Cannabis Allergy in Occupationally Exposed Cannabis Workers, Recreational Users and Non-Users

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ABSTRACT

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Introduction: The expansion of the U.S. cannabis industry has created thousands of new jobs in cultivation, processing and distribution. While little is known about occupational hazards in the Cannabis industry, pilot studies suggest an increased risk of respiratory exposures and associated adverse health outcomes, including immunologic sensitization to Cannabis. These prior studies are confounded by a high rate of personal cannabis use among employees. Our current study addresses this limitation by characterizing the prevalence of work-related allergic and irritant respiratory symptoms in cannabis employees compared to recreation cannabis users and non-cannabis users without workplace exposure.

Methods: A cross-sectional study of cannabis workers, recreational users (defined as cannabis use ≥ 3 days/ week) and non-users was conducted. Cannabis workers (n=42) were recruited from two indoor cannabis grow facilities in Seattle, Washington. A demographically similar group of recreational cannabis users (n=20) and non-users (n=20) without history of occupational or personal cannabis cultivation were recruited from the surrounding community. A questionnaire was used to gather information on respiratory, ocular, nasal and dermal health symptoms as well as health history, cannabis use history, tobacco smoking status, and occupational exposure to dusts, gases and other respiratory hazards from all participants. A

subset of consenting employees with work-related symptoms (n = 21) and the non-occupationally exposed participants underwent measurement of spirometry, fractional exhaled nitrogen oxide (FeNO) and skin prick testing (SPT) for sensitization to cannabis / hemp and other common allergens. Adjusted odds ratios were determined using multivariate logistic regression to characterize the association between atopic symptoms and cannabis exposure in occupationally exposed and non-occupationally exposed participants.

Results: Ninety-seven percent (97%) of the employees surveyed were recreational cannabis users, with 81% (n = 25) smoking cannabis multiple times per day. Per study inclusion criteria, all of the recreational-cannabis users reported cannabis use at least three times per week and the non-users denied recent cannabis exposure. While the average age of participants across exposure categories were similar, the cannabis employees were more likely to be male and non-Hispanic white than the non-occupationally exposed participants (55% vs 33% and 81% vs 65% respectively).

Cannabis employees had an average 9.2 ppb (95% confidence interval 0.17 to 18.6, p-value 0.05) higher FeNO in comparison to the non-occupationally exposed participants. While there was a trend towards decreased spirometry in the cannabis employees vs non-occupationally exposed participants (mean FVC% predicted: 96.4% vs 101.7% and mean FEV1% predicted: 91.0% vs 96.8% respectively), these differences did not reach statistical significance. There were no significant differences in FeNO or spirometry between recreational users and non-users. The odds of having a positive skin prick test to cannabis was 2.97 (95% CI 1.11- 7.11, p-value 0.008) in the occupational vs non-occupational exposed group. Multivariate analysis demonstrated that occupational exposure to cannabis was associated with a 56% increase in FeNO among cannabis workers (95% CI 3% - 125%). Adjusting for medical history, tobacco use and demographics, the odds ratio of atopic or irritant symptoms among cannabis workers compared to non-users of cannabis without occupational exposure 30.06 (95% CI 5.77, 231.38; $p<0.001$).

Conclusions: Cannabis employees exhibited a higher FeNO, a trend towards decreased spirometry and increased odds of cannabis sensitization on SPT in comparison to recreational-cannabis users and non-users. More robust observation of these workers, the work environment

and their occupational exposures should be undertaken to develop appropriate preventive strategies and to develop respiratory protection standards for workers in this adolescent industry.

Because Spacetiger will always remind me to see the feets and stars of things.

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CHAPTER ONE: Background and Significance

Cannabis is a Fast-Growing Agricultural Industry

The study of cannabis and its derivatives has been considered taboo for decades owing to the fact that the US Federal Government has relegated it to Schedule I status[1] under the Controlled Substances Act. In spite of this, interest in the medicinal and recreational properties of cannabinoids has grown unabated in popular culture, among scientists, physicians of all disciplines, alternative therapy seekers and self-styled psychonauts, inspiring state governments to independently legalize the cultivation and consumption of cannabis products. The cannabis industry has experienced exponential growth over the last decade owing to legislative action at the state level to legalize or decriminalize cannabis products. As of February 2022, 37 states, four territories and the District of Columbia permit the use of cannabis products in some capacity[1]. Twenty of these states and territories, including Washington state, now permit non-medical use of cannabis products [Figure 1].

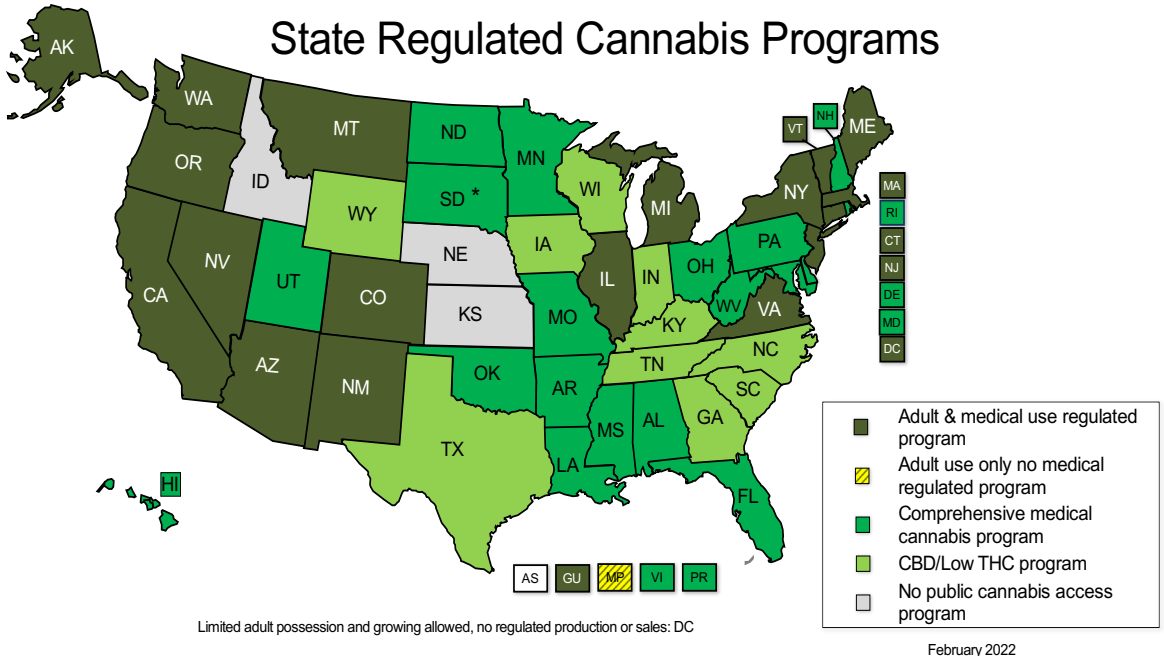


Figure 1: US State and Territory Regulation of Cannabis as of Feb 2022, NCSL Data

[1] Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse.

The result of these actions has been a boom in demand for high-quality legally-produced cannabis goods which has spawned both domestic and global agricultural industries to meet this demand. Global legal cannabis market size was valued at USD 22.1 billion in 2022 and is expected to expand at a compound annual growth rate of 25.3% in the next decade[2]. The North American market accounts for over 65% of the revenue share in the cannabis industry as of 2021 but Asian markets are the fastest-growing accounting for cultural increase in acceptance of cannabis in countries on that continent. Asian market growth is driven by several factors. Clinical trials in Japan and approval of cannabidiol (CBD) compounds for medicinal use may be encouraged by Japan's disproportionate geriatric population has been an important factor there. China has been growing hemp, a part of the cannabis plant used to make fibers. Its oils and by-products are frequently used in beauty products. Since 2019, the cultivation of cannabis has increased for the production of CBD to export for medicinal purposes. Thailand has been one of the forerunners in legalizing the use of cannabis for medical purposes in Asia[3].

Domestically, five states dominate the cultivation of cannabis [Figure 2]. In 2020, Washington state ranked fifth among the states for allocation of marijuana cultivation licenses[4].

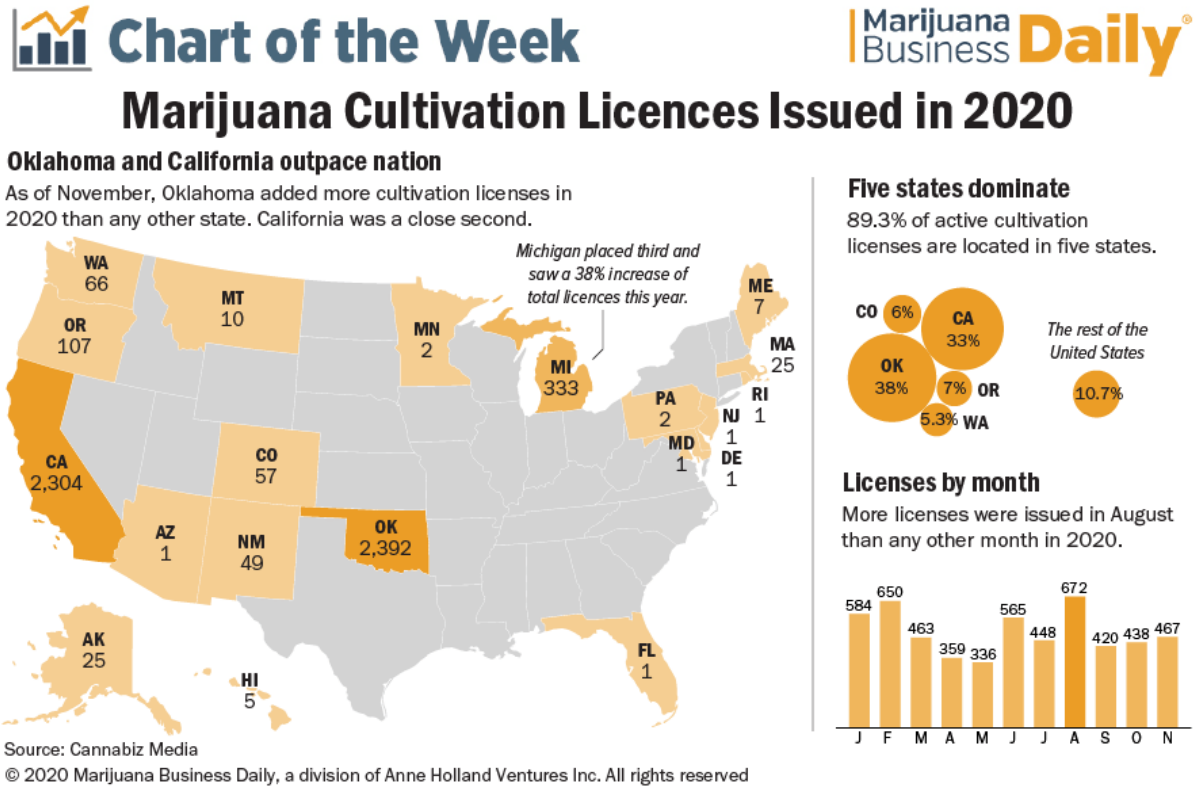


Figure 2: Marijuana Cultivation Licenses Issued in 2020. Reproduced with fair-use provisions for academic and scientific use.

The domestic cannabis industry achieved sales of USD $17.5 billion in 2020. Success has also been a driver of municipal revenues. Washington state collected a total of $559.5 million in legal marijuana income and license fees in fiscal year 2021, including $4.1 million in cannabis license fees[5]. These trends have been noticed by venture capitalists and institutions thus a variety of market investment funds have become available to retail investors over the last five years.

Cannabis Production is an Agricultural Occupation

The cannabis industry can be essentially organized into three categories. Growers and retailers cultivate and package cannabis products for sale to end consumers. Biopharmaceutical companies develop and market cannabis-based drugs subject to rigorous FDA oversight. Ancillary businesses provide products and services to cannabis companies without handling actual cannabis plants. Similarly, direct employment defines positions created specifically by and within the cannabis industry whereas related employment describes jobs that have developed as a result of the presence of the industry itself.

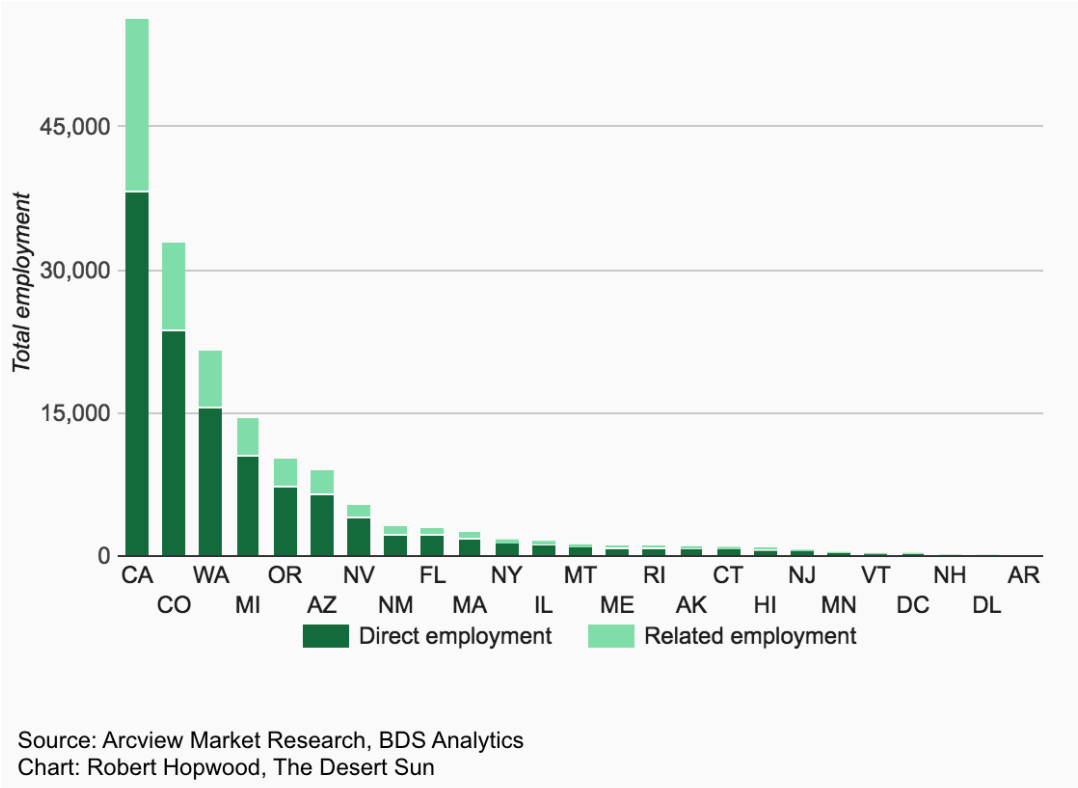


Figure 3: Cannabis Direct and Related Employment by State, 2020. Reproduced with fair-use provisions for academic and scientific use.

Enormous growth in the cannabis industry has increased demand for workers in every occupational segment. As of 2022, the cannabis industry employed more than 428,00 persons[6], over 24,000 of those in Washington state, with more than 15,000 directly employed in the Washington state cannabis industry by 2020 data[7] [Figure 3]. In 2017 the cannabis industry job growth rate was 445%[8].

The birth of the cannabis industry created a new subdivision of agricultural workers. As the industry entered adolescence, specific work tasks evolved. In stark contrast to the stigmatized era of the 1960s and '70s where basement horticulturalists cultivated plants in secret, street-level dealers distributed products illicitly and head shops sold paraphernalia for "tobacco use only", these roles now have clearly defined job tiles, task descriptions, occupational exposures and occupational risks.

Legal cannabis is cultivated outdoors, indoors and in greenhouses. Indoor cultivation is advantageous because it affords better control of pollination, prevention cross-contamination, ensures crop security and generally provides higher yields[9]. This work focused specifically on individuals who handle cannabis indoors as part of their occupation.

As with any agricultural process, cannabis cultivation begins with growing plants. Modern cultivation favors genetic consistency. Rather than growing plants from seeds, cuttings from mature plants of a selected strain are removed to produce clones[10]. These tasks are typically the purview of a "Master Grower" or an experienced "Trimmer" working under supervision. Master growers typically have post-graduate degrees, professional training or substantial experience with horticulture[11]. Trimmers are the most common entry-level position in cannabis cultivation and they perform a variety of tasks including removing buds and stems at harvest, trimming leaves for aesthetic appeal, and drying high quality flowers known as "buds". These operations typically take place directly within the "grow room" or "nursery"[2].

Once clones reach the vegetative stage they are transferred to larger pots, or in some cases a hydroponic system. They are watered and fertilized under grow lamps under the supervision of the growers. Grow lights on timed cycles - some of which emit UV radiation in addition to visible wavelengths - are used to induce flowering and further control yields[12].

[2] Job descriptions are not yet strictly codified across the industry so this terminology does carry the caveat of occasional variability between operations.

When fully matured, plants are harvested and dried. Hand trimmed buds may be individually packaged by "Packagers" (another entry-level role that engages in close handling of product) for sale to end-consumers for smoking[11]. Less appealing or lower quality product may be mechanically separated and then ground into coarse powders and packed into pre-rolled joints (marijuana cigars) or extracted for further processing to create high-THC concentrates or oils. These materials will be further refined by "Extraction Technicians" in a laboratory setting using modern chemistry techniques. Extraction technicians typically have post graduate level skills in analytic or synthetic chemistry[11]. Concentrates and oils will be used by chefs to produce edible cannabis products.

