Examining the Effect of Salbutamol Use in Asthma and/or EIB

Whilst Exercising in Ozone Air Pollution

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Introduction

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 (De Rezende et al., 2014). As the world's population continues to develop, industrialization and urbanization have led to a larger number of people living in areas with increased ambient air pollution (Barbera et al., 2010). Exposure to air pollutants, such as particulate matter and ozone, have been associated with increased mortality and hospitalization due to cardiovascular and respiratory disease (Brunekreef & Holgate, 2002). This presents a potential issue because increased ventilation during exercise results in a proportionate increase in the amount of inhaled air pollution (Carlisle & Sharp, 2001). 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 (Guarnieri & Balmes, 2014). β_2 agonists, including salbutamol, are commonly prescribed to this population and their use is increased in regions with higher levels of ozone pollution (Pepper et al., 2020). However rodent studies have indicated potential negative consequences of β_2 agonists including increased protein leakage and lung inflammation (Henriquez et al., 2019). Therefore, further research is required on the effects of using β_2 agonists in ozone air pollution by people with asthma and/or EIB.

Background

Ozone gas is produced when volatile organic compounds and gases from the NO_X family found in smog react with ultraviolet (UV) radiation from the sun. This means that ozone pollution is more prominent during sunny weather due to increased levels of UV radiation (Sillman, 2003). As a result, when the weather is nice and people are more inclined to exercise outside, ozone

pollution levels are at their highest. The World Health Organization classifies ozone as a respiratory irritant and recommends that one-hour exposures to ozone should not exceed 100 parts per billion (ppb) (WHO, 2018). However, there are a few issues with this recommendation when considering individuals with asthma and/or EIB. Firstly, highly populated areas where ozone pollution is an issue are not able to keep ozone levels below 100 ppb so people with asthma and/or EIB may be exposed to one-hour doses higher than this. For example, ozone levels can reach an hourly average concentration above 200 ppb during September at 3pm in Mexico City (Huerta et al., 2004). Secondly, people with asthma and/or EIB are more sensitive to respiratory irritants so ozone levels at 100 ppb have a larger effect on this population than individuals without respiratory disease. Finally, increased ventilation during exercise increases the amount of inhaled air pollution, thereby also increasing the dose of ozone

A study by Kreit et al. showed that people with asthma exercising in ozone had larger decrements in pulmonary function compared to healthy controls (1989). A potential explanation for this is that ozone exacerbates existing airway narrowing in people with EIB and/or asthma during exercise by influencing both the autonomic nervous system and the immune system. The airways have heavy vagal afferent innervation in the form of unmyelinated C-fibers. Ozone can trigger transient receptor potential ankyrin 1 (TRPA1) receptors on these C-fibers leading to increased parasympathetic output from the medulla to the airways resulting in bronchoconstriction (Taylor-Clark, 2020). Ozone has a standard redox potential of +2.07 V making it one of the most powerful known oxidants. As a result, inhaled ozone creates oxidative stress by either oxidative destruction of biomolecules or the formation of free radicals (Mustafa, 1990). This oxidative stress initiates an immune response in the form of airway inflammation (Mustafa, 1990).

Salbutamol is a short-acting β_2 agonist that works by binding to β_2 adrenergic receptors leading to increased sympathetic output to the lungs resulting in bronchodilation. Typically, individuals with EIB will take salbutamol 15 minutes before exercising (Jartti, 2001). This is potentially beneficial when exercising in ozone because it would counter the increased parasympathetic output caused by ozone exposure. However, a study conducted by Gong et al. showed that inhaled salbutamol did not decrease ozone-related pulmonary function impairment in healthy individuals compared to placebo after exercising in ozone (1988). This suggests that the primary mechanism of impaired lung function due to ozone may be related to inflammation rather than bronchoconstriction. It is not known if ozone exacerbates bronchoconstriction specifically in people with asthma and/or EIB exercising in ozone, but since bronchoconstriction could occur anyway in this population during exercise, regardless of ozone, β_2 agonists may still be beneficial.

