contact Tracing
The researcher may be required by public health authorities to share your contact information if there is a chance that you have been exposed to COVID-19 during a study visit. You will find more information about contact tracing on the BC Centre for Disease control website: http://www.bccdc.ca/health-info/diseases-conditions/covid-19/self-isolation/contact-tracing.

How does contact tracing work?
If public health authorities ask the researcher to provide a list of people who they have been in contact with, the researcher will be required to share your contact details. The researcher will not share information about the purpose of your contact, the name of the study, or anything about the research topic. Your contact tracing information will be kept securely and separate from de-identified research records and will be deleted 30 days after your last contact with the researcher It is important to know that because of this your anonymity will not be preserved.

What if I want to withdraw from the study?
If at any time you decide to withdraw from the study, the research team will only continue to store your contact information for as long as required by public health authorities. Unless otherwise stated, other data you have contributed will be removed from the study when you withdraw.

Risks of in-person contact during the research
For research that involves in-person activities such as focus groups, interviews or observations, the researchers will be following safety plans that have been approved by the University. They include: safe use of facilities (including outdoor spaces) and experimental equipment, proof of vaccination, personal protective equipment, and physical distancing. The researchers in this study are vaccinated.

If you are required to use public transit to get to or from a research location, this may increase your risk of being exposed to COVID-19. We encourage you to take all precautions, including wearing a face mask while in public, washing your hands, avoiding touching your face, and keeping a safe physical distance from others (at least 2 metres or 6 feet). Please let the researcher know if you want more information about the safety plans that have been put in place.

What if I have COVID-19 symptoms or am diagnosed with COVID-19?
Before every research activity, the researcher will ask each person who is present a series of questions about their health. The questions have been recommended by public health authorities, and ask about physical symptoms, if you have been in contact with people who are sick, and other questions. Based on your responses, the researcher will decide if it is safe to proceed with the in-person activity.

Ensure that you keep the research team's contact information (included on the consent form) so you can share it with public health authorities in the event that you become sick after participating in research.

Thank you!

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SUBJECT CONSENT TO PARTICIPATE

The consent form is not a contract and as such that the subject does not give up any legal rights by signing it.

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time.
- I understand that there is no guarantee that this study will provide any benefits to me.

I will receive a signed copy of this consent form for my own records.

I consent to participate in this study.

Subject's Signature	Printed Name	Date

Signature of Person Obtaining Consent	Printed name	Study Role	Date

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If this consent process has been done in a language other than that on this written form, with the assistance of an interpreter/translator, indicate:

Language: _____
Was the subject assisted during the consent process in one of ways listed below?
☐Yes ☐No

If yes, please check the relevant box and complete the signature space below:

☐ The consent form was read to the subject, and the person signing below attests that the study was accurately explained to, and apparently understood by, the subject (please check if subject is unable to read).

☐ The person signing below acted as an interpreter/translator for the subject, during the consent process (please check if an interpreter/translator assisted during the consent process).

_____	_____	_____
Signature of Person Assisting in the Consent Discussion Witness Signature	Printed Name	Date

_____	_____	_____
Investigator Signature	Printed Name	Date

My signature above signifies that the study has been reviewed with the study subject by me and/or by my delegated staff. My signature may have been added at a later date, as I may not have been present at the time the subject's signature was obtained.