Ancillary roles include retail sales, logistic support, physical security, legal advisory, accounting, business operations, personnel management and public relations[13]. Facilities operation and safety is typically the purview of the master grower since cultivation usually does not take place during facility modifications[9].

A supplemental description of job tasks is adapted from Ghodsian in Appendix 1[14]. It bears mentioning that the job and tasks descriptions provided here are intended to supply a broad overview of the cultivation process. Smaller scale operations with few employees may utilize a single worker in several roles.

Cannabis and the Family *Cannabaceae*

Much of the knowledge of health effects of occupational exposure to cannabis is based on inferences from studies of plants from the same taxonomic family[15]. *Cannabis sativa*, first described in Europe is significantly different from *Cannabis indica*, named after India where it originated but both are valued for their high levels of cannabinoids including delta-9-tetrahydrocannadinol (THC) and cannabidiol (CBD). The hop plant, *Humulus lupulus*, is from the same family as the cannabis plant, *Cannabaceae*. Hemp is derived from the same plant genus and species as recreational marijuana, cannabis sativa, but has been bred to produce fiber rather than THC, the psychoactive component of cannabis. Some hemp varieties have been developed to produce CBD which has been shown in limited studies to have analgesic properties[16].

Epidemiology studies in both the hemp and hop industries report a high rate of respiratory illnesses, including byssinosis, chronic bronchitis, reactive airways dysfunction

syndrome, and asthma.[17,18,19] There have also been a few published studies of workers in forensic laboratories, law enforcement officers dismantling illegal grows, and employees of recreational Cannabis facilities.[20,21,22] These raise concern for allergic symptoms amongst cannabis workers, including eye irritation, nasal congestion, eczema, and asthma.

Hazards and Potential Health Effects of Occupational Exposure to Cannabis

Workers in indoor grow facilities are subject to a variety of potential hazards. As the industry enters its adolescence, understanding of the occupational hazards and industrial hygiene implications of cannabis cultivators has lagged. Some areas yet to be addressed include quantification of exposure to biological agents such as organic dusts, volatile organic compounds (VOCs), or pesticides, exposure to UV radiation and excessive noise levels[15]. These hazards are especially prominent among the growers, harvesters and processors in grow facilities who work in enclosed spaces [Figure 4, 5].

Figure 4: Cannabis processor working with ground product. ©Tahlequah Daily Press. Usage Rights: Creative Commons License

Figure 5: Cannabis workers tending plants at an indoor grow facility in Seattle, WA. ©Seattle Times. Usage Rights: Creative Commons License

A comprehensive guide was published by the Colorado Department of Public Health and Environment in early 2017 describing worker health and safety in the cannabis industry[23]. Health and safety professionals from government agencies and research institutes conducted walkthroughs of cannabis grow operations. Their report, based on expert judgment, identified a range of biological, chemical, and physical health hazards. It cited significant concern for potential hazardous respiratory exposures, including pesticides, molds, endotoxins, volatile organic compounds (VOCs), and particulate matter (PM). In addition to the findings in this report, a recent National Institute for Occupational Safety and Health (NIOSH) health hazard evaluation in a grow facility in Minnesota also reported diacetyl and 2,3-pentedione in screening air samples.[24]

Indoor cannabis cultivation facilities may achieve humidity levels of up to 70%, which strongly promotes the growth of molds. In a study of potential exposures to first responders, 40% of grow facilities had a fivefold increase in in levels of microscopic and viable spores compared to outdoor levels. 57% of grow rooms had at least a fivefold increase in levels of viable *Penicillium* or *Aspergillius* species[25].

These molds are most likely to be inoculated to the respiratory tract through inhalation but indoor cannabis workers can also be exposed to other dermal and respiratory allergens, irritants and sensitizers. Non-specific lipid transfer protein and thaumatin-like protein, components of the Cannabis plant, have both been proposed as potential allergens that can induce IgE specific antibodies[26].

Bacterial endotoxins, associated with byssinosis, have been correlated with levels of respirable dusts in agricultural settings including machine harvesting of vegetables and nuts, mowing of weeds and hemp processing facilities[27,28].

Chemical hazards are a fundamental part of industrial agriculture. In cannabis cultivation these include carbon dioxide, carbon monoxide, VOCs, pesticides and disinfectants. Workers encounter these potential chemical hazards as part of the cultivation process. Carbon dioxide is added to the air in some indoor cultivation facilities to enhance plant growth. Carbon monoxide is often present due to the exhaust from engines, including diesel generators, present in the cannabis farms. Pesticides may be applied with automated systems or directly applied by growers handling the plants. Pesticide residues may later contaminate the skin of cannabis processors. VOCs are plentiful in cannabis plants, the best known ones are the terpenes which

give marijuana its characteristic flavor and smell[29]. It has been proposed that reaction of terpenes with oxidizing agents found in indoor grow facilities could yield reactants which cause respiratory symptoms[9].

Washington state has noted an increase in the number of complaints of exposures to harmful substances in the cannabis industry[30]. Indoor-grow facility respiratory illness is gaining more attention in research circles. The causes of respiratory illness remain ambiguous but there is evidence that is multifaceted.

The National Institute for Occupational Safety and Health (NIOSH) in 2015 indicated that workers on cannabis farms were likely exposed to aerosolized bacteria and mold. Approximately, 40% of bacterial populations in this study were identified as endotoxin producing gram-negative bacteria that can increase the risk of hypersensitivity pneumonitis, chronic bronchitis, organic dust toxic syndrome, asthma, and allergic sensitization[31]. *Botrytis cinerea* was identified as the major mold species in personal air samples, and has been linked to hypersensitivity pneumonitis[32].

A separate case report describes the development of allergic hypersensitivity to *Cannabis sativa* pollen in a laboratory worker manifesting with intense rhinoconjunctivitis following two years of occupational exposure[33].

One group of German researchers suggests an immunologic response to cannabis and hashish in a laboratory technician and a physician who handled the two frequently for 25 and 16 years, respectively[34]. Neither were recreational cannabis users nor did they have history of atopy, yet they suffered from nasal congestion, sneezing, hand eczema, and mild asthma while working with cannabis. In the same study these patients were matched to twelve controls without history of exposure. Of the controls (8 atopic and 4 non-atopic), only two of the atopic persons produced a positive specific IgE.

Previous Work on Cannabis Allergy and Occupational Cannabis Exposure

The evidence describing occupational hazards of handling and working in close proximity to cannabis plants, particularly in environments where there was high risk for frequent prolonged exposure to respirable fine dusts from plant materials, is sparse but compelling. The suggested adverse dermal and respiratory outcomes associated with indoor grow facilities motivated Sack

et. al to investigate the association between cannabis exposure and health effects in workers at indoor cannabis growing facilities in Washington state[35]. That cross-sectional study sought to identify the prevalence of work-related allergic and respiratory symptoms in indoor cannabis cultivators at an indoor grow facility in Seattle, WA. A questionnaire was used to gather data on respiratory, ocular, nasal, and dermal symptoms. A subset of employees with work-related symptoms underwent repeated cross-shift and cross-week measurement of spirometry, fractional exhaled nitrogen oxide (FeNO), and skin prick testing for *Cannabis* sensitization. Exposure to *Cannabis* dust was classified based on self-described tasks, expert opinion, and exposure monitoring of particulate matter.

Twenty-two (71%) employees reported one or more work-related symptoms: 65% respiratory, 39% ocular, 32% nasal, and 26% dermal. There was a trend toward increased likelihood of work-related symptoms with increasing exposure to *Cannabis* dust. Of the employees with work-aggravated symptoms, 50% had borderline-high or high FeNO, 70% had abnormal spirometry, and 50% had evidence of *Cannabis* sensitization on skin prick testing.

A high proportion of employees with work-aggravated symptoms had findings consistent with probable work-related asthma based on high FeNO, airflow obstruction on spirometry, and *Cannabis* sensitization on skin prick testing. In spite of the high prevalence of work-related allergic and particularly respiratory symptoms in the employees, it was observed that 97% of the employees were recreational cannabis users [Table 1]. Due to the high incidence of recreational cannabis use among these workers, the relative influence of occupational versus recreational exposure to *Cannabis* dust on the respiratory health and sensitization status of these workers could not be resolved.

Study Motivation

This thesis seeks to address the confounding imposed by the frequent recreational use of cannabis among indoor grow facility workers in the previous pilot study performed by our group. By developing an appropriate control group of recreational cannabis users and non-users who do not have occupational exposure to cannabis, this work aims to determine and characterize the prevalence of *Cannabis* allergy, respiratory symptoms, lung function and airway inflammation in

these control groups, and to compare this with our previous study's cohort of occupationally exposed cannabis cultivators.

Specific Aims and Hypothesis

This work has two primary aims:

Aim 1: To identify and develop an appropriate control group of individuals without occupational cannabis exposure for comparison to the occupationally exposed group

Aim 2: To determine the prevalence of work-related allergic and irritant findings in cannabis employees compared to recreational cannabis users and non-users without occupational exposure

Hypothesis: Occupationally exposed cannabis workers will have higher prevalence of work related allergic and irritant findings than recreational users or non-users without occupational exposure.

As is often the case with new industries or technology, there is little understanding of the occupational hazards and potential health risks for workers in this adolescent industry. This work can serve as a pilot for a larger proposed study by providing evidence for occupational exposure as the key factor for allergic symptoms, despite recreational use status. It can motivate future studies of indoor grow facilities, particularly as the cannabis industry continues to grow, in order to define areas of focus for worker safety. It should be noted that because the cannabis industry exists in a legal gray area, governed by state laws, robust and consistent safety standards and regulation have yet to develop. This study can bring institutional focus to these deficiencies.

CHAPTER TWO: Methods

Study Design

This project utilized a cross-sectional study design to determine the prevalence of cannabis related allergic symptoms, respiratory symptoms, lung function changes and airway inflammation in recreational cannabis users and non-users who are not occupationally exposed to cannabis and to compare them to occupationally exposed individuals from indoor grow facilities. The cross-sectional study design is appropriate for evaluation of prevalence in the control group participants. In this study design, sample population is defined and individuals within that population are classified on the basis of existence of conditions of interest.[36] The collection of health metrics and the quantification of respiratory illness or immune mediated reactions to cannabis are the intended objective measurements. In previous work the chief exposure was occupational cannabis exposure and outcomes were respiratory symptoms or clinical findings. These exposures and outcomes were maintained for this study. Comparison groups consisted of workers occupationally exposed to cannabis, those exposed to cannabis in a non-occupational setting (i.e. recreational and/or medicinal cannabis users) and those with no significant exposure to cannabis.

Study Location and Subject Recruitment

Primary data collection for this study took place at the University of Washington Medical Center Roosevelt Clinic in suites equipped for pulmonary examination from June 2021 through August 2021. Participants from the control group engaged in all activities at this location. This study also leveraged the previously collected data from occupationally exposed cannabis workers. Those data were collected at two indoor cannabis producer/processor facilities in Washington State from October 2018 through January 2019. Both facilities have a relatively small workforce of approximately ~20-45 full time employees. Their job duties include cultivating the cannabis plant, harvesting, drying, curing, and fully processing it into a variety of consumer products – primarily buds and pre-rolled joints. The facilities consist of several grow rooms for different stages of growth, a drying room for drying the plants after harvest, a large processing room to

process the dry plants, and several smaller rooms for hand trimming, packaging/labeling, and an office area. One of the facilities also has a dedicated room for preparing cannabis extracts. In addition to growing their own product indoors, one of the two facilities also processes a large volume of outdoor grown product.

The occupational cohort was recruited from the employees at the two cannabis grow facilities. The control group was recruited from respondents to a request for research participants published in various print and electronic formats in the city of Seattle, Washington state.

The study was reviewed and approved by the University of Washington Institutional Review Board: *Study 04380: Respiratory Health and Indoor Air Quality in Washington's Cannabis Industry* for the occupational group, *Study 12771: Cannabis Allergy in Workers* for the non-occupationally exposed group.

Population and Inclusion Criteria

Based on demographics of the prior study in indoor cannabis workers, for the control populations a cohort of 40 male and female individuals, aged 21 – 70 years old, living in the Puget Sound region of Washington state were recruited from the community at large. These individuals were defined as the "Non-Occupationally Exposed Control Group". Subjects were intended to broadly match the characteristics of the 42-person occupational group.

These 40 individuals were split evenly between recreational cannabis users and non-users resulting in two groups: a group of 20 recreational users and a group of 20 non-users, both without occupational cannabis exposure. Subjects were compensated for their participation.

Control group subject inclusion and exclusion criteria were as follows:

Inclusion criteria

i. Potential subjects must be between 21-70 years of age and live in the Puget Sound region of Washington state
ii. Participants must provide informed consent and sign a consent form
iii. For the non-exposed subjects:

a. Must not have used cannabis in the past 30 days
b. Have no history of occupational exposure to Cannabis

iv. For recreational cannabis users:
a. At least daily use of cannabis for the past 90 days
b. Have no history of occupational exposure to cannabis

v. Agreement to avoid anti-histamine use prior to testing

Exclusion criteria

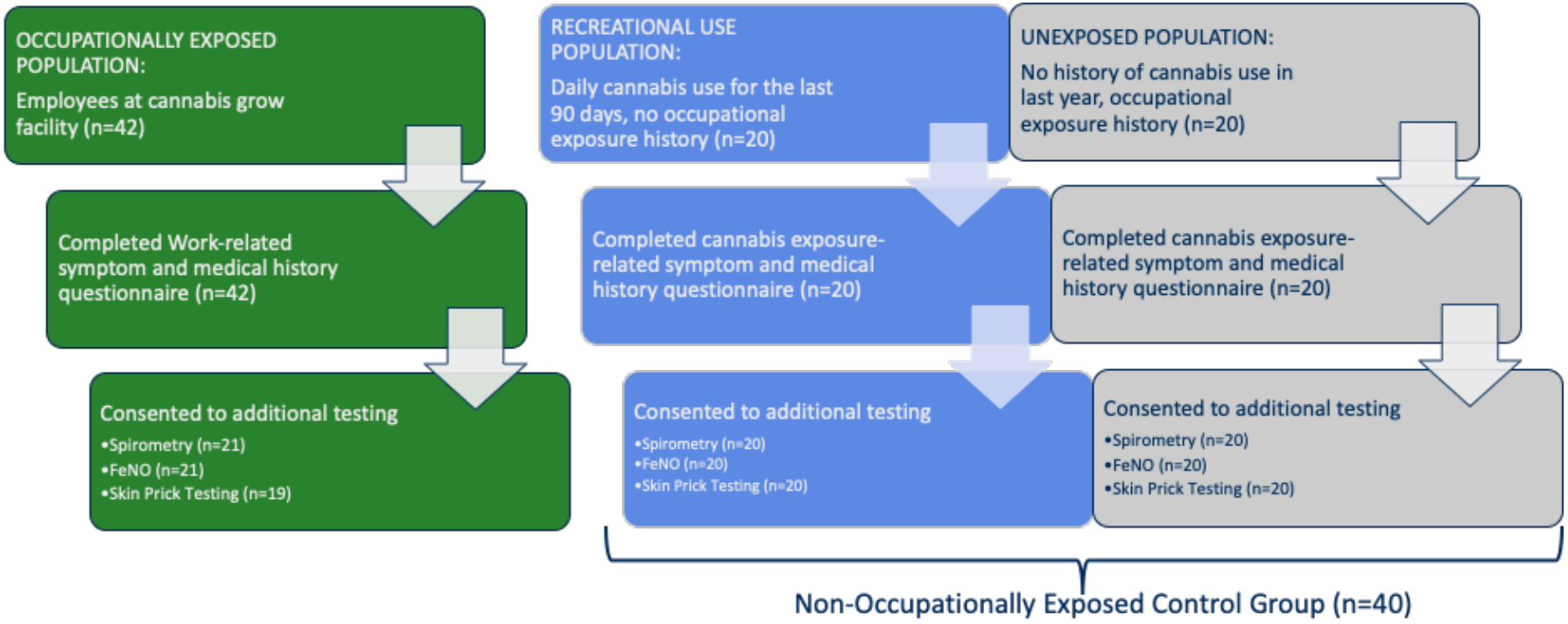
i. Current or prior history of occupational exposure to cannabis
ii. Current use of illicit inhalants (cocaine, methamphetamine, volatile paints, etc.)
iii. Participant withdraws consent to participate in the study
iv. For the non-exposed cohort:
a. Current cannabis use
b. Home cannabis cultivation
c. Current environmental exposure to cannabis plants or smoke
v. For recreational cannabis users:
a. Infrequent (less than daily) use of cannabis
b. Home cannabis cultivation
c. Current or prior history of occupational exposure to cannabis

Data from 42 indoor cannabis facility workers who participated in the original study by Sack et. al.[35] was utilized for the occupationally exposed population.[3]

Each participant from all three groups completed an exposure-related symptom and medical history questionnaire. Those who consented were then administered additional respiratory and allergic testing. This is illustrated in Figure 6 and described in detail in the next section.

[3] Sack et. al. collected data at two facilities but reported results using data from only one of those facilities. This thesis uses the entirety of the data collected by Sack et. al. for their project.

Figure 6: Cross-sectional study design.



Materials, Equipment and Techniques

Each participant was assigned a unique anonymous identifier for the purposes of study records-keeping. All collected data was linked by the anonymous identifiers and recorded in a secure database.