A potential issue of salbutamol use in ozone relates to its effect on inflammation (Henriquez et al., 2019). Recent rodent studies by Henriquez et al. have shown that inflammatory cytokine levels, after exposure to ozone, are higher in rodents that were given a β_2 agonist compared to placebo (2019). This could potentially be related to salbutamol's known ability to increase fluid transport across the alveolar membrane (Perkins et al., 2006). However, it is not known if β_2 agonist use in humans would have the same effect. If the same effect does indeed occur in humans, it is also unknown whether Increases in inflammation greater in asthma/EIB compared to healthy individuals. It is important to learn if salbutamol use exacerbates airway inflammation because chronic airway inflammation in people with asthma has been related to airway remodelling that increases the severity of future asthma attacks (Brightling et al., 2012). As a result, significant increases in airway inflammation, despite potential improvements in

immediate pulmonary function, may be a reason for contraindication of salbutamol use in people with asthma and/or EIB when exercising in ozone air pollution.

Objective

- Determine if using salbutamol before exercising in ozone air pollution is harmful for individuals with asthma and/or EIB because of increased airway inflammation.

Hypothesis

- People with asthma and/or EIB who take salbutamol before exercising in ozone will have improved pulmonary function but higher levels of inflammation after exercise compared to placebo medication.

Methods

Sample and Recruitment

The target population for this study is individuals with asthma and/or EIB living in urban environments. The predicted sample representing this population will be people with asthma and/or EIB living in the Greater Vancouver area. The sample will be recruited by self-selection sampling. This will be accomplished through the use of posters on public advertising boards around campus at the University of British Columbia (UBC). A virtual form of the poster will also be posted on the UBC School of Kinesiology website and the in the UBC psychology graduate student council's newsletter. The poster and online advertisement will outline, in lay language, the purpose of the study, inclusion and exclusion criteria, the design of the study, the potential benefits and risks to the participants, and contact information to enroll in the study. Participants who hear of this study through word of mouth may also contact the research team if interested.

Table 1. List of study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1) Have asthma and/or EIB related airway narrowing during exercise 2) Able to perform maximal exercise 3) Between 18 to 50 years of age 4) Able to communicate sufficiently using the English language	1) Use inhaled corticosteroids 2) History of smoking 3) Chronic respiratory disease other than asthma or EIB 4) Upper respiratory tract infection within the last 4 months 5) Pregnant or potentially pregnant 6) Allergy to salbutamol

As shown in **Table 1** above, there are four inclusion criteria for this study. The first criterion, diagnosed with asthma and/or EIB, represents the population of interest for this study. During the first lab visit, participants will perform a eucapnic voluntary hyperpnea test (see Procedures section) to be screened for airway narrowing triggered by exercise. The second inclusion criterion, able to perform maximal exercise, reduces the risk of physical harm by preventing participants who may be harmed by exercising from participating. Participants will be screened for this ability on the first day by filling out the physical activity readiness questionnaire (PAR-Q+). The third inclusion criterion, between 18 and 50 years of age, reduces the risk of physical harm by preventing people with age-related risks to ozone exposure from participating in the study. Compared to adults, the developing lungs of children and young adults are more susceptible to the oxidative stress of ozone which can cause life-long decrements in lung function (Goldizen et al., 2016). For this reason, only adults aged 18 and older will be included. Older adults, age greater than 65 years, are more susceptible to ozone-induced health effects compared to younger adults due to decreased physiological, metabolic, and compensatory processes (Shumake et al., 2013). An upper age limit of 50 years was chosen because we want to test a

relatively homogenous group with a reduced risk of occult medical conditions that may confound the findings. Furthermore, we have a long track record of conducting exercise and exposure studies in this age group without incident. As a result, only adults under the aged 50 and younger will be included. The final communication criteria, able to communicate sufficiently using the English language, ensures that participants will be able to fully understand the risks of the study and have any questions answered.

As shown in **Table 1** above, there are six exclusion criteria. The first exclusion criterion, regular use of inhaled corticosteroids, prevents the effects of corticosteroid medication on fraction of exhaled nitric oxide (FeNO) measurement, a measure of lung inflammation (see Measures/Instruments section), from biasing the study results. Inhaled corticosteroids are a type of medication that are prescribed to some people with asthma which decreases FeNO (Bjermer et al., 2014). The second exclusion criterion, history of smoking, prevents the influence of smoking history on FeNO measurement from biasing the study results. People who regularly smoke, or used to smoke, were shown to exhibit 30-60% lower levels of FeNO (Malinovschi et al., 2006). The third exclusion criterion, chronic respiratory disease other than asthma or EIB, prevents the influence of other chronic respiratory diseases on spirometry measures from biasing study results. Spirometry is a method of measuring pulmonary function (see Measures/Instruments section) and can be used to diagnose multiple different obstructive and restrictive respiratory diseases because of recognizable changes in spirometry measures such as forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC (Morris, 1976). The fourth exclusion criterion, upper respiratory tract infection in the last four months, prevents the influence of upper respiratory tract infections on FeNO measurements from biasing the study results. Upper respiratory tract infection can increase FeNO by 50-150% for up to four weeks after infection

(Bjermer et al., 2014). Finally, the exclusion of pregnant or potentially pregnant individuals prevents potential ozone-related complications during pregnancy. Exposure to ozone during various stages of pregnancy has been associated with increased chances of premature birth, stillbirth, and preeclampsia (Salam et al., 2005). The sixth exclusion criteria, allergic to salbutamol, avoids physical harm from exposing people who are allergic to salbutamol to this medication.

Sample size was calculated using data from previous studies that examined changes in FEV_1 in people with EIB. Two studies by Anderson et al., in 2001 used a similar crossover design and found a detectable difference of 12% reduction in FEV_1 with a standard deviation of 14%. Calculation for a crossover design based on analysis of variance F-tests using these values with a power of 0.8 and an alpha level of 0.05 led to a sample size of 24 subjects. Previous data from FeNO in an asthmatic population where considered to make sure this sample size would be appropriate for FeNO measurement. Changes in FeNO measurements biased on a study by Niu et al., in 2018 showed a larger effect size than FEV_1 so the sample size based on FEV1 measurement is more conservative.

Measures/Instruments

The two independent variables in this study are ozone pollution status and medication (salbutamol) status. Both independent variables will have a nominal level of measurement with two levels. The two levels of ozone air pollution are: 170 ppb ozone and room air. Room air in the lab where data collection will be done has low levels of ozone (typically less than 10 ppb) and other pollutants. While wearing nose clips, participants will be exercising on a stationary bike breathing in air from a mouthpiece that is connected to a sealed chamber. The sealed chamber will contain an ACT-5000 ozone generator (ACT-series, 2021). The ozone generator will either be turned on or off depending on the allocated treatment. The concentration of ozone will be

confirmed using an electrochemical ozone sensor that will be set up in the chamber. Electrochemical ozone sensors have been validated using linear association models that have reported R^2 values of 0.98 (Afshar-Mohajer et al., 2018). For the salbutamol condition, participants will take two puffs from a meter dose inhalers (MDI) designed to deliver 100 μg of salbutamol per puff or a trainer MDI for the placebo condition. To ensure reliability of the dose delivered participants will be told standardized instruction for using an MDI. Adhering to these instructions increases the consistency of the dose delivered (Sanchis et al., 2013). In addition, an aerochamber will be attached to the MDI which further increases dose consistency (Newman, 2004). Medication status will have two levels: 200 μg of salbutamol and placebo salbutamol.

The main two dependent variables are spirometry and FeNO. Both dependent variables will have a ratio level of measurement. Pulmonary function will be measured using spirometry which includes multiple measures taken from a single test (Miller et al., 2005). Conceptually, a spirometry test involves taking a maximal inspiration followed by a maximal expiration held for six seconds then using data collected from that maneuver to create different measures of pulmonary function (Miller et al., 2005). Measures taken from spirometry tests include FEV_1, FVC, and mid volume forced expiratory flow (FEF_{25-75}). FEV_1 is the maximal amount of air that can be expired in one second, FVC is the maximal volume of air that can be expired, and FEF_{25-75} is the rate of expiration between 25% and 75% of FVC (Miller et al., 2005). For pre and post exercise measurements, spirometry will be measured twice and the attempt with the highest values will be used. A series of FVC maneuvers with graded expiratory efforts, to account for thoracic gas compression, can be used to generate maximal expiratory flow-volume (MEFV) curves before and after an exercise intervention (Guenette et al., 2010). Tidal flow-volume loops (FVL) during exercise can be plotted within the MEFV curves using inspiratory capacity (IC) maneuvers were

participants take a maximal inspiration after a normal breath out (Guenette et al., 2013). Spirometry is the gold-standard for measuring pulmonary function and has a high level of face validity and content validity (Miller et al., 2005). Spirometry can be used to diagnose different respiratory diseases because changes in FEV_1, FVC, and FEF_{25-75} match how one would expect these values to change based on the nature of the diseases (Miller et al., 2005). When taking spirometry measurements, it is important to ensure the participants maximally inhale and exhale to get an accurate reading. This can be accomplished by conducting a few practice measurements on an orientation day.