Health Symptoms and Medical History Questionnaire

A questionnaire adapted from the European Community Respiratory Health Survey (Appendix 2) was administered to each non-occupationally exposed group participant (n=40)[37]. The questionnaire collected basic sociodemographic information and information on respiratory, dermal, nasal and ocular health symptoms as well as personal medical history, family medical history, and current and prior medication use. The questionnaire requested detailed information on tobacco and cannabis exposure and use. Occupational history, current environmental and occupational exposures, and details of symptoms experienced when handling cannabis were evaluated. The instrument was designed to present questions analogous to those asked of the occupational cohort in the Sack et. al. study, with a particular focus on symptomatic events associated with handling, breathing odors from, vaporizing, smoking or ingesting cannabis products. Sack et. al. describes data collection for the cannabis workers in detail[35].

Questionnaire data were collected and managed using REDCap electronic data capture tools hosted at The University of Washington in Seattle, WA.[38,39] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Most of the questionnaires (n=22) were administered using a computer interface. However, due to technical difficulties experienced by participants a portion of the questionnaires (n=18) were completed by hand on paper and later entered manually by this author for analysis.

The chief outcome metric, atopy with handling of or when working with cannabis products, was considered positive if participants responded in the affirmative to questions such as ‘Do you experience red or watery eyes when handling cannabis products?’, ‘Have you ever

experienced wheezing when handling cannabis products?' A personal history of asthma or atopy would be considered positive with an affirmative response to questions such as 'Has a doctor ever diagnosed you with asthma?' or 'Do you have seasonal allergies that require you to use antihistamines?' Table 1 provides detailed descriptions of the questionnaire responses and their associated categories.

Evaluation of Pulmonary Inflammation: Measurement of Fractional Exhaled Nitric Oxide (FeNO)

Measurement of fractional exhaled nitric oxide (FeNO) is a non-invasive method to evaluate the presence of and severity of airway inflammation. A portable electrochemical analyzer, NIOX VERO (Morrisville, NC), was used to obtain FeNO measurements from each participant. Participants were instructed on the proper technique by a trained physician then encouraged to inhale through a personal mouthpiece to total lung capacity and exhale slowly with a steady pressure. Quality control was performed for the unit each day of data collection following NIOX VERO specifications. Airway inflammation was determined through measurement of FeNO in accordance with ATS guidelines[40].

Evaluation of Pulmonary Function

Pulmonary function testing was performed with participants in the seated position using an NDD EasyOne Air portable spirometer (Andover, MA, USA) pre- and post- bronchodilator (15mins after administration of albuterol by meter dose inhalation). Repeatability was verified according to ATS guidelines outlined by Miller.[41] Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio were obtained. These results are compared to the predicted values given by National Health and Nutrition Examination Survey (NHANES) III reference equation.[42] These are expressed as the $FEV1_{\%Predicted}$ $FVC_{\%Predicted}$ and $FEV1/FVC_{\%Predicted}$. A fixed cutoff of 80% of predicted was be used to define normal.

Decreased pulmonary function was classified using ATS criteria as in Pellegrino et. al.[43]:

i. Obstructive: FEV1/FVC below 0.70
ii. Restrictive: FEV1 or FVC below 80% with a FEV1/FVC equal or above 0.70
iii. Mixed: FEV1 and FVC below 80% with a FEV1/FVC below 0.70

Table 1: Questionnaire prompts for outcome metrics for atopy with cannabis exposure and independent variables of medical and allergy history.

<table>
<tr>
<td>Outcome:

Does the participant have any self-reported symptoms either at work or with handling?

Did the participant experience any symptoms in the last 12 months?</td>
<td>Independent Variable:

Atopic history such as eczema, history or assessment of asthma, history of allergy, ‘have you ever’ questions</td>
</tr>
<tr>
<td rowspan="4">Questionnaire prompt:

1. Do you experience red, watery or itchy eyes [at work or] with handling of cannabis products?
2. Do you experience a runny nose or sneezing…?
3. …shortness of breath…
4. …wheezing…
5. …cough or congestion…
6. Have you experienced coughing or wheezing in the last 12 months?
a. Have you been breathless when wheezing?
b. Have you experienced the wheezing or whistling without a cold?
7. Have you had tightness in your chest in the last 12 months?
8. Been awoken by attack of shortness of breath in the last 12 months?
9. Been awoken by attack of coughing in the last 12 months?
10. Had shortness of breath at rest in the last 12 months?
11. Had shortness of breath after strenuous activity in the last 12 months?
12. Had an itchy rash for at least 6 months?
a. Have you had this rash in the last 12 months?
b. Has it affected skinfolds?
c. Has it affected your hands / wrists / arms?
13. Have you had itchy or watery eyes in the past 12 months?
a. Are you using any medications for your eyes?
14. Have you had nasal irritation in the past 12 months?
a. Was this accompanied by itchy watery eyes?
b. Are you taking any medications for nasal symptoms?
15. Have you had an attack of asthma at any time in the last 12 months?</td>
<td>Questionnaire prompts:

1. Do you have or have you ever had asthma?
2. Do you have hayfever?
3. Do you have eczema (skin allergies)?
4. Have you ever had eczema?
5. Do you have nasal allergies incl hayfever?
6. Do you have any food allergies?
7. Have you ever been diagnosed with asthma by a doctor?</td>
</tr>
<tr>
<td>1. Do you have eczema (skin allergies)?
2. Have you ever had eczema?

If either are positive then the participant has a positive eczema history.</td>
</tr>
<tr>
<td>1. Do you have hayfever?
2. Do you have nasal allergies including hayfever?
3. Do you have any food allergies?

If any are positive then participant has a positive allergy history.</td>
</tr>
<tr>
<td>1. Do you have asthma?
2. Have you ever had asthma?
3. Have you ever been diagnosed with asthma by a doctor?

If any are positive then the participant has a positive asthma history.</td>
</tr>
<tr>
<td>If any of the above are positive then participant is considered to have a “positive” response for sensitivity to cannabis.</td>
<td>If any of the above categories are positive then the participant is considered to have a history of atopy.</td>
</tr>
</table>

Diagnosis was assigned to subjects demonstrating response to bronchodilator therapy as follows from Johnson[44]:

i. Obstructive case, response to bronchodilator:
   a. Asthma: FEV1 increase > 12% or FVC increase > 200 ml
   b. Pulmonary disease with irreversible obstruction: No response
ii. Mixed case, response to bronchodilator:
   a. COPD: Increase in FVC to > lower normal predicted limit
   b. Restrictive pulmonary disease: no response

Statistical comparisons between the occupationally exposed and unexposed groups did not include the post-bronchodilator data because the occupationally exposed group did not receive bronchodilator testing. Diagnoses assigned to the subjects without occupational exposure were ultimately not utilized for this study however they were stored for use in future studies.

Both FVC and FEV1 are expressed in liters and adjusted to percent predicted based on subjects' age, gender, height, and race. Weight and height are used to calculate body mass index (BMI). Consequently, subjects' height and weight were measured and recorded prior to testing.

Evaluation of Sensitization to family Cannabaceae: Skin Prick Testing

A one-time skin prick test was performed on each subject for hemp and selected allergens found in the Pacific Northwest region of the USA. Allergen extracts were purchased from ALK-Abello, Inc. (Round Rock, TX, USA), and included cat dander, cockroach antigen, and dust mites. The hemp slurry (Preroll Mix #1; Provided by LeBlanc CNE, Seattle, WA) was prepared with a ground mixture of leaves and flowers to make a fine powder and mixed with 1-2mL of sterilized saline. A 10% histamine solution was used as a positive control and sterilized saline solution as a negative control. The largest wheal diameter was assessed 20 min after application to the forearm. A positive response was defined as a wheal diameter greater than or equal to 3 mm, erythema or pseudopodia with no reaction to the negative control (to rule out dermatographism) and positive reaction to histamine (to rule out non-responsiveness).

Participants were screened before testing for use of antihistamine medications in the last 48 hours.

The occupationally exposed cohort in the previous study by Sack et. al.[35] were additionally tested against mold species *Helminthosporium, Alternaria, Penicillium,* and *Aspergillus* which are commonly found in the Pacific Northwest. Cannabis slurries were prepared using two strains of cannabis from the occupationally exposed participants' facilities.

Data Analysis, Statistical Methods

Questionnaire data for the control populations was either recorded directly into the REDCap instrument (Appendix 2) through the computer interface by study participants or manually entered by this author from handwritten paper questionnaires completed by participants at the study site. Native REDCap tools were used to generate a portion of the descriptive tables describing sociodemographics, medical history, and occupational history profiles. The remainder of the questionnaire data were exported and pre-processed using Excel (Microsoft, Redmond WA). These data were then collated into a data table by combing the results of FeNO testing, pulmonary function testing and skin prick testing. This was imported into RStudio version 1.3.1093 where subsequent analyses were performed (RStudio PBC, Boston, MA). RStudio is an integrated development environment for the open-source R statistical package.

Simple calculations were performed to determine the prevalence of asthma, atopy, eczema, tobacco smoking, cannabis use, and atopic symptoms with cannabis exposure.

Comparisons of means between groups were performed considering occupational exposure and ignoring recreation use status (two groups) and accounting for recreational use status (three groups). Comparisons of means for continuous variables, such as FeNO and pulmonary function values, were performed using linear model analysis of variance (ANOVA) at the alpha = 0.05 level. Tests of significance for categorical or binary variables, such as the outcome variable of allergic or irritant symptoms with exposure or the results of skin prick testing were performed with Pearson's Chi-squared test. In some cases of stratified comparisons, where sample sizes become small, Fisher's exact test is instead applied.

To verify that that the control group was a good relative approximation of the occupational group, the Chi-square test was used to compare means along sociodemographic

lines and between social histories of participants, again considering only occupational cannabis exposure and then considering both occupational cannabis exposure and recreational use. Again, all statistical tests were performed at the alpha = 0.05 significance level.

Measures of association

In two group comparisons (occupationally exposed vs non-exposed) crude odds ratios were calculated relative to the unexposed (no occupational exposure) group. For three group comparisons (occupationally exposed, recreational users without occupational exposure and non-users without occupational exposure), odds ratios were computed relative to non-cannabis users. For comparisons across race and sex we calculated from Caucasian race and male sex. Similarly, for medical history or symptomatic results the point of comparison is the case where the predictor of interest is absent.

Linear Regression Modeling of FeNO and Pulmonary Function

This work sought to define the relationship between health measurements and occupational exposure to cannabis status. This was explored using a multiple linear regression model, examining relationships between FeNO as the dependent variable, occupational exposure to cannabis as the predictor of interest (POI), and biometrics, the presence or absence of atopy, and tobacco smoking status as confounders versus precision variables.

The model was defined a-priori, drawing on expert knowledge of physiology and previous work on modeling of FeNO[35,45]. The general model for FeNO is defined as:

$$\text{FeNO} = F(\text{cannabis exposure status, age, sex, height, atopy})$$

Note that other scientists have used gender in their models but only observed an effect when they had large sample sizes, while height and gender have been shown to be important variables[45,46]. Positive specific IgE from blood testing has been used in prior work to define atopy. In this project, self-report of asthma, hay fever or eczema (see Table) 1 is used as a proxy. Including tobacco smoking in the basic model for FeNO, the relationship becomes:

FeNO = *F*(cannabis exposure status, age, sex, height, atopy, tobacco smoking status)

Variations of the model equation to search for interactions and confounders were explored. The relationship between FeNO and occupational cannabis exposure status was explored both ignoring and accounting for recreational marijuana use with and without occupational exposure to cannabis. Occupational exposure to cannabis, recreational cannabis use status, sex, a history of atopy (equivalent to the set of eczema history, allergy history and or asthma history), and tobacco smoking status were treated as categorical co-variates. FeNO is a continuous outcome variable in this relationship. Age and height are continuous covariates.

Initial analysis of FeNO between groups demonstrated right skew data therefore a log-transformation was applied to improve normality. We observed evidence of a decreasing trend in log-FeNO with both age and log-age in the male occupational group and in both sexes in the recreational group, with an increasing trend with age in non-users, and the female occupational group. A linear relationship with tobacco smoking was also observed. This analysis is presented in Appendix 5.

Due to small sample sizes, the cohort of past tobacco smokers and current tobacco smokers was consolidated into a single group, demonstrating an increase in log-FeNO with increasing pack-years in the non-users, a decrease in the recreational group and an increase in the occupationally exposed group.

The following model was defined based on the preliminary analysis:

$$\log(FeNO) = \beta_0 + \beta_{1a}X + \beta_{1b}X + \beta_2X + \beta_3X + \beta_4X + \beta_5X + \beta_6X$$

Where:

β_0 is the intercept

β_1 is the coefficient for either

occupational exposure (a)

or recreational use exposure (b)

β_2 is the sex coefficient

β_3 is the age coefficient

β_4 is the height coefficient

β_5 is the coefficient for positive report of work or handling related atopic symptoms

β_6 is the coefficient for tobacco smoking status

The same approach was used to examine the relationship between pulmonary function measures and occupational cannabis exposure. Here we defined $FEV1_{\%Predicted}$ as the dependent variable with tobacco smoking status and occupational exposure to cannabis status as independent categorical variables.

$$FEV1_{\%Predicted} = F(\text{cannabis exposure status, tobacco smoking status})$$

Traditionally, FEV1 is a function of BMI as well however these data were not fully available from the occupationally exposed group. As with FeNO, variations of the models were explored considering occupational exposure to cannabis and recreational cannabis use as distinct categories in the first case and ignoring recreational cannabis use in the non-occupationally exposed group in the second. Interactions with tobacco smoking were also explored.

Initial analysis of $FEV1_{\%Predicted}$ did not demonstrate excessive skewness so a simple linear model relating $FEV1_{\%Predicted}$ to occupational status and tobacco smoking was examined:

$$FEV1_{\%\mathrm{Predicted}} = \beta_0 + \beta_{1a}X + \beta_{1b}X + \beta_2X$$

Where:

β_0 is the intercept

β_1 is the coefficient for either

occupational exposure (a)

or recreational use exposure (b)

β_2 is the coefficient for tobacco smoking status

Logistic Regression: Adjusted Odds Ratios

The relationship between occupational exposure to cannabis and report of dermal, ocular, nasal, and respiratory symptoms was determined using multiple logistic regression models:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X + \varepsilon_n$$

Where β_o is the estimated log odds ratio of reporting atopic symptoms for the reference condition of no occupational cannabis exposure and β_1 represents the change in log odds ratio with occupational cannabis exposure. ε_n represents the sum of the residuals. Age, sex, ethnicity, history of asthma, eczema or allergy and tobacco smoking status were considered as confounding covariates thus an adjusted model was used:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X + \beta_2 X + \beta_3 X + \beta_4 X + \beta_5 X + \beta_6 X + \beta_7 X + \beta_8 X + \varepsilon_n$$

Where β_2 adjusts for age, β_3 adjusts for sex, β_4 adjusts for ethnicity, β_5 adjusts for a history of asthma, β_6 adjusts for a history of eczema, β_7 adjusts for a history of allergy and β_8 adjusts for tobacco smoking. Due to limited sample size, age was divided into three categorical groups: 21-37 years, 37-52 years and 52-70 years. Ethnicity was considered as white and non-white, again due to sample size limitations. A version of this model exploring three comparison groups (occupational exposure, recreational exposure and non-use without occupational exposure), wherein recreational cannabis use was an additional covariate was also defined.

CHAPTER THREE: Results

Descriptive Tables and Demographics

42 participants were successfully recruited from the community surrounding Seattle, Washington between June and August 2021. Two participants were disqualified. One participant was removed from the recreational user group due to recent antihistamine use. One participant was removed from the non-user group due to third-trimester pregnancy presenting unacceptable risk to participant health and safety in the judgement of the primary investigator. All participants who met inclusion criteria participated fully in every aspect of the study. Data collected in the previous study of Sack et. al.[35] in occupationally exposed cannabis workers were also used. These included health symptom questionnaires from 42 workers in an indoor grow facility. All 42 completed the symptom questionnaire. 21 proceeded to pulmonary testing (spirometry and FeNO measurement) and 19 underwent skin prick testing.

Of the 40 non-occupational participants, 20 were at least daily users of cannabis products without prior occupational experience in the cannabis industry. The remainder either denied ever using cannabis products (n=7) or had not used cannabis products in the last 30 days (n=13). No participants from either group reported home marijuana cultivation, the preparation of cannabis products at home or the use of illicit inhalants.

The mean age of the entire non-occupational group was 36.2 years (standard deviation (SD) +/- 14.47) with mean age of non-users 37.2 (SD +/- 16.24) and recreational users 35.2 (SD +/- 12.3) years respectively. 62.5% (n=25) of participants self-identified as White or Caucasian, but not Hispanic or Latino, 17.5% (n=7) as Hispanic or Latino, 7.5% (n=3) as Black or African-American, but not Hispanic or Latino and 12.5% (n=5) as Asian. 65% (n=26) were female and 35% (n=14) were male. One participant did not self-identify as either sex for unknown reasons and this person was considered to be male for data analysis. 11 participants (27.5%) reported either current or prior tobacco smoking.

No significant difference was observed between recreational cannabis users and non-users using linear ANOVA to compare age means and the chi-squared test to compare counts within categories looking at demographic metrics. There was no significant difference between occupationally exposed to cannabis and non-occupationally exposed groups, ignoring

recreational cannabis use status. Accounting for recreational cannabis use status there was again no significant difference demographically between the three groups.

A significant difference in tobacco smoking history and habits was observed between the occupational and non-occupational groups. 29 of 42 cannabis workers (69.1%) were either current or former tobacco smokers, with 17 (40.5%) reporting smoking tobacco at least once in the last 30 days compared to the non-occupational group of whom only two (5%) were current tobacco smokers and only eleven (27.5%) reported any tobacco smoking history ($p < 0.001$).

Cannabis workers also reported near-universal use of cannabis products (n=41, 97.6%).

This is summarized in Tables 2, 3 and 4. Additional demographic tables are supplied in Appendix 4.

Table 2: Control group demographics, smoking history and cannabis usage. 1. Linear model ANOVA 2. Pearson's Chi-squared test

	Non-User (N=20)	*Recreational (N=20)*	*Total (N=40)*	*p- value*
Age				0.668[1]
N	20	20	40	
Mean (SD)	37.2 (16.62)	35.2 (12.3)	36.2 (14.47)	
Range	21.0 - 68.0	21.000 - 57.0	21.000 - 68.0	
Sex				0.185[2]
Female	15 (75.0%)	11 (55.0%)	26 (65.0%)	
Male	5 (25.0%)	9 (45.0%)	14 (35.0%)	
Reported ethnicity				0.295[2]
Asian	3 (15.0%)	2 (10.0%)	5 (12.5%)	
Black or African-American, but not Hispanic or Latino	0 (0.0%)	3 (15.0%)	3 (7.5%)	
Hispanic or Latino	3 (15.0%)	4 (20.0%)	7 (17.5%)	
White or Caucasian, but not Hispanic or Latino	14 (70.0%)	11 (55.0%)	25 (62.5%)	
Highest Education Level				0.495[2]
4-year college graduate	10 (50.0%)	9 (45.0%)	19 (47.5%)	
Grade 1-11	0 (0.0%)	1 (5.0%)	1 (2.5%)	
High school or GED	0 (0.0%)	2 (10.0%)	2 (5.0%)	
More than 4-year college degree	7 (35.0%)	5 (25.0%)	12 (30.0%)	
Some college or 2-year degree	3 (15.0%)	3 (15.0%)	6 (15.0%)	
Tobacco smoking status				0.145[2]
Current (Past 30 days)	0 (0.0%)	2 (10.0%)	2 (5.0%)	
Formerly (More than 30 days ago)	3 (15.0%)	6 (30.0%)	9 (22.5%)	
Never	17 (85.0%)	12 (60.0%)	29 (72.5%)	
Last reported cannabis use				< 0.001[2]
Never used marijuana	7 (35.0%)	0 (0.0%)	7 (17.5%)	
Used marijuana in the last 30 days	0 (0.0%)	20 (100.0%)	20 (50.0%)	
More than 30 days ago	13 (65.0%)	0 (0.0%)	13 (32.5%)	

Table 3: Demographic, smoking status and cannabis use comparison of occupational and non-occupational groups. 1. Linear model ANOVA 2. Pearson's Chi-squared test

	Non-Occupational (N=40)	*Occupational (N=42)*	*Total (N=82)*	*p value*
Age				0.077[1]
N	40	42	82	
Mean (SD)	36.2 (14.47)	31.5 (8.38)	33.8 (11.91)	
Range	21.0 - 68.0	21.0 - 56.0	21.0 - 68.0	
Sex				0.345[2]
Female	26 (65.0%)	23 (54.8%)	49 (59.8%)	
Male	14 (35.0%)	19 (45.2%)	33 (40.2%)	
Reported ethnicity				0.176[2]
Alaskan native	0 (0.0%)	1 (2.4%)	1 (1.2%)	
Asian	5 (12.5%)	1 (2.4%)	6 (7.3%)	
Black or African-American, but not Hispanic or Latino	3 (7.5%)	1 (2.4%)	4 (4.9%)	
Hispanic or Latino	7 (17.5%)	5 (11.9%)	12 (14.6%)	
White or Caucasian, but not Hispanic or Latino	25 (62.5%)	34 (81.0%)	59 (72.0%)	0.176[2]
Highest Education Level				0.016[2]
4-year college graduate (Bachelor's degree)	19 (47.5%)	16 (38.1%)	35 (42.7%)	
Grade 1-11	1 (2.5%)	2 (4.8%)	3 (3.7%)	
High school or GED	2 (5.0%)	8 (19.0%)	10 (12.2%)	
More than 4-year college degree (Graduate, Professional School, Master's, Ph.D. etc.)	12 (30.0%)	3 (7.1%)	15 (18.3%)	
Some college or 2-year degree	6 (15.0%)	13 (31.0%)	19 (23.2%)	
Tobacco smoking status				< 0.001[2]
Current (Past 30 days)	2 (5.0%)	17 (40.5%)	19 (23.2%)	
Formerly (More than 30 days ago)	9 (22.5%)	12 (28.6%)	21 (25.6%)	
Never	29 (72.5%)	13 (31.0%)	42 (51.2%)	
Last reported cannabis use				< 0.001[2]
Never used marijuana	7 (17.5%)	1 (2.4%)	8 (9.8%)	
Used marijuana in the last 30 days	20 (50.0%)	41 (97.6%)	61 (74.4%)	
Used more than 30 days ago	13 (32.5%)	0 (0.0%)	13 (15.9%)	

Table 4: Demographic, smoking history and cannabis use comparison between occupationally exposed cannabis workers, recreational cannabis users and non-users without occupational exposure. 1. Linear model ANOVA 2. Pearson's Chi-squared test.

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
Age					0.183[1]
N	20	42	20	82	
Mean (SD)	37.150 (16.624)	31.500 (8.382)	35.150 (12.296)	33.768 (11.908)	
Range	21.000 - 68.000	21.000 - 56.000	21.000 - 57.000	21.000 - 68.000	
Sex					0.279[2]
Female	15 (75.0%)	23 (54.8%)	11 (55.0%)	49 (59.8%)	
Male	5 (25.0%)	19 (45.2%)	9 (45.0%)	33 (40.2%)	
Reported ethnicity					0.162[2]
Alaskan native	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (1.2%)	
Asian	3 (15.0%)	1 (2.4%)	2 (10.0%)	6 (7.3%)	
Black or African-American, but not Hispanic or Latino	0 (0.0%)	1 (2.4%)	3 (15.0%)	4 (4.9%)	
Hispanic or Latino	3 (15.0%)	5 (11.9%)	4 (20.0%)	12 (14.6%)	
White or Caucasian, but not Hispanic or Latino	14 (70.0%)	34 (81.0%)	11 (55.0%)	59 (72.0%)	
Highest Education Level					0.076[2]
4-year college graduate (Bachelor's degree)	10 (50.0%)	16 (38.1%)	9 (45.0%)	35 (42.7%)	
Grade 1-11	0 (0.0%)	2 (4.8%)	1 (5.0%)	3 (3.7%)	
High school or GED	0 (0.0%)	8 (19.0%)	2 (10.0%)	10 (12.2%)	
More than 4-year college degree (Graduate, Professional School, Master's, Ph.D. etc.)	7 (35.0%)	3 (7.1%)	5 (25.0%)	15 (18.3%)	
Some college or 2-year degree	3 (15.0%)	13 (31.0%)	3 (15.0%)	19 (23.2%)	
Tobacco smoking status					< 0.001[2]
Current (Past 30 days)	0 (0.0%)	17 (40.5%)	2 (10.0%)	19 (23.2%)	
Formerly (More than 30 days ago)	3 (15.0%)	12 (28.6%)	6 (30.0%)	21 (25.6%)	
Never	17 (85.0%)	13 (31.0%)	12 (60.0%)	42 (51.2%)	

Prevalence of Work or Handling Related Health Symptoms

Participants were asked to report on their personal history of dermal, ocular, nasal and respiratory symptoms, pertinent atopic or pulmonary medical diagnoses and treatments as well as specific symptoms they associate with handling or use of cannabis products (Appendix 2). Cannabis handling questions were intended to be analogous to the work-related symptom queries of the health symptoms baseline questionnaire utilized by Sack et. al. that aimed to identify the prevalence of work-related health symptoms[35]. Historical questions were intended to be analogous to the questions from that questionnaire that sought to identify the prevalence of overall symptoms. These prevalence data are presented comprehensively in Appendix 4.

There was a significant difference between recreational cannabis users and non-users ($p=0.004$) observed in reported symptoms with handling of cannabis products among participants without occupational exposure. 80% (n=16) of recreational users vs. 35% (n=7) of non-users reported at least one symptom with cannabis handling. A significant difference between groups was also observed between the cannabis workers and the control group without occupational exposure, ignoring recreational cannabis use ($p < 0.001$) with greater than 90% of cannabis workers (38 of 42) reporting at least one work related symptom compared to 57.5% (23 of 40) participants without occupational cannabis exposure reporting the symptoms with cannabis exposure. This significant different in groups is still observed when the control group is split into cannabis non-users and recreational users and all three are compared, however there was not a significant difference in symptom prevalence comparing only occupationally exposed workers to recreational cannabis users (Tables 5-8, see also Appendix 4).

Table 5: Report of any work or handling related symptoms; comparison between recreational cannabis users and non-users. 1. Pearson's Chi-squared test

Reported work-related symptoms, symptoms during handling or cannabis associated atopic symptoms in last 12 months?	*Non-User (N=20)*	*Recreational users without occupational exposure (N=20)*	*Total (N=40)*	*p value*
No	13 (65.0%)	4 (20.0%)	17 (42.5%)	< 0.004[1]
Yes	7 (35.0%)	16 (80.0%)	23 (57.5%)	

Table 6: Report of any work or handling related symptoms; comparison between cannabis workers, and those without occupational exposure. 1. Pearson's Chi-squared test

Reported work-related symptoms, symptoms during handling or cannabis associated atopic symptoms in last 12 months?	*No occupational exposure (N=40)*	*Occupation-ally Exposed (N=42)*	*Total (N=82)*	*p value*
No	17 (42.5%)	4 (9.5%)	21 (25.6%)	< 0.001[1]
Yes	23 (57.5%)	38 (90.5%)	61 (74.4%)	

Table 7: Report of any work or handling related symptoms; comparison between cannabis workers and recreational users only. 1. Pearson's Chi-squared test

Reported work-related symptoms, symptoms during handling or cannabis associated atopic symptoms in last 12 months?	*Recreational users without occupational exposure (N=20)*	*Occupation-ally Exposed (N=42)*	*Total (N=62)*	*p value*
No	4 (20.0%)	4 (9.5%)	21 (25.6%)	0.456[1]
Yes	16 (80.0%)	38 (90.5%)	61 (74.4%)	

Table 8: Report of any work or handling related symptoms; comparison between occupational cannabis workers, recreational users and non-users. 1. Pearson's Chi-squared test

Reported work-related symptoms, symptoms during handling or cannabis associated atopic symptoms in last 12 months?	*Non-User (N=20)*	*Occupation-ally Exposed (N=42)*	*Recreational users without occupational exposure (N=20)*	*Total (N=82)*	*p value*
No	13 (65.0%)	4 (9.5%)	4 (20.0%)	21 (25.6%)	< 0.001[1]
Yes	7 (35.0%)	38 (90.5%)	16 (80.0%)	61 (74.4%)	

Symptom prevalence with handling of cannabis is higher in recreational cannabis users compared to non-users and highest in occupationally exposed cannabis users compared to either recreational users or non-users without occupational exposure. The significant differences when comparing occupational and non-occupational groups with handling of cannabis were observed with reports of nasal and sinus symptoms and shortness of breath. 5% of the non-occupational group (n=2) compared to 38.1% (n=16) of the cannabis workers ($p < 0.001$) reported ocular symptoms. 28.6% of cannabis workers (n=12) report shortness of breath with work tasks whereas only 5% (n=2) of the controls report similar symptoms when consuming or handling

cannabis (p = 0.005). Other comparisons did not yield statistically significant findings when compared this way (Appendix 4).

Increased respiratory symptom prevalence is more readily apparent when comparison is made between occupationally exposed cannabis workers, recreational users and non-users as separate groups. Taken as separate groups, both occupationally exposed cannabis workers and recreational cannabis users reported a history of wheezing (42.9%, n=18 and 35%, n=7 respectively, p=0.002), chest tightness (35.7%, n=15 and 10%, n=2 respectively, p=0.002), history of cough (31.0%, n=13 and 10%, n=2 respectively, p=0.007) and dyspnea on exertion (28.6%, n=12 and 20%, n=4 respectively, p=0.03) compared to zero reports of any of these in the non-users (Appendix 4, Table 16).

There were no significant differences in prevalence of historical dermal, nasal or ocular symptoms between the cannabis workers, recreational users and non-users (Appendix 4, Table 19).

We further considered symptoms that, based on questionnaire responses, were specifically associated with handling or working with cannabis. Increased prevalence of work or handling related symptoms was also observed when comparing the occupationally exposed workers to the individual control groups (recreational users and non-users) (Figure 7). There was a significantly higher prevalence of ocular, nasal, and respiratory symptoms in the cannabis workers compared to non-users (Table 6). Similar observations were made within the control group comparing just between recreational users and non-users, however (Table 9, 10).

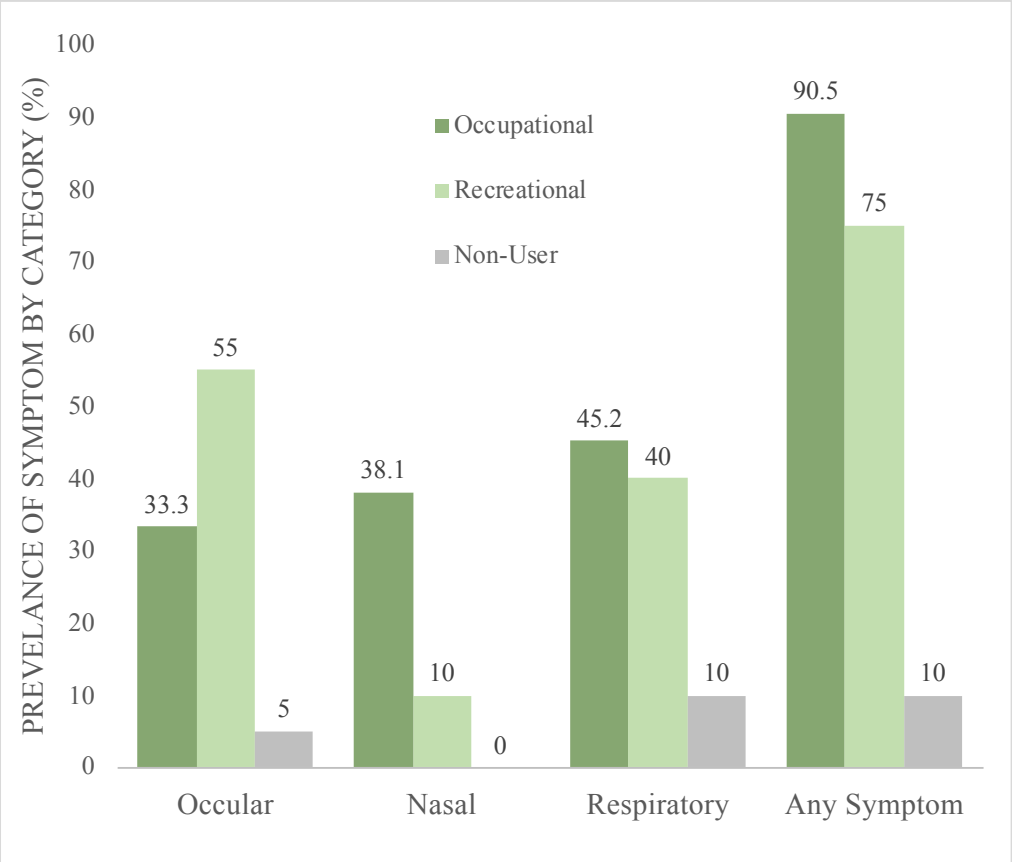


Figure 7: Prevalence of work related or handling related symptoms by exposure group and symptom category.

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
Red or watery eyes					0.003[1]
No	19 (95.0%)	28 (66.7%)	9 (45.0%)	56 (68.3%)	
Yes	1 (5.0%)	14 (33.3%)	11 (55.0%)	26 (31.7%)	
Nasal or sinus symptoms					0.001[1]
No	20 (100.0%)	26 (61.9%)	18 (90.0%)	64 (78.0%)	
Yes	0 (0.0%)	16 (38.1%)	2 (10.0%)	18 (22.0%)	
Shortness of breath					0.013[1]
No	20 (100.0%)	30 (71.4%)	18 (90.0%)	68 (82.9%)	
Yes	0 (0.0%)	12 (28.6%)	2 (10.0%)	14 (17.1%)	
Wheezing					0.121[1]
No	20 (100.0%)	35 (83.3%)	16 (80.0%)	71 (86.6%)	
Yes	0 (0.0%)	7 (16.7%)	4 (20.0%)	11 (13.4%)	
Cough or congestion					0.022[1]
No	18 (90.0%)	23 (54.8%)	12 (60.0%)	53 (64.6%)	
Yes	2 (10.0%)	19 (45.2%)	8 (40.0%)	29 (35.4%)	

Table 9: Symptoms experienced with handling or work-related exposure to cannabis by cannabis workers, recreational users and non-users. 1. Pearson's Chi-squared test.