Airway inflammation will be measured using FeNO. FeNO is defined as the fraction of exhaled nitric oxide in expired air which acts as a biomarker for airway inflammation (Barnes & Liew, 1995). FeNO will be measured using a NObreath-v2 FeNO monitor. When taking a FeNO measurement, participants will breathe at a steady rate for ten seconds into the mouthpiece of the FeNO monitor (Bjermer et al., 2014). For pre and post exercise measurements FeNO will be measured four times in a row. The first measurement will be thrown out and the last three will be averaged and recorded. We chose to throw away the first measurement because the first FeNO reading on our device tends to be much lower than subsequent readings. FeNO has high convergent validity shown by strong correlation with other markers of airway inflammation including bronchoalveolar lavage fluid eosinophil counts, airway hyperresponsiveness, and bronchial biopsy eosinophil score (Khalili et al., 2007). Since FeNO can be influenced by other variables it is important to control for these variables as much as possible. This can be done by excluding people who smoke and have recently had an upper respiratory tract infection. Participants will also be asked to avoid the following foods that are high in nitrates 12 hours before each lab visit including (rocket, spinach, lettuce, radish, beetroot, Chinese cabbage, turnips, cabbage, green beans, leeks,

spring onion, cucumber, carrot, potato, garlic, sweet pepper, green pepper) which can artificially elevate FeNO measurements (Bjermer et al., 2014). In addition, participants will be asked to avoid alcohol consumption 24 hours before each visit (ATS, 2005), and asked to avoid drinking and eating one hour before the test (ATS, 2005).

Rating of symptoms (dyspnea, cough, sore throat, headache, chest pain, and chest tightness) and blood pressure will also be measured. The selected symptoms were chosen because they have been recognized or are related to symptoms of ozone exposure (Lippmann, 1989). Dyspnea will be measured subjectively using a modified Borg scale that has previously been used to measure dyspnea and validated against other dyspnea measures (Gaber et al., 2019). The other symptoms will be subjective rated on a scale from 0-5. Blood pressure will be measured using an automated sphygmomanometer. In accordance with Hypertension Canada's guidelines on blood pressure measurement, blood pressure will be measured three times and the first measure will be thrown away while the latter two are averaged (Nerenberg et al., 2018).

Study Design

This research design can be characterized as a placebo-controlled crossover design with pre-post measures. There are two independent variables: ozone pollution status and medication status. The two levels of ozone pollution status are 170 ppb ozone and room air. The two levels of medication status are 200 μg of salbutamol and placebo medication. Participants will perform 30 minutes of submaximal exercise at 60% of their VO_{2max} in all four conditions. These conditions are salbutamol + ozone, placebo + ozone, salbutamol + room air, and placebo + room air. The order of the conditions on the experimental days will be randomized to one of four sequences. The four conditions will be labelled A (ozone + inhaler A), B (ozone + inhaler B), C (room air + inhaler A), and D (room air + inhaler B). The researchers will not know which inhaler (A or B) is placebo

and which is salbutamol to facilitate blinding. The four condition sequences will be ABCD, BDAC, CABD, DCBA. These sequences represent a Latin Square crossover design, which is uniform both within periods and within sequences. In other words, each condition appears only once in each sequence and only once at a particular spot within the four sequences. This means that the sequences are balanced with respect to first order carry over effects because each condition precedes every other condition only once. For example, condition D is fist only once and is preceded by condition A, B, and C only once. FeNO, spirometry, blood pressure, and symptom measures will be obtained before and immediately after, 30 minutes after, and 1 hour after exercise in each condition. Pre and post measures will be compared from the four conditions to examine how exercising in different combinations of ozone pollution and medication influence pulmonary function (spirometry) and inflammation (FeNO). The medication condition will be double blinded to control for the placebo effect and expectancy bias of the research. This will be done by having a placebo inhaler and a salbutamol inhaler labeled A and B by someone who is not collecting data. That way neither the participant nor the researcher collecting data will know whether placebo or real salbutamol is being used in a particular condition. The ozone condition will also be double blinded . This will be done by having the participant breathe air from a tube connected to a sealed chamber, which they will not be able to see inside, that has an ozone generator that is controlled on the opposite side of the chamber. A separate researcher will be controlling the ozone chamber and on room are day will pretend to operate the generator for the room air conditions and actually operate the generator for the ozone conditions. Ozone levels will be recorded for all conditions and revealed to the main researcher after data collection is completed.