	Non-User (N=20)	*Recreational (N=20)*	*Total (N=40)*	*p value*
Red or watery eyes				0.003[1]
No	19 (95.0%)	9 (45.0%)	56 (68.3%)	
Yes	1 (5.0%)	11 (55.0%)	26 (31.7%)	
Nasal or sinus symptoms				0.147[1]
No	20 (100.0%)	18 (90.0%)	64 (78.0%)	
Yes	0 (0.0%)	2 (10.0%)	18 (22.0%)	
Shortness of breath				0.147[1]
No	20 (100.0%)	18 (90.0%)	68 (82.9%)	
Yes	0 (0.0%)	2 (10.0%)	14 (17.1%)	
Wheezing				0.035[1]
No	20 (100.0%)	16 (80.0%)	71 (86.6%)	
Yes	0 (0.0%)	4 (20.0%)	11 (13.4%)	
Cough or congestion				0.028[1]
No	18 (90.0%)	12 (60.0%)	53 (64.6%)	
Yes	2 (10.0%)	8 (40.0%)	29 (35.4%)	

Table 10: Symptoms experienced with handling of cannabis by recreational users and non-users without comparison to the occupationally exposed group. 1. Pearson's Chi-squared test.

Sensitization to Cannabis and Hemp: Skin Prick Testing

19 occupationally exposed cannabis workers and the non-occupationally exposed cohort consisting of 20 recreational users and 20 non-users were tested for sensitization to members of the family *cannabaceae*. None of the non-users demonstrated a positive SPT result. 31.6% (n=6) of the occupationally exposed group and one recreational user demonstrated sensitization. The occupationally exposed group demonstrated higher rates of sensitization to a statistically significant degree (chi-squared p=0.005 for comparison amongst cannabis workers, recreational cannabis users without occupational exposure and non-users, Fisher's exact test p=0.044 for comparison between cannabis workers and recreational users without occupational exposure) (Figure 8, see also Appendix 4 Tables 19-22).

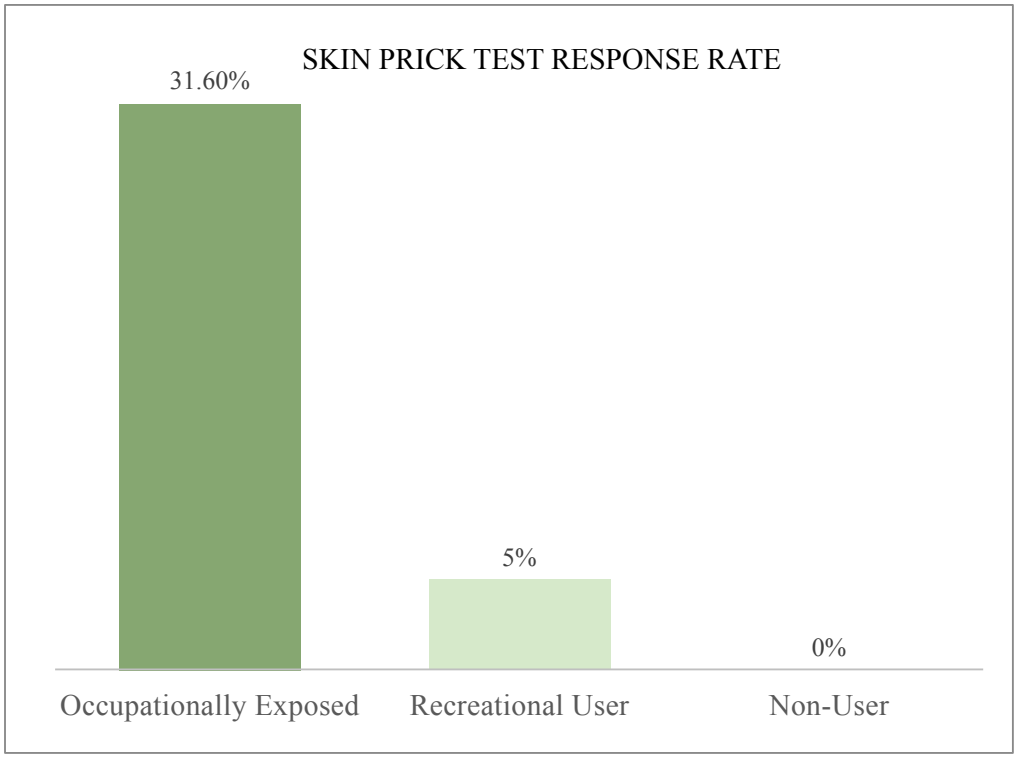


Figure 8: Skin prick test response rate by percentage. Occupational group n=6, Recreational use group n=1, Non-users n=0.

Effect of Occupational Cannabis Exposure on Pulmonary Inflammation: FeNO

FeNO was significantly elevated in the occupationally exposed group in comparison with the group without occupational exposure (p=0.003) and comparing between recreational users and non-users (p=0.011). Mean FeNO in the occupationally exposed group was 30.6 ppb (SD 26.37 ppb Range 6-102 ppb) compared to 15.6 ppb in the group without occupational exposure (Figure 9, Table 11).

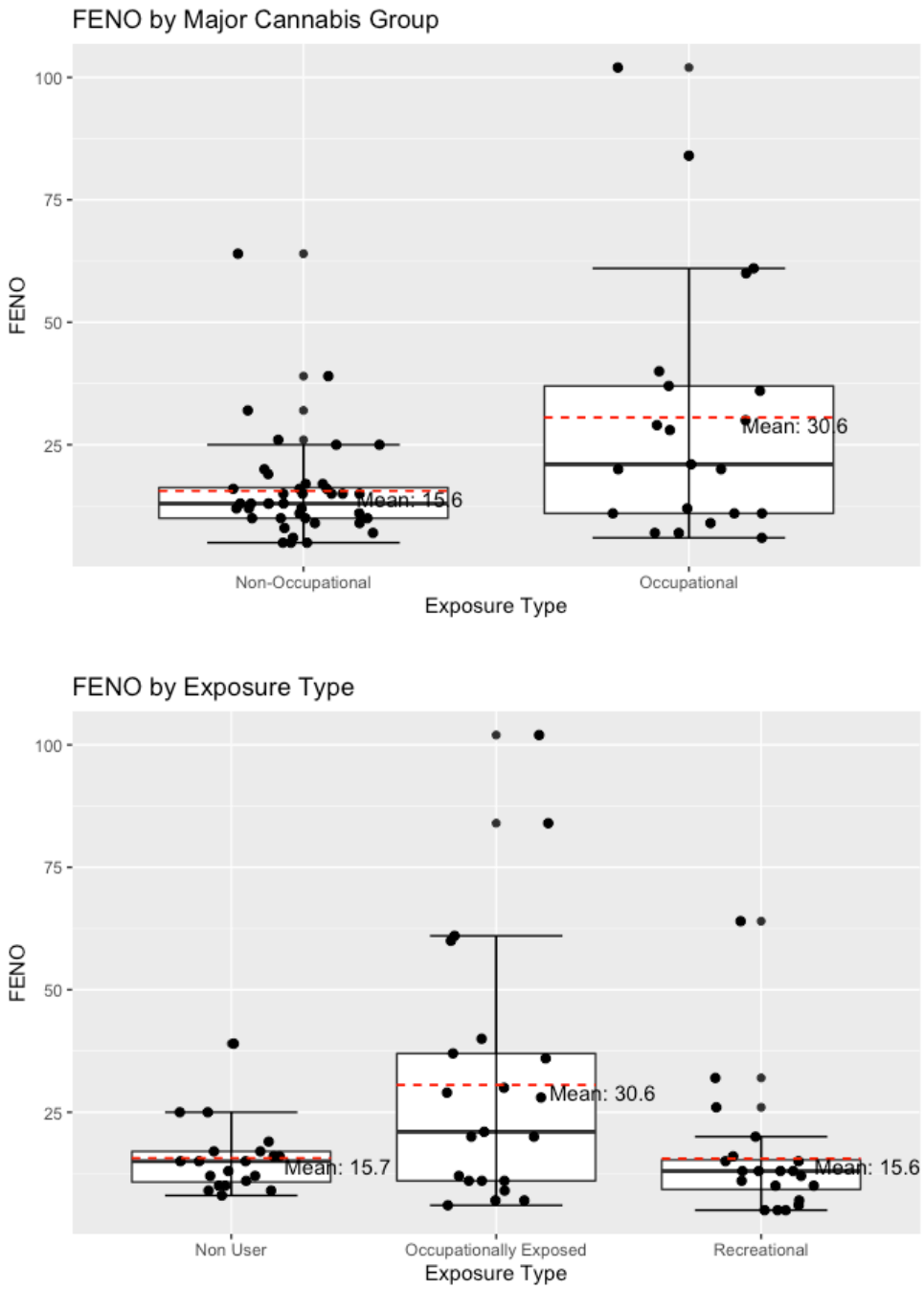


Figure 9: Effect of Occupational Cannabis Exposure on FeNO (ppb)

Table 11: FeNO results for cannabis workers, non-users without occupational exposure and recreational users without occupational exposure. 1) Linear model ANOVA

FeNO	*Non-User (N=20)*	*Cannabis Workers (N=21)*	*Recreational Users without Occupational Exposure (N=20)*	*Total (N=61)*	*p value*
Mean (SD)	15.650 (7.26)	30.571 (26.37)	15.55 (13.31)	20.75 (18.87)	0.011[1]
Range	8.00 - 39.00	6.00 - 102.00	5.00 - 64.00	5.00 - 102.00	

Effect of Occupational Cannabis Exposure on Pulmonary Function: $FEV1_{\%Predicted}$

Pulmonary function tests demonstrated inconsistent results between exposure groups and cannabis use profiles. It was decided to examine $FEV1_{\%Predicted}$ for a deeper relationship to occupational cannabis exposure in order to maintain consistency with the previous study and owing to the fact that $FEV1_{\%Predicted}$ is frequently used to guide diagnostic decisions, declines rapidly in the early stages of obstructive pulmonary disease and its decline is associated with occupational pulmonary pathology. $FEV1_{\%Predicted}$ additionally adjusts for important covariates such as age, gender, height and ethnicity without reducing power from small sample sizes.[47,48,49,17].

A modest decrease in mean $FEV1_{\%Predicted}$ was observed in cannabis workers, regardless of recreational use status, but these results were not statistically significant (Figure 10, Table 12).

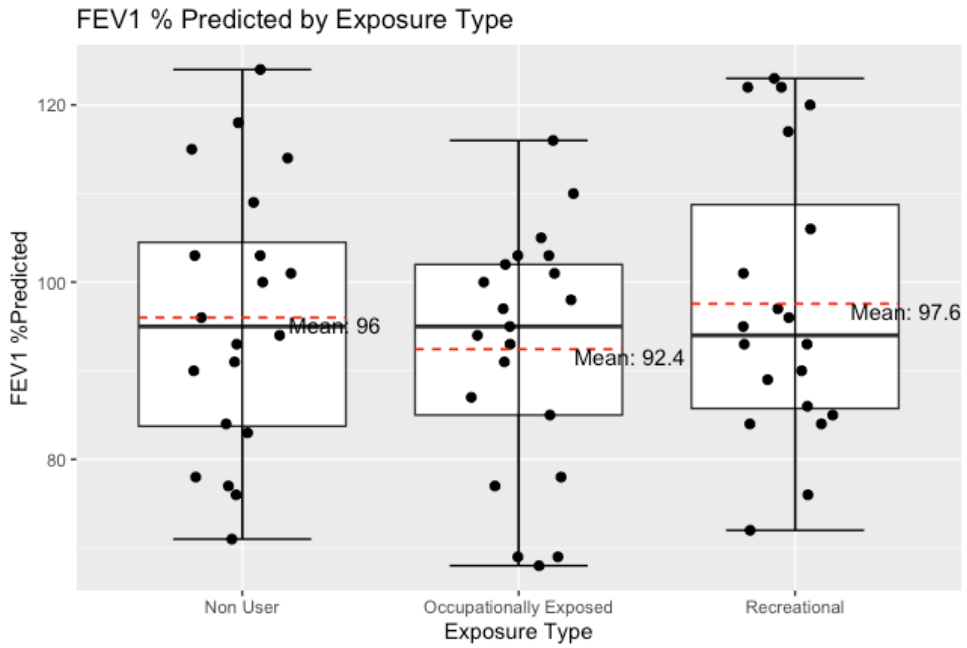


Figure 10: Effect of occupational cannabis exposure on $FEV1_{\%Predicted}$. A modest decrease was observed in cannabis workers that was not statistically significant.

Table 12: FEV1 %Predicted results for cannabis workers, non-users without occupational exposure and recreational users without occupational exposure. 1) Linear model ANOVA

FEV1 %Pred	*Non-Users (N=20)*	*Cannabis Workers (N=21)*	*Recreational Users Without Occupational Exposure (N=20)*	*Total (N=61)*	*p value*
Mean (SD)	96.00 (15.15)	92.43 (13.71)	97.55 (15.84)	95.28 (14.81)	0.531[1]
Range	71.00 - 124.00	68.00 - 116.00	72.00 - 123.00	68.00 - 124.00	

Measures of Association and Odds of Reporting Allergic or Irritant Symptoms

The crude odds ratios of experiencing allergic or irritant symptoms for occupationally exposed cannabis workers compared to the entire non-occupational group was 7.02 (95% CI 2.10, 23.45; p<0.001) For cannabis workers compared to non-users without occupational exposure the crude odds of experiencing allergic or irritant symptoms was 17.64 (95% CI 4.44, 70.16; p<0.001). Within the control group without occupational exposure we found the crude odds of reporting these symptoms for recreational users compared to non-users was 7.43 (95% CI 1.78, 31.04; p=0.004).

Multiple logistic regression was used to adjust for the effects of sociodemographic factors, occupational exposure to cannabis status, historical ocular, pulmonary or dermal symptoms and tobacco smoking (Table 9). Adjusting for these factors in cannabis workers and comparing to the entire group without occupational exposure, considering only occupational exposure to cannabis as a factor and ignoring recreational use, the adjusted odds of experiencing allergic or irritant symptoms was 9.45 (95% CI 2.35, 51.19; p=0.004). Comparing cannabis workers to non-users without occupational exposure the odds of experiencing allergic or irritant symptoms was 30.06 (95% CI 5.77, 231.38; p<0.001).

The effect of adjusting for individual confounders was also examined. This is shown in Appendix 4. Measure of association are summarized in Table 13. As stated in chapter two, medical history adjusts for prior medical history of atopy in the form of asthma, eczema, or allergy. Social history includes adjustment for tobacco smoking status. Demographics adjusts for age, sex and ethnicity.

Table 13: Crude and Adjusted Odds Ratios of atopic or irritant symptoms in cannabis workers and recreational users without occupational exposure relative to non-users without occupational exposure

Atopic or irritant symptoms at present or in the last 12 mos.	*Non-Users (N=20)*	*Cannabis workers (N=42)*	*Recreational users without occupational exposure (N=20)*
Crude OR [OR, CI, p]	1	17.64 (4.44, 70.16), <0.001[2]	7.43 (1.78, 31.04), 0.004[1]
Adjusted OR			
Adjustment for medical history and tobacco use only	1	14.42 (3.76, 66.94), <0.001[2]	7.21 (1.75, 35.54), 0.009[2]
Adjustment for medical history, tobacco use and demographics	1	30.06 (5.77, 231.38), <0.001[2]	10.76 (2.19, 71.71), 0.006[2]

The crude odds ratios for individual symptoms within each group during handling (workers with occupational cannabis exposure and recreational users without occupational exposure) are presented in Appendix 4, Table 24.

Linear Regression Modeling: FeNO

Tests for normality and heteroscedasticity verified model acceptability of the linear regression model for FeNO (Appendix 5).

Variations of the FeNO model were examined, including versions where a simplified model using only occupational exposures to cannabis and tobacco smoking was evaluated (assuming that $\beta_{2,3,4,5} = 0$) and a model evaluating the interaction of tobacco smoking with occupational exposure to cannabis status. Due to FeNO's close relationship to sex and age the first modified model was rejected. The interaction models either did not improve fit or did not yield a statistically significant set of coefficients.

Similarly, the regression model was examined comparing cannabis workers to the entire group without occupational exposure to cannabis and then comparing individually those occupationally exposed and recreationally exposed to cannabis to non-users. The models comparing only to non-users failed to reach significance, even at the alpha = 0.1 level.

Comparison between cannabis workers and those without occupational exposure to cannabis, ignoring recreational use status, did render a significant result. Adjusting for tobacco

smoking, demographics and evidence of atopy, geometric mean FeNO is 1.5 (95% CI 1.03, 2.35 p = 0.035) times higher in occupationally exposed cannabis workers than those without occupational exposure regardless of recreational cannabis use status. This is equivalent to a 56% increase in FeNO (95% CI 3%, 135%) with occupational exposure to cannabis. If an interaction between tobacco smoking and occupational exposure to cannabis were assumed, geometric mean FeNO would be 1.9 (95% CI 0.85, 3.35 p = 0.135) times higher in cannabis workers than those without occupational exposure to cannabis (equivalent to a median 90% increase) but again, this second reported result is not statistically significant.

Linear Regression Modeling: $FEV1_{\%Predicted}$

Models of $FEV1_{\%Predicted}$ explored the effect of cannabis on FEV1 considering occupational vs non-occupational exposure status as well as recreational cannabis use and non-use. These models did not reach statistical significance. Interaction between smoking and occupational exposure to cannabis was also examined. These model variants did not reach statistical significance either.

Organizing by just occupational exposure to cannabis or no occupational cannabis exposure, occupational exposure adjusting for tobacco smoking is associated with a 3.5% decrease in FEV1% predicted (not significant). If we assume interaction between tobacco smoking and occupational cannabis exposure, this would be a 7.9% decrease (again, not significant). 95% CI for change of $FEV1_{\%Predicted}$ in occupationally exposed workers, without tobacco smoking interaction: (-10.76, 5.79; p = 0.47); 95% CI for change of $FEV1_{\%Predicted}$ with tobacco smoking interaction in cannabis workers: (-16.49, 4.57; p = 0.45).

CHAPTER FOUR: Discussion

This study sought to establish a demographically similar group of controls without occupational exposure to cannabis to address limitations discovered when examining allergic and respiratory symptoms in employees of indoor cannabis grow facilities. It extends the previous work by further elucidating prevalence of health symptoms and accounting for recreational use of cannabis among cannabis workers.

There was a high prevalence of symptoms among both cannabis workers and recreational cannabis users, with 90% of cannabis workers and 75% of recreational users experiencing at least one ocular, nasal or respiratory symptom (Figure 7). The high rate of symptom prevalence is consistent with previous work by this author's group that demonstrated higher symptomatic prevalence than similar studies.[14,35]

It would be difficult to attribute symptoms entirely to occupational exposure solely on the basis of the prevalence data shown, as the significant exposure appears to be to cannabis and not specifically to the work environment (Tables 9 and 10). This work attempted to disentangle the role of recreational cannabis use and occupational exposure to cannabis by adjusting for demographic factors, medical history and occupational exposure to cannabis vs recreational cannabis use using multivariate logistic regression (Results, also Appendix 4).

Measures of association more clearly demonstrate the effect of occupational exposure to cannabis. The crude odds ratios of experiencing allergic or irritant symptoms for occupationally exposed cannabis workers compared to the entire non-occupationally exposed group was 7.02 (95% CI 2.10, 23.45; $p<0.001$). For cannabis workers compared to non-users without occupational exposure the crude odds of experiencing allergic or irritant symptoms was 17.64 (95% CI 4.44, 70.16; $p<0.001$). Within the control group without occupational exposure we found the crude odds of reporting these symptoms for recreational users compared to non-users was 7.43 (95% CI 1.78, 31.04; $p=0.004$). Adjusting for these factors in cannabis workers and comparing to the entire group without occupational exposure the adjusted odds of experiencing allergic or irritant symptoms was 9.45 (95% CI 2.35, 51.19; $p=0.004$). Comparing cannabis workers to cannabis non-users without occupational exposure to cannabis the odds of experiencing allergic or irritant symptoms was 30.06 (95% CI 5.77, 231.38; $p<0.001$). Regardless of cannabis use profile, cannabis workers have higher odds of experiencing

respiratory, dermal, ocular or nasal symptoms. A comparable study from Colorado focusing on cannabis workers' symptoms after handling pesticides observed increased prevalence of work-related symptoms among cannabis workers but did not report measures of association[50]. The study performed for this thesis may be the first to report results of this type.

Occupational exposure was clearly associated with sensitization to cannabis, significantly more so than recreational use, with 35% of cannabis workers compared to 5% of recreational users and zero non-users demonstrating cannabis sensitivity on skin prick testing. One possible limitation of SPT is that sensitization to cannabis could not be solely attributed to occupational exposure owing to the fact that nearly all of the occupational participants are also recreational cannabis users. Studies of allergic hypersensitivity to cannabis report the highest levels of sensitization on SPT in habitual recreational consumers.[51] In that study of hypersensitivity to cannabis in patients with allergy and illicit drug use history, 58% (24 of 74 total enrolled subjects, mean duration of regular cannabis consumption 19.7 +/- 9.4 years), of subjects with regular use history demonstrated SPT sensitization to a cannabis extract. The study design used here inherently addresses the possibility of confounding due to recreational cannabis use. What remains unclear is whether recreational cannabis use is a risk factor for sensitization during occupational cannabis exposure. Additionally, the specific epitope of cannabis or plants of family *cannabaceae* that persons are sensitized to has yet to be elucidated. It is possible that individuals sensitized to cannabis could be cross-reacting with other substances present in cannabis farms, including mold or mildew, or plan allergens such as thaumatin-like protein or lipid transfer proteins. We attempted to investigate the relationship between reported history of allergy and SPT positivity but were limited by sample size. Further, it cannot yet be ruled out that potential allergens affecting cannabis workers are cannabis specific. Molds, mildews and oxidized VOCs are present in grow rooms and on cannabis plants, are implicated in allergic sensitization and should be investigated as potential sensitizers.

An additional limitation is the use of industrial hemp as the allergen in the recreational/ non-users vs THC-containing cannabis in the occupational group. While the two sources of plant material likely have similar allergen profiles, there may be enough differences to account for the difference in prevalence rates that we observed.

Our study group compared measures of lung inflammation and pulmonary function between cannabis workers, recreational users of cannabis who were not occupationally exposed

to cannabis and cannabis abstaining groups. The study motivating the work which took place entirely among workers in indoor grow facilities observed that four out of five sensitized workers also had decreased lung function consistent with ATS criteria for work-related asthma. Consistent with our previous results[35] there was a trend in decreased pulmonary function that demonstrates a trend toward decreased FEV1 in occupationally exposed cannabis workers (Figure 10). The results for change in $FEV1_{\%Predicted}$ between groups was not statistically significant.

Attempts to construct a regression model for $FEV1_{\%Predicted}$ did not yield a statistically significant relationship. In general, the data obtained from pulmonary function testing was inconsistent and did not show substantial differences among groups. Overall, the insignificant pulmonary function data was unexpected, especially in light of results from previous study. A high prevalence of acute and chronic decrease in lung function was previously reported in hemp workers of two mills[17], and many studies have reported decreases in lung function in sensitized individuals, those exposed to respirable particulates, those with atopy and those with tobacco smoking history. It is possible that this effort was limited by the small sample sizes used in this study.

A statistically significant increase in FeNO was observed. Our previous work noted that FeNO appeared to be chronically elevated in sensitized workers[35]. Here it has been shown that there is a difference between groups, whether they are observed through the lens of work exposure or cannabis exposure profile. In spite of this, more evidence may be required to conclude that occupational cannabis exposure is the sole culprit for elevations in FeNO and it is possible that FeNO reported here may in fact underestimate airway inflammation of the cannabis workers. The cannabis workers in this study were not perfectly matched to the control group in an important metric: tobacco smoking. They had higher prevalence of tobacco smoking, higher number of current daily smokers, greater number of pack-years and more frequent daily smoking of cannabis. Elevated FeNO (> 50 ppb) is likely to indicate airway eosinophilia that is responsive to steroid therapy. Studies have also shown that peak FeNO is lower in tobacco smokers than matched controls. The paradoxical result, of elevated FeNO in the occupational group who also happen to smoke both tobacco and cannabis, requires further investigation.

Linear regression modeling was performed to define a relationship between occupational exposure and FeNO. It was identified that geometric mean FeNO is 1.5 times higher in cannabis

workers regardless of recreational use status. It would be advantageous in future studies to clearly elucidate the role of tobacco smoking, cannabis smoking and their interaction with FeNO. Cannabis smoking and vaping intensity should also be evaluated.

Summary

This thesis sought to extend previous work by developing a demographically similar control group for comparison to workers in an indoor cannabis grow facility in Washington state (Aim 1). This was achieved by enrolling 40 participants without occupational exposure to cannabis or cannabis cultivation or processing history. They were subdivided into two groups: 20 were daily cannabis users and 20 non-users without cannabis exposure. The groups were similar to each other and to the group of cannabis workers, with the exception of tobacco smoking and recreational cannabis use. The cannabis workers had higher prevalence of daily or recent tobacco smoking and virtually all of the workers were daily marijuana users.

This work sought to characterize and compare work-related symptoms between the three groups (Aim 2). Occupationally exposed cannabis workers had higher rates of sensitization on skin prick testing, evidence of chronic airway inflammation regardless of recreational cannabis use status, a trend toward decreased pulmonary function, and much higher odds of reporting atopic symptoms with exposure to cannabis or cannabis products.

Limitations and Recommendation for Future Studies

This study has some limitations.

Limited study population limits sample sizes and limits the power of statistical analyses. This limits the robustness of calculations. This is best appreciated in the wide confidence intervals of the reported measures of association and the difficulty in fitting models. Similarly, this author suspects that the lack of substantial findings from pulmonary function testing contrary to expectations can be attributed to lack of power imposed by small sample sizes. Performing detailed analyses within sub groups, for example, to search for relationship between history of a specific kind of atopy and elevated FeNO or cannabis smoking frequency and pulmonary function, is challenging with the limited numbers enrolled. Future studies should recruit more participants.

Many participants in the occupational group were cigarette smokers. Future participants should be matched, if possible on the basis of their tobacco smoking history.

Workers from the previous study, the data from which was used here were recruited from two regional growing facilities which might not be representative of other indoor facilities, nor of the overall cannabis production industry which includes indoor, outdoor and shade house grows of a variety of sizes. Future studies should consider capturing a variety of work environments.

To assess history of atopy in the non-occupational population a report of symptoms was used as a proxy for IgE blood testing. Some sensitized individuals may not demonstrate symptoms, so this approach may not be the most accurate. Additionally, since a questionnaire was used there could be a degree of recall bias.

Finally, this cross-sectional study captures workers currently in the cannabis industry. It is possible that there is some healthy worker effect unseen in these results. It is conceivable that workers have already left the industry due to intractable pulmonary or allergic complaints. A longitudinal study tracking cannabis workers throughout their careers would best address the question of long-term effects of occupational exposure.

CHAPTER FIVE: Conclusion

This work demonstrates plainly that cannabis workers have higher odds of developing allergic or irritant type symptoms and that these symptoms are in part attributable to the work environment. What are the implications for this industry?

The cannabis industry is exploding through its adolescence and the workforce is rapidly growing to match. One motivation of this work was to spur thoughtful conversation on the need for evolution of cannabis business regulation. Currently, owing to the schedule I status of cannabis, these businesses are regulated largely by individual states. With state level regulations comes inconsistency in safety standards and enforcement. This has implications for worker safety. For example, at present the only applicable federal standard for indoor grow facilities is the respirable dust standard. OSHA prescribes a permissible exposure limit for respiratory dust not to exceed 5.0 mg/m3 over an 8-hour time weighted average. However, this standard may not be adequately protective for exposure to cannabis dust as the size of particles that reach the lower airways may be much smaller and the amount required to induce allergic sensitization may be far smaller. The practices within facilities are inconsistent and employers, safety officers and workers are provided with inadequate guidance to ensure that workers are adequately protected from cannabis related workplace hazards.

This work may not seem immediately generalizable as it focused on one group of workers from a grow facility in Washington state and one group of Seattleites in the area surrounding the Puget Sound but these results are provocative. The trends and associations lend themselves to further exploration.

The cannabis industry can take immediate action on the basis of these results. Risk management strategies that leverage the hierarchy of occupational controls, particularly engineering, administrative, and PPE measures to limit cannabis dust exposure should be developed. An excellent role model for the cannabis industry may be the best practices of other agricultural industries such as hops farming, grain production and hemp product manufacturing.

Long term, what becomes of these workers when they develop occupationally related pulmonary or atopic illness as a result of their work? Without clearly defined, causal definitions these potential future patients may languish.

As ever, industry and technology always move faster than science and law.

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APPENDICES

Appendix 1: Table of Work Tasks in a Typical Grow Facility Adapted from Ghodsian[14]

Task	Description
Office	Performing administrative or sales duties
Inventory	Record keeping for materials to make sure that the inventory is well stocked
Delivery	Delivering products to retail shops
Picking Order	Finding products from the warehouse to fulfill customer orders
Order Fulfillment	Processing products from point of sales inquiry to delivery to the customer
Waste Disposal	Disposing of any unwanted materials
Labeling	Labeling products, such as packaged flowers, tubed pre-roll joints, and concentrates
Cleaning	General cleaning of the facility
Packaging	Packaging flowers and other products
Weighing	Weighing flowers, concentrates, and oils for packaging
Hand- trimming	Shaping and forming sellable buds from the newly bucked plants
Pre-roll	Filling and compacting pre-rolled cones by hand
Tubing	Placing two rolled joints into their packaging at a time until the lot is depleted
Spraying	Spraying plants with pesticides
Growing	General pruning
Plant Survey	Checking plants quality
Consolidating	Combining materials for delivery
Spinning	Verifying the weight of pre-rolled joints and tapping down the ground leaf and spinning them in order to form a flag used for lightening them with the excess paper
Sifting	Separating out undesired plant materials, such as leaves and stems using a sift box
Grinding	Grinding dried flowers to a coarse powder to be used in pre-roll joints, concentrates, and oils.
Knock Boxing	Filling and compacting pre-rolled cones using an instrument
Harvesting	Removing large stems from fully mature plants and hang them to dry

Appendix 2: Health Symptoms Questionnaire

Health Effects Baseline Questionnaire

Test version. Please try it out.

Thank you!

Subject Identifier

_____
(TECHNICIAN: INPUT THE SUBJECT IDENTIFIER)

Technician Initials

_____
(Enter the initials of the UW researcher helping you complete this survey, if applicable)

DEMOGRAPHICS

What is your age?	_____
What is your biological sex (your genetic sex at birth)?	◯ Male ◯ Female (We use this to calculate values related to your respiratory health)
What is your self-described race/ethnicity?	◯ White or Caucasian, but not Hispanic or Latino ◯ Black or African-American, but not Hispanic or Latino ◯ Hispanic or Latino ◯ Asian ◯ Other (We need for this to accurately calculate your respiratory test results for the study.)
What is the highest degree or level of education that you completed?	◯ No schooling ◯ Grade 1-11 ◯ High school or GED ◯ Some college or 2-year degree ◯ 4-year college graduate (Bachelor's degree) ◯ More than 4-year college degree (Graduate, Professional School, Master's, Ph.D. etc.)

SMOKING STATUS AND SMOKING HISTORY

Do you now, or have you ever, smoked tobacco cigarettes?	◯ Never ◯ Current (Past 30 days) ◯ Formerly (More than 30 days ago)
How old were you when you first started smoking tobacco?	_____
On average, about how many tobacco cigarette a day do / did you smoke?	_____ (If you smoke less than one cigarette a day please enter '1'. One "pack" is equivalent to 20 cigarettes.)
How old were you when you quit smoking?	_____
Do live with someone who smokes?	◯ Yes ◯ No

Have you ever used any of these tobacco products?			
	Never	Current (Past 30 days)	Formerly (More than 30 days ago)
Pipe	◯	◯	◯
Cigars / Cigarillos	◯	◯	◯
Snuff	◯	◯	◯
Chewing tobacco	◯	◯	◯
Vape / E Cigarette	◯	◯	◯
Hookah	◯	◯	◯

Marijuana Use History

Have you ever used marijuana products?	◯ I have never used marijuana ◯ I have used marijuana in the last 30 days ◯ I used to use marijuana but I haven't used it recently (more than 30 days ago)
How old were you when you first started using marijuana products?	_____
When did you last use a marijuana product?	◯ In the last hour. ◯ In the last 24 hours. ◯ Yesterday. ◯ In the last week. ◯ More than a week ago. (This could help us determine if recent use has an effect on any reaction we identify.)
If you used to consume marijuana products, how old were you when you quit?	_____

Please complete the following table that summarizes the ways in which you use / used marijuana. If you are a current user, please report your *current* usage pattern.

	Multiple times daily	Once a day	More than once a week	More than once a month	Every few months	Once or twice a year
Smoking (bowls, bongs, pipes, etc.)	◯	◯	◯	◯	◯	◯
Edibles, drinks, teas	◯	◯	◯	◯	◯	◯
Vaping	◯	◯	◯	◯	◯	◯
Dabbing	◯	◯	◯	◯	◯	◯
Topicals	◯	◯	◯	◯	◯	◯

Have you ever had a doctor's order, like a medical prescription, medical marijuana card or "green card" for marijuana products?
◯ Yes
◯ No

Do live with someone who currently consumes marijuana products?
◯ Yes
◯ No

Do you live with someone who works in the marijuana industry (cultivation, sales, distribution etc)?
◯ Yes
◯ No

Do you currently cultivate marijuana at home?
◯ Yes
◯ No

Do you prepare marijuana products for someone at home?
◯ Yes
◯ No

ALTERNATIVE SUBSTANCE USE HISTORY

Do you use any non-prescription inhalants? (For example: paint, whippits, amphetamine, etc.)	◯ Yes ◯ No
Please specify what you use.	_____
How do you use it?	_____
How old were you when you started using it?	_____
When did you last use this inhalant?	◯ In the last hour. ◯ In the last 24 hours. ◯ Yesterday. ◯ In the last week. ◯ More than a week ago. (This could help us determine if recent inhalant use has an effect on any reaction we identify.)

OCCUPATIONAL HISTORY

What is your current occupation?	_____ (If you are not currently working, please enter your most recent occupation.)
When did you start this position?	_____
Are / were you regularly exposed to any fumes, gas, dust or vapors during your job?	◯ Yes ◯ No
Are you concerned about any workplace exposures?	◯ Yes ◯ No
If you answered yes to above, describe what they are:	_____
Do you have any work-related health concerns?	◯ Yes ◯ No
Please describe them:	_____
Have you ever been employed in cannabis cultivation or processing?	◯ Yes ◯ No

MEDICAL HISTORY

Do you have any chronic medical conditions? ◯ Yes ◯ No

Please list them:

_____

MEDICATION HISTORY

Please list the medications and supplements you are taking. Begin by typing the name of a medication you are using. The most common dosages are also shown. If you are not certain of your dosage or your dosage is not shown in the list, please let one of the researchers know.