Procedures

Participants will visit the lab on five occasions. It will also be expected that participants will take no leukotriene modifier medication (Singulair or Montelukast) 24 hours before each visit, no short acting beta agonists 8 hours before each visit, no long acting beta agonists 48 hours before each visit, and no anti-histamines 72 hours before each visit. These pre-visit restrictions control for potential confounding effects on the eucapnic voluntary hyperpnea (EVH) test and FeNO measurement. Participants will be asked to avoid supplementation with vitamin C, vitamin E, and multivitamins over the course of the 5 visits. This prevents changes in the response to ozone related to vitamin supplementation (Gomes et al., 2011). Finally, participants will be asked to avoid exercise 24 hours before each lab visit. This is to ensure there is no diminishment in asthma and/or EIB severity related to a refractory period following exercise (Stickland et al., 2012). Day one will be a screening day and will involve: obtaining consent, collecting height, weight, age, and sex, screening participants for EIB, conducting a VO_{2max} test, and orienting participants to FeNO and spirometry measurement. Participants will re-read and sign a consent form in addition to reviewing and signing a PAR-Q+. They will then do practice spirometry and FeNO measurements to orient themselves to the procedure of these measures. Then, participants will complete a EVH test to screen for EIB. The EVH test requires participants to voluntarily hyperventilate regular air that has a higher than normal CO_2 concentration for 6 minutes to replicate breathing during exercise. This mimics the stimulus that leads to airway narrowing in EIB (Hull et al., 2016). The higher than normal CO_2 concentration prevents CO_2 levels in the blood from dropping leading to loss of consciousness. Spirometry measures are obtained before and after EVH and compared. A 10% or greater decrease in FEV_1 will be used to confirm the presence of EIB (Hull et al., 2016). Participants will then take salbutamol at the treatment dose (200μg and perform a VO_{2max} test on a cycle ergometer. Performing a VO_{2max} text will allow for the exercise intensity to be standardized

in subsequent trials at 60% of VO_{2max}. A graded exercise test with a ramp protocol will be performed while expired gas is analyzed using a metabolic cart to measure VO_{2max} (Beltz et al., 2016). Participants will conduct a self-selected warm-up. Following the warm up, participants 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 they feel that they can no longer continue or until they can no longer maintain a cadence of 60 rotations per minute (rpm). VO_{2max} will be considered achieved if three of the following four criteria are met: heart rate (HR) >90% of age-predicted maximum, respiratory exchange ratio >1.15, plateau of oxygen consumption per minute (VO_2) with increasing work load, and volitional exhaustion (Beltz et al., 2016). Age-predicted maximum heart rate will be calculated as 220 – age (years).

Participants will return to the lab on four separate occasions to complete the four exercise trials in a random order. During each visit, participants will take two puffs from an MDI, wait 15 minutes, and then pre-exercise measures will be taken. Pre-exercise FeNO, blood pressure, and symptoms will be measured and then participants will put on a headset that includes a mouth piece that will be used for spirometry and will control inspired air during exercise. Pre-exercise spirometry will be measured and then participants will perform a self-selected warm-up. Once they are ready, participants will exercise at a resistance that will elicit 60% of their VO_{2max} for 30 minutes while breathing through a one-way valve connected to a sealed chamber. The chamber will either contain room air or 170 ppb ozone being generated by an ozone generator. After 5 minutes and 25 minutes of exercise participants will do an IC. After 30 minutes are complete, post-exercise blood pressure, symptoms, spirometry and FeNO will be measured. All visits will be separated by 48 hours to prevent carryover effects from previous exposure to ozone or salbutamol.

This 48-hour duration was chosen because it is longer than five half-lives of salbutamol medication.