Hint: Inhalers, birth control pills and IUDs, home oxygen, vitamins, fish oil and herbal supplements also count!

Are you currently taking any prescription medications or supplements?	◯ Yes ◯ No (If you are using more than 15 medications, please notify a research technician to help you record your medications.)
Medication 1	_____ (Start typing a medication name)
Medication 2	_____ (Start typing a medication name)
Medication 3	_____ (Start typing a medication name)
Medication 4	_____ (Start typing a medication name)
Medication 5	_____ (Start typing a medication name)
Medication 6	_____ (Start typing a medication name)
Medication 7	_____ (Start typing a medication name)
Medication 8	_____ (Start typing a medication name)
Medication 9	_____ (Start typing a medication name)
Medication 10	_____ (Start typing a medication name)

Medication 11

(Start typing a medication name)

Medication 12

(Start typing a medication name)

Medication 13

(Start typing a medication name)

Medication 14

(Start typing a medication name)

Medication 15

(Start typing a medication name)

Have you ever been told that you have any of the following medical conditions?

If you need help understanding any of these terms, please ask one of the researchers for assistance!

	Yes	No	Don't know
Asthma	◯	◯	◯
Hay Fever (allergies affecting the nose or eyes)	◯	◯	◯
Chronic Bronchitis	◯	◯	◯
COPD (Chronic Obstructive Pulmonary Disease)	◯	◯	◯
Pneumonia or Bronchopneumonia	◯	◯	◯
Eczema (skin allergy)	◯	◯	◯

Does anyone in your family have asthma?

◯ Yes ◯ No
(If you are unsure or are adopted please choose 'NO'.)

Who?

☐ Grand- parent ☐ Mother
☐ Aunt (Mom's side) ☐ Uncle (Mom's side)
☐ Cousin (Mom's side)
☐ Father ☐ Aunt (Dad's side)
☐ Uncle (Dad's side) ☐ Cousin (Dad's side)
☐ Brother ☐ Sister ☐ Child

Health Concerns Related to Marijuana Use

Do you have any concerns about the impact your marijuana use could have on your health?

◯ Yes
◯ No

What are they?

_____

The following questions relate to health symptoms.

Have you ever had eczema or any kind of skin allergy?	◯ Yes ◯ No
Have you ever had an itchy rash that has been coming and going for at least 6 months?	◯ Yes ◯ No
a) Have you had this itchy rash in the past 12 months?	◯ Yes ◯ No
b) Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttock or around the neck, ears or eyes?	◯ Yes ◯ No
c) Has this itchy rash at any time affected any of the following places: the hands, wrists, or forearms?	◯ Yes ◯ No
In the past 12 months, have you had a problem with itchy, red or watery eyes?	◯ Yes ◯ No
a) Are you currently taking any medications (including eye drops, pills, capsules or tablets) for the treatment of your eye symptoms?	◯ Yes ◯ No
Do you have nasal allergies, including hay fever?	◯ Yes ◯ No
Do you have any food allergies?	◯ Yes ◯ No

If YES, are you allergic to any of the following:

	Yes	No
Tomatoes	◯	◯
Peaches	◯	◯
Grapefruit	◯	◯
Almonds or chestnuts	◯	◯
Eggplants	◯	◯
Apples	◯	◯
Bananas	◯	◯

In the past 12 months, have you ever had problems with nasal irritation, nose bleeds, sneezing, or a runny or a blocked nose when you did not have a cold or the flu?
◯ Yes
◯ No

a) Has this nose problem been accompanied by itchy, red or watery eyes?
◯ Yes
◯ No

b) Are you currently taking any medications (including nasal sprays, pills, capsules or tablets) for the treatment of your nasal symptoms?
◯ Yes
◯ No

Have you ever had wheezing or whistling in your chest, anytime in the last 12 months?
◯ Yes
◯ No

a) Have you been at all breathless when the wheezing noise was present?
◯ Yes
◯ No

b) Have you had this wheezing or whistling when you did not have a cold?
◯ Yes
◯ No

Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?
◯ Yes
◯ No

Have you been awoken by an attack of shortness of breath at any time in the last 12 months?
◯ Yes
◯ No

Have you been awoken by an attack of coughing at any time in the last 12 months?
◯ Yes
◯ No

Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?
◯ Yes
◯ No

Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?
◯ Yes
◯ No

Have you ever had asthma?
◯ Yes
◯ No

a. Have you ever been diagnosed with asthma by a doctor?
◯ Yes
◯ No

b. Have you had an attack of asthma any time in the last 12 months?	◯ Yes ◯ No
c. Are you currently taking any medications (including inhalers, aerosols or tablets) for asthma?	◯ Yes ◯ No

Do you develop or have worsening of the following symptoms when you consume or are in contact with marijuana products?

	Yes	No
Red or watery eyes ?	◯	◯
Runny nose, nasal congestion or sneezing?	◯	◯
Hives, itchiness or inflamed skin	◯	◯
Shortness of breath	◯	◯
Wheezing or chest tightness	◯	◯
Coughing or phlegm production	◯	◯
Swelling of the tongue or severe breathing difficulty	◯	◯
Anaphylaxis or severe allergic reaction	◯	◯

Appendix 3: Questionnaire Used in Study of Work-Related Health Symptoms

Prior work by this project team evaluated worker's health related symptoms. This questionnaire was used to obtain the data from the occupationally exposed group previously published.

Health Effects Baseline Questionnaire
Technician initials: _____
Subject identifier: _____

---

1. What is your age? ____
2. What is your biological sex? □ Male □ Female

3. What is your self-described race/ ethnicity?
   □ Caucasian
   □ Hispanic/ Latino
   □ Black or African American
   □ Asian
   □ Other (please specify) _____

4. What is the highest degree or level of education that you completed?
   □ No schooling
   □ Grade 1-11
   □ Completed high school
   □ Some college but no degree
   □ Bachelor's degree
   □ Graduate or Professional school

5. Do you now, or have you ever, smoked tobacco cigarettes?

□ Never □ Current (past 30 days) □ Past (year quit)
If you answered "Never," go to question 9

6. How old were you when you first started smoking tobacco cigarettes? _____

7. On average, about how many tobacco cigarettes a day do/ did you smoke? _____

8. Do live with a current smoker? □ Yes □ No

9. Have you ever used any other tobacco products?

	Never	Current (past 30 days)	Past
Pipe			
Cigars/ cigarillos			
Snuff			
Chewing tobacco			
Electronic cigarette			
Hookah			

10. Have you ever consumed marijuana products?

□ Never □ Current (past 30 days) □ Past (_____ year quit)

If you answered "Never," go to question 12

11. Please complete the following table that summarizes the ways in which you use/ used marijuana? If you are using currently (past 30 days), please indicate current use patterns.

	Multiple times daily	Once a day	Once a week or more	About once a month	Every few months	Once or twice a year
Edible						
Smoked						
Smokeless/vape						
Dabbing						
Topical						

12. What is your job title? _____

a) For how long have you held this position? __ years __ months ___ days
b) For how long have you worked at this facility? __ years __ months ___ days
c) For how long have you worked in the marijuana industry? __ years __months __days
d) How many hours per week do you work in this job? ____

13. Do you perform any of the following tasks at work?

(please indicate typical % time spent on each)

Task	Yes	No	% time
Nursery worker			
Sort/grade dry product			
Trimmer			
Roll joints			
Packaging			
Preparation of concentrates/distillates			
Office work			
Waste Disposal			
Other (please specify)			

14. Do you ever wear any of the following when you work? If you answer yes to any of the questions, please specify % time you use this equipment, and the specific tasks where you use this equipment

a) Gloves? □ Yes □ No
   % time _____
   Tasks _____
b) Safety goggles? □ Yes □ No
   % time _____
   Tasks _____

c) Dust mask? □ Yes □ No
% time _____
Tasks _____

d) Cartridge respirator? □ Yes □ No
% time _____
Tasks _____

15. Do you perform any other paid work regularly? □ Yes □ No

a) What kind of work? _____

b) How many hours per week? _____

16. Have you ever been involved with cannabis cultivation or processing outside of this specific facility?

□ Never □ Currently □ Previously

17. Please list any prior jobs

18. Do you have any chronic medical conditions? □ Yes □ No If yes, please list them:

19. Are you on any medications? □ Yes □ No If yes, please list the names and dose:

Medication	Dose

20. Have you ever been told that you have any of the following medical conditions?

	Yes	No	Don't know	Age at diagnosis
Asthma				
Hay fever (allergies involving the nose and/ or eyes)				
Chronic bronchitis				
Chronic obstructive pulmonary disease (COPD)				
Pneumonia or bronchopneumonia				
Eczema (skin allergy)				

21. Does anyone in your family have asthma? □ Yes □ No If yes, please specify

22. Do you have any work-related health concerns? □ Yes □ No
If yes, please describe: _____

The following questions relate to health symptoms		
23. Have you ever had eczema or any kind of skin allergy?	□ Yes	□ No
24. Have you ever had an itchy rash that has been coming and going for at least 6 months? If "No", go to question 27 below.	□ Yes	□ No
a) Have you had this itchy rash in the past 12 months?	□ Yes	□ No
b) Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttock or around the neck, ears or eyes?	□ Yes	□ No
c) Has this itchy rash at any time affected any of the following places: the hands, wrists, or forearms?	□ Yes	□ No
25. If you answered yes to one of the statements in questions 23 and 24 above, does contact with certain materials, chemicals or anything else in your work makes this rash worse?	□ Yes	□ No
What? _____		
26. Does the rash improve when you are away from your normal work?	□ Yes	□ No
27. In the past 12 months, have you had a problem with itchy, red or watery eyes? If "No," go to question 31 below.	□ Yes	□ No
a) Are you currently taking any medications (including eye drops, pills, capsules or tablets) for the treatment of your eye symptoms?	□ Yes	□ No
28. When you are at work, do you develop symptoms of itchy, red, or watery eyes?	□ Yes	□ No
29. If you answered yes to one of the statements in questions 27 or 28, does contact with certain materials, chemicals or anything else in your work make your symptoms worse?	□ Yes	□ No
What? _____		
30. If you answered yes to one of the statements in questions 28 or 29 above, do these problems related to your work lessen or disappear during the weekend or during holidays?	□ Yes	□ No
31. Do you have nasal allergies, including hay fever?	□ Yes	□ No

32. In the past 12 months, have you ever had problems with nasal irritation, nose bleeds, sneezing, or a runny or a blocked nose when you did not have a cold or the flu? If "No", go to question 36 below.	□ Yes	□ No
a) Has this nose problem been accompanied by itchy, red or watery eyes?	□ Yes	□ No

b) Are you currently taking any medications (including nasal sprays, pills, capsules or tablets) for the treatment of your nasal symptoms?	□ Yes	□ No
33. When you are at work, do you develop symptoms of nasal irritation, sneezing, a runny or a blocked nose?	□ Yes	□ No
34. If you answered yes to one of the statements in questions 31 to 33 above, does contact with certain materials, chemicals or anything else in your work make your symptoms worse?	□ Yes	□ No
What? _____		
35. If you answered yes to one of the statements in questions 33 or 34 above, do these problems related to your work lessen or disappear during the weekend or during holidays?	□ Yes	□ No
36. Have you ever had wheezing or whistling in your chest, anytime in the last 12 months?	□ Yes	□ No
a) Have you been at all breathless when the wheezing noise was present	□ Yes	□ No
b) Have you had this wheezing or whistling when you did not have a cold?	□ Yes	□ No
37. Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	□ Yes	□ No
38. Have you been awoken by an attack of shortness of breath at any time in the last 12 months?	□ Yes	□ No
39. Have you been awoken by an attack of coughing at any time in the last 12 months?	□ Yes	□ No
40. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?	□ Yes	□ No
41. Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?	□ Yes	□ No
42. Have you ever had asthma?	□ Yes	□ No
a. Have you ever been diagnosed with asthma by a doctor?	□ Yes	□ No
b. Have you had an attack of asthma any time in the last 12 months?	□ Yes	□ No
c. Are you currently taking any medications (including inhalers, aerosols or tablets) for asthma?	□ Yes	□ No
43. Do you experience any of the following while you are at work?		
a. Start to cough?	□ Yes	□ No
b. Start to produce sputum?	□ Yes	□ No
c. Start to wheeze?	□ Yes	□ No
d. Start to feel short of breath or get chest tightness?	□ Yes	□ No

e. Start to have a sore throat, hoarseness or loss of voice?	□ Yes	□ No
44. If you answered "yes" to any of the respiratory symptoms described in questions 36-43, does contact with certain materials, chemicals or anything else in your work make your symptoms worse?	□ Yes	□ No
What? _____		
45. If you answered yes to one of the statements in questions 36 to 45, do these respiratory symptoms lessen or disappear when you are away from work, including evenings, weekends or during holidays?	□ Yes	□ No

Appendix 4: Supplemental Tables

These supplemental data tables are intended to provide additional descriptive data and breakdowns of the groups studied in this project. 1) Indicates Pearson's Chi-Squared test 2) Indicates linear model ANOVA 3) Indicates Fisher's exact test.

Table 14: Respiratory symptom breakdown within control group participants, last 12 months

	Non-User (N=20)	*Recreational (N=20)*	*Total (N=40)*	*p value*
History of wheezing				0.004[1]
No	20 (100.0%)	13 (65.0%)	33 (82.5%)	
Yes	0 (0.0%)	7 (35.0%)	7 (17.5%)	
History of wheezing with SOB				0.147[1]
No	20 (100.0%)	18 (90.0%)	38 (95.0%)	
Yes	0 (0.0%)	2 (10.0%)	2 (5.0%)	
Wheezing when subject did not have a cold				0.008[1]
No	20 (100.0%)	14 (70.0%)	34 (85.0%)	
Yes	0 (0.0%)	6 (30.0%)	6 (15.0%)	
Chest tightness				0.147[1]
No	20 (100.0%)	18 (90.0%)	38 (95.0%)	
Yes	0 (0.0%)	2 (10.0%)	2 (5.0%)	
Awoken by SOB				0.147[1]
No	20 (100.0%)	18 (90.0%)	38 (95.0%)	
Yes	0 (0.0%)	2 (10.0%)	2 (5.0%)	
History of coughing				0.147[1]
No	20 (100.0%)	18 (90.0%)	38 (95.0%)	
Yes	0 (0.0%)	2 (10.0%)	2 (5.0%)	
Dyspnea at rest				0.311[1]
No	20 (100.0%)	19 (95.0%)	39 (97.5%)	
Yes	0 (0.0%)	1 (5.0%)	1 (2.5%)	
Dyspnea with exertion				0.035[1]
No	20 (100.0%)	16 (80.0%)	36 (90.0%)	
Yes	0 (0.0%)	4 (20.0%)	4 (10.0%)	
History of asthma				0.212[1]
No	18 (90.0%)	15 (75.0%)	33 (82.5%)	
Yes	2 (10.0%)	5 (25.0%)	7 (17.5%)	
Asthma was diagnosed by a doctor				0.212[1]
No	18 (90.0%)	15 (75.0%)	33 (82.5%)	
Yes	2 (10.0%)	5 (25.0%)	7 (17.5%)	
Has had an asthma attack				1.000[1]
No	19 (95.0%)	19 (95.0%)	38 (95.0%)	
Yes	1 (5.0%)	1 (5.0%)	2 (5.0%)	

Table 15: Respiratory symptom breakdown, control group vs cannabis workers, last 12 months

	Non-Occ (N=40)	*Occupational (N=42)*	*Total (N=82)*	*p value*
History of wheezing				0.013[1]
No	33 (82.5%)	24 (57.1%)	57 (69.5%)	
Yes	7 (17.5%)	18 (42.9%)	25 (30.5%)	
History of wheezing with SOB				0.157[1]
No	38 (95.0%)	36 (85.7%)	74 (90.2%)	
Yes	2 (5.0%)	6 (14.3%)	8 (9.8%)	
Wheezing when subject did not have a cold				0.053[1]
No	34 (85.0%)	28 (66.7%)	62 (75.6%)	
Yes	6 (15.0%)	14 (33.3%)	20 (24.4%)	
Chest tightness				< 0.001[1]
No	38 (95.0%)	27 (64.3%)	65 (79.3%)	
Yes	2 (5.0%)	15 (35.7%)	17 (20.7%)	
Awoken by SOB				0.016[1]
No	38 (95.0%)	32 (76.2%)	70 (85.4%)	
Yes	2 (5.0%)	10 (23.8%)	12 (14.6%)	
History of coughing				0.002[1]
No	38 (95.0%)	29 (69.0%)	67 (81.7%)	
Yes	2 (5.0%)	13 (31.0%)	15 (18.3%)	
Dyspnea at rest				0.056[1]
No	39 (97.5%)	36 (85.7%)	75 (91.5%)	
Yes	1 (2.5%)	6 (14.3%)	7 (8.5%)	
Dyspnea with exertion				0.034[1]
No	36 (90.0%)	30 (71.4%)	66 (80.5%)	
Yes	4 (10.0%)	12 (28.6%)	16 (19.5%)	
History of asthma				0.481[1]
No	33 (82.5%)	32 (76.2%)	65 (79.3%)	
Yes	7 (17.5%)	10 (23.8%)	17 (20.7%)	
Asthma was diagnosed by a doctor				0.654[1]
No	33 (82.5%)	33 (78.6%)	66 (80.5%)	
Yes	7 (17.5%)	9 (21.4%)	16 (19.5%)	
Has had an asthma attack				0.685[1]
No	38 (95.0%)	39 (92.9%)	77 (93.9%)	
Yes	2 (5.0%)	3 (7.1%)	5 (6.1%)	

Table 16: Reported respiratory symptoms among all three groups, last 12 months.