Ethical Considerations

Risks to participants related to physical harm for this study include: severe asthma attack, complications from maximal exercise, exposure to ozone, and salbutamol side effects. There will be a few instances during the study where participants will have a higher risk of having a severe asthma attack. These include the EVH test and the conditions where participants will be exercising in ozone. Having people with asthma and/or EIB exercise with placebo medication in the presence of a respiratory irritant could elicit an asthma attack (Balmes, 1993). Rescue medication, labelled salbutamol, the participant's own medication and oxygen will be kept nearby in the event of an emergency. Participants will also be reminded that they can stop the test at any time if breathing becomes too difficult. Potential complications of maximal exercise include: vomiting, abnormal blood pressure, fainting, heartbeat disorder, and rare instances of heart attack (Gibbons et al., 1989). To mitigate this risk, participants will fill out a PAR-Q+ on their first visit to the lab before signing the consent form. The PAR-Q+ is designed to screen for individuals that should speak to a physician before exercising (Warburton et al., 2018). Participants will be asked to immediately report any unusual symptoms during the test and be reminded that they may stop the test at any time. An automated external defibrillator (AED) will be present on site and researchers on site will trained in standard first aid. Potential symptoms of exposure to ozone include cough, pain with inspiration, and shortness of breath (Lippmann, 1989). This risk will be mitigated by using a dose of ozone that does not exceed real-world levels of ozone exposure. This low dose of ozone will reduce the risk of experiencing symptoms from ozone exposure. In addition, this means that the

risk related to ozone exposure would not exceed the level of risk that would occur in the daily lives of the participants. Participants will also have the ability to stop the exposure to ozone at any time. Some potential temporary side effects of salbutamol use include: nervousness, tremor, headache, dryness of the mouth, changes in taste or smell, cough, nausea, and dizziness. Some rare but serious side effects include: pounding heartbeat, chest pain, irregular heartbeat, rapid breathing, and confusion. Allergic reaction is rare but can result in rash, itchy tongue, severe dizziness, and trouble breathing (Burggraaf et al., 2001). This risk is avoided by only including participants in the study who have been prescribed salbutamol by their physician. A physician would not prescribe salbutamol if the side effects outweighed the benefits of the medication or the patient was allergic to the medication. If the participants do experience any serious side effects, immediate care will be provided by the researchers who are trained in standard first aid, and the participant will be taken to the nearest emergency room located approximately 250 meters away. On experimental days a physician will always be available to be onsite within ten minutes and at least one person collecting data will have a Standard First Aid with CPR/AED C certification. We have also created an emergency action plan and attached it to box 9.8.A of the application. This lab has a long track record of using this type of physician supervision with exercise studies in individuals with and without asthma, using higher intensity exercise, and even higher intensity exposures to air pollution like diesel exhaust ([H08-03055], [H09-01154], [H10-02028], [H10-00902], [H12-00539]). These studies have all been completed without incident. To ensure informed consent, a consent form will be sent to any individual interested in participating with enough time for them to review it and contact a member of the research team if they have any questions. This consent form will contain: the general purpose of the study and what the participant will be expected to do, foreseeable risks and potential benefits, alternatives to participation, contact information of the

researcher, assurance that the participant can end their participation at any time, and contact information of the relevant research ethics board (TCPS 2, 2018). The relevant research ethics board for this study is the Clinical Research Ethics Board (CREB) which reviews clinical research done at the University of British Columbia. At the first lab visit, a printed version of the consent form will be provided for the participant to review and sign. Upon documenting consent there will be: a restatement of the study purpose and description of the study tasks, sufficient prompts to encourage participants to ask questions, a reminder of the participant's right to refuse anything they find disturbing or uncomfortable, an assurance of their right to leave at any time without penalty, a statement indicating that by signing the consent form the participant is not waving any legal rights, and the provision of contact information of the researcher and CREB (TCPS 2, 2018).

Application of Findings

It is important to learn if salbutamol use exacerbates airway inflammation when exercising in ozone because chronic airway inflammation in people with asthma has been related to airway remodelling that increases the severity of future asthma attacks. In many cases, people with asthma and EIB are able to tolerate exercise without salbutamol use. This study will provide some information on whether this is a better strategy for preventing future more serious asthma attacks or not. This information can be used by physicians who prescribe salbutamol and by people with asthma and/or EIB.

Knowledge Translation

There are multiple stakeholders who may be interested in the results of this study including: clinicians, asthma and/or EIB patients, and air pollution policy makers. Publishing a paper in academic journals such as the European Respiratory Journal or the American Journal of

Respiratory and Critical Care Medicine would make this information available to clinicians and policy makers. Poster presentations at conferences such as the American Thoracic Society Conference would also enable communication of this information to clinicians and policy makers. Infographics that simplify the findings and recommendations could be used to communicate the information to non-expert stake holders such as patients with asthma and/or EIB. Web-based summaries, podcasts, and blogs could also be used to communicate this information to a larger population.

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