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
History of wheezing					0.002[1]
No	20 (100.0%)	24 (57.1%)	13 (65.0%)	57 (69.5%)	
Yes	0 (0.0%)	18 (42.9%)	7 (35.0%)	25 (30.5%)	
History of wheezing with SOB					0.208[1]
No	20 (100.0%)	36 (85.7%)	18 (90.0%)	74 (90.2%)	
Yes	0 (0.0%)	6 (14.3%)	2 (10.0%)	8 (9.8%)	
Wheezing when subject did not have a cold					0.013[1]
No	20 (100.0%)	28 (66.7%)	14 (70.0%)	62 (75.6%)	
Yes	0 (0.0%)	14 (33.3%)	6 (30.0%)	20 (24.4%)	
Chest tightness					0.002[1]
No	20 (100.0%)	27 (64.3%)	18 (90.0%)	65 (79.3%)	
Yes	0 (0.0%)	15 (35.7%)	2 (10.0%)	17 (20.7%)	
Awoken by SOB					0.037[1]
No	20 (100.0%)	32 (76.2%)	18 (90.0%)	70 (85.4%)	
Yes	0 (0.0%)	10 (23.8%)	2 (10.0%)	12 (14.6%)	
History of coughing					0.007[1]
No	20 (100.0%)	29 (69.0%)	18 (90.0%)	67 (81.7%)	
Yes	0 (0.0%)	13 (31.0%)	2 (10.0%)	15 (18.3%)	
Dyspnea at rest					0.138[1]
No	20 (100.0%)	36 (85.7%)	19 (95.0%)	75 (91.5%)	
Yes	0 (0.0%)	6 (14.3%)	1 (5.0%)	7 (8.5%)	
Dyspnea with exertion					0.030[1]
No	20 (100.0%)	30 (71.4%)	16 (80.0%)	66 (80.5%)	
Yes	0 (0.0%)	12 (28.6%)	4 (20.0%)	16 (19.5%)	
History of asthma					0.393[1]
No	18 (90.0%)	32 (76.2%)	15 (75.0%)	65 (79.3%)	
Yes	2 (10.0%)	10 (23.8%)	5 (25.0%)	17 (20.7%)	
Asthma was diagnosed by a doctor					0.442[1]
No	18 (90.0%)	33 (78.6%)	15 (75.0%)	66 (80.5%)	
Yes	2 (10.0%)	9 (21.4%)	5 (25.0%)	16 (19.5%)	
Has had an asthma attack					0.921[1]
No	19 (95.0%)	39 (92.9%)	19 (95.0%)	77 (93.9%)	
Yes	1 (5.0%)	3 (7.1%)	1 (5.0%)	5 (6.1%)	

Table 17: Tobacco and nicotine habits of participants

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
Smoking status					< 0.001[1]
Current (Past 30 days)	0 (0.0%)	17 (40.5%)	2 (10.0%)	19 (23.2%)	
Formerly (More than 30 days ago)	3 (15.0%)	12 (28.6%)	6 (30.0%)	21 (25.6%)	
Never	17 (85.0%)	13 (31.0%)	12 (60.0%)	42 (51.2%)	
Living with smoker					0.335[1]
No answer	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	
No	18 (90.0%)	39 (92.9%)	17 (85.0%)	74 (90.2%)	
Yes	1 (5.0%)	3 (7.1%)	3 (15.0%)	7 (8.5%)	
Pack Years					0.032[2]
N	3	26	7	36	
Mean (SD)	2.583 (2.222)	2.847 (4.615)	12.707 (17.462)	4.742 (9.139)	
Range	0.050 - 4.200	0.075 - 22.000	0.250 - 48.000	0.050 - 48.000	
Pipe use					0.073[1]
No answer	1 (5.0%)	0 (0.0%)	2 (10.0%)	3 (3.7%)	
Current (Past 30 days)	0 (0.0%)	2 (4.8%)	2 (10.0%)	4 (4.9%)	
Formerly (More than 30 days ago)	1 (5.0%)	8 (19.0%)	0 (0.0%)	9 (11.0%)	
Never	18 (90.0%)	32 (76.2%)	16 (80.0%)	66 (80.5%)	
Cigar use					0.186[1]
No answer	1 (5.0%)	0 (0.0%)	2 (10.0%)	3 (3.7%)	
Current (Past 30 days)	0 (0.0%)	4 (9.5%)	0 (0.0%)	4 (4.9%)	
Formerly (More than 30 days ago)	4 (20.0%)	13 (31.0%)	5 (25.0%)	22 (26.8%)	
Never	15 (75.0%)	25 (59.5%)	13 (65.0%)	53 (64.6%)	
Snuff use					0.101[1]
No answer	1 (5.0%)	0 (0.0%)	3 (15.0%)	4 (4.9%)	
Formerly (More than 30 days ago)	1 (5.0%)	3 (7.1%)	0 (0.0%)	4 (4.9%)	
Never	18 (90.0%)	39 (92.9%)	17 (85.0%)	74 (90.2%)	
Vaping					0.009[1]
No answer	0 (0.0%)	0 (0.0%)	3 (15.0%)	3 (3.7%)	
Current (Past 30 days)	0 (0.0%)	7 (16.7%)	1 (5.0%)	8 (9.8%)	

Formerly (More than 30 days ago)	3 (15.0%)	11 (26.2%)	6 (30.0%)	20 (24.4%)	
Never	17 (85.0%)	24 (57.1%)	10 (50.0%)	51 (62.2%)	
Hookah					0.012[1]
No answer	0 (0.0%)	0 (0.0%)	3 (15.0%)	3 (3.7%)	
Current (Past 30 days)	0 (0.0%)	1 (2.4%)	1 (5.0%)	2 (2.4%)	
Formerly (More than 30 days ago)	5 (25.0%)	22 (52.4%)	5 (25.0%)	32 (39.0%)	
Never	15 (75.0%)	19 (45.2%)	11 (55.0%)	45 (54.9%)	

Table 18: Cannabis use profiles

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
Subject reported use status					< 0.001[1]
I have never used marijuana	7 (35.0%)	1 (2.4%)	0 (0.0%)	8 (9.8%)	
I have used marijuana in the last 30 days	0 (0.0%)	41 (97.6%)	20 (100.0%)	61 (74.4%)	
I used to use marijuana but I haven't used it recently (more than 30 days ago)	13 (65.0%)	0 (0.0%)	0 (0.0%)	13 (15.9%)	
Most recent use episode					< 0.001[1]
N/A	7 (35.0%)	42 (100.0%)	0 (0.0%)	49 (59.8%)	
In the last 24 hours.	0 (0.0%)	0 (0.0%)	11 (55.0%)	11 (13.4%)	
In the last hour.	0 (0.0%)	0 (0.0%)	3 (15.0%)	3 (3.7%)	
In the last week.	0 (0.0%)	0 (0.0%)	4 (20.0%)	4 (4.9%)	
More than a week ago.	13 (65.0%)	0 (0.0%)	0 (0.0%)	13 (15.9%)	
Yesterday.	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (2.4%)	
Smoking					< 0.001[1]
More than once a month	2 (10.0%)	2 (4.8%)	1 (5.0%)	5 (6.1%)	
More than once a week	3 (15.0%)	4 (9.5%)	5 (25.0%)	12 (14.6%)	
Multiple times daily	1 (5.0%)	33 (78.6%)	6 (30.0%)	40 (48.8%)	
Never	8 (40.0%)	1 (2.4%)	2 (10.0%)	11 (13.4%)	
Once a day	0 (0.0%)	1 (2.4%)	5 (25.0%)	6 (7.3%)	
Once or twice a year	6 (30.0%)	1 (2.4%)	1 (5.0%)	8 (9.8%)	
Edibles					< 0.001[1]
Every few months	1 (5.0%)	11 (26.2%)	4 (20.0%)	16 (19.5%)	
More than once a month	0 (0.0%)	10 (23.8%)	8 (40.0%)	18 (22.0%)	
More than once a week	0 (0.0%)	7 (16.7%)	4 (20.0%)	11 (13.4%)	
Never	12 (60.0%)	5 (11.9%)	2 (10.0%)	19 (23.2%)	
Once a day	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (2.4%)	

Once or twice a year	7 (35.0%)	9 (21.4%)	0 (0.0%)	16 (19.5%)	
Vaping					< 0.001[1]
Every few months	0 (0.0%)	9 (21.4%)	5 (25.0%)	14 (17.1%)	
More than once a month	0 (0.0%)	5 (11.9%)	0 (0.0%)	5 (6.1%)	
More than once a week	0 (0.0%)	11 (26.2%)	4 (20.0%)	15 (18.3%)	
Multiple times daily	1 (5.0%)	5 (11.9%)	4 (20.0%)	10 (12.2%)	
Never	14 (70.0%)	8 (19.0%)	3 (15.0%)	25 (30.5%)	
Once a day	0 (0.0%)	1 (2.4%)	1 (5.0%)	2 (2.4%)	
Once or twice a year	5 (25.0%)	3 (7.1%)	3 (15.0%)	11 (13.4%)	
Dabs					< 0.001[1]
Every few months	0 (0.0%)	5 (11.9%)	2 (10.0%)	7 (8.5%)	
More than once a month	0 (0.0%)	2 (4.8%)	2 (10.0%)	4 (4.9%)	
More than once a week	0 (0.0%)	6 (14.3%)	0 (0.0%)	6 (7.3%)	
Multiple times daily	1 (5.0%)	12 (28.6%)	0 (0.0%)	13 (15.9%)	
Never	15 (75.0%)	10 (23.8%)	6 (30.0%)	31 (37.8%)	
Once a day	0 (0.0%)	3 (7.1%)	0 (0.0%)	3 (3.7%)	
Once or twice a year	4 (20.0%)	4 (9.5%)	10 (50.0%)	18 (22.0%)	
Topicals					0.003[1]
Every few months	0 (0.0%)	10 (23.8%)	4 (20.0%)	14 (17.1%)	
More than once a month	0 (0.0%)	4 (9.5%)	0 (0.0%)	4 (4.9%)	
More than once a week	0 (0.0%)	7 (16.7%)	0 (0.0%)	7 (8.5%)	
Multiple times daily	1 (5.0%)	1 (2.4%)	0 (0.0%)	2 (2.4%)	
Never	15 (75.0%)	10 (23.8%)	7 (35.0%)	32 (39.0%)	
Once a day	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (1.2%)	
Once or twice a year	4 (20.0%)	9 (21.4%)	9 (45.0%)	22 (26.8%)	
MJ Card					< 0.001[1]
Holds a marijuana card	0 (0.0%)	42 (100.0%)	0 (0.0%)	42 (51.2%)	
No	20 (100.0%)	0 (0.0%)	19 (95.0%)	39 (47.6%)	

Yes	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (1.2%)	
Lives with a marijuana user					< 0.001[1]
N/A	0 (0.0%)	42 (100.0%)	0 (0.0%)	42 (51.2%)	
No	17 (85.0%)	0 (0.0%)	9 (45.0%)	26 (31.7%)	
Yes	3 (15.0%)	0 (0.0%)	11 (55.0%)	14 (17.1%)	
Lives with an occupational cultivator					< 0.001[1]
N/A	0 (0.0%)	42 (100.0%)	1 (5.0%)	43 (52.4%)	
No	20 (100.0%)	0 (0.0%)	18 (90.0%)	38 (46.3%)	
Yes	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (1.2%)	
Cultivates at home					< 0.001[1]
N/A	0 (0.0%)	42 (100.0%)	0 (0.0%)	42 (51.2%)	
No	20 (100.0%)	0 (0.0%)	20 (100.0%)	40 (48.8%)	
Prepares products at home for someone else					< 0.001[1]
N/A	0 (0.0%)	42 (100.0%)	0 (0.0%)	42 (51.2%)	
No	20 (100.0%)	0 (0.0%)	20 (100.0%)	40 (48.8%)	

Table 19: Reported diagnoses from medical professionals

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
Asthma					0.455[1]
N/A	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	
Don't know	0 (0.0%)	2 (4.8%)	1 (5.0%)	3 (3.7%)	
No	17 (85.0%)	31 (73.8%)	14 (70.0%)	62 (75.6%)	
Yes	2 (10.0%)	9 (21.4%)	5 (25.0%)	16 (19.5%)	
Hayfever					0.426[1]
N/A	2 (10.0%)	0 (0.0%)	1 (5.0%)	3 (3.7%)	
Don't know	1 (5.0%)	1 (2.4%)	1 (5.0%)	3 (3.7%)	
No	15 (75.0%)	30 (71.4%)	14 (70.0%)	59 (72.0%)	
Yes	2 (10.0%)	11 (26.2%)	4 (20.0%)	17 (20.7%)	
COPD					0.301[1]
N/A	2 (10.0%)	0 (0.0%)	1 (5.0%)	3 (3.7%)	
No	18 (90.0%)	41 (97.6%)	19 (95.0%)	78 (95.1%)	
Yes	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (1.2%)	
Chronic Pneumonia					0.135[1]
N/A	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (2.4%)	
No	18 (90.0%)	40 (95.2%)	17 (85.0%)	75 (91.5%)	
Yes	2 (10.0%)	2 (4.8%)	1 (5.0%)	5 (6.1%)	
Eczema					0.176[1]
N/A	3 (15.0%)	0 (0.0%)	1 (5.0%)	4 (4.9%)	
Don't know	1 (5.0%)	2 (4.8%)	0 (0.0%)	3 (3.7%)	
No	14 (70.0%)	30 (71.4%)	16 (80.0%)	60 (73.2%)	
Yes	2 (10.0%)	10 (23.8%)	3 (15.0%)	15 (18.3%)	

Table 20: Pulmonary function testing results

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
FEV1					0.041[1]
N	20	21	20	61	
Mean (SD)	2.940 (0.844)	3.565 (0.810)	3.314 (0.650)	3.278 (0.803)	
Range	0.970 - 4.280	2.330 - 4.950	1.880 - 4.640	0.970 - 4.950	
FVC					0.086[1]
N	20	21	20	61	
Mean (SD)	3.832 (0.831)	4.469 (0.934)	4.255 (0.976)	4.190 (0.940)	
Range	1.780 - 5.240	3.200 - 6.110	2.500 - 6.440	1.780 - 6.440	
FEV1/FVC Ratio					0.592[1]
N	20	21	20	61	
Mean (SD)	0.806 (0.067)	0.797 (0.069)	0.784 (0.067)	0.796 (0.067)	
Range	0.665 - 0.919	0.646 - 0.919	0.613 - 0.918	0.613 - 0.919	
FEV1 % Pred					0.531[1]
N	20	21	20	61	
Mean (SD)	96.000 (15.145)	92.429 (13.706)	97.550 (15.836)	95.279 (14.812)	
Range	71.000 - 124.000	68.000 - 116.000	72.000 - 123.000	68.000 - 124.000	
FVC % Pred					0.205[1]
N	20	21	20	61	
Mean (SD)	99.250 (15.365)	95.667 (10.326)	103.850 (17.245)	99.525 (14.695)	
Range	64.000 - 133.000	72.000 - 114.000	76.000 - 128.000	64.000 - 133.000	
FEV1/FVC Ratio % Pred					0.628[1]
N	20	21	20	61	
Mean (SD)	96.350 (7.343)	96.048 (7.507)	94.200 (7.997)	95.541 (7.551)	
Range	85.000 - 110.000	76.000 - 111.000	76.000 - 111.000	76.000 - 111.000	

Table 21: FeNO testing results

	Non-User (N=20)	*Occupationally Exposed (N=42)*	*Recreational (N=20)*	*Total (N=82)*	*p value*
FeNO					0.011[1]
N	20	21	20	61	
Mean (SD)	15.650 (7.264)	30.571 (26.370)	15.550 (13.312)	20.754 (18.869)	
Range	8.000 - 39.000	6.000 - 102.000	5.000 - 64.000	5.000 - 102.000	

Table 22: Skin Prick Testing sensitivity to cannabis or hemp, non-users vs. recreational users without occupational exposure.

	Non-User (N=20)	*Recreational Users (N=20)*	*Total (N=40)*	*p value*
Saline				1.000[1]
No Reaction	20 (100.0%)	20 (100.0%)	40 (100.0%)	
Histamine				1.000[1]
No Reaction	1 (5.0%)	1 (5.0%)	2 (5.0%)	
Reaction	19 (95.0%)	19 (95.0%)	38 (95.0%)	
Hemp/Cannabis Sensitivity				0.311[1]
No Reaction	20 (100.0%)	19 (95.0%)	39 (97.5%)	
Reaction	0 (0.0%)	1 (5.0%)	1 (2.5%)	

Table 23: Skin Prick Testing sensitivity to cannabis or hemp, cannabis workers compared to those without occupational exposure.

	Non-Occupational (N=40)	*Occupational (N=19)*	*Total (N=59)*	*p value*
Saline				1.000[1]
No Reaction	40 (100.0%)	19 (100.0%)	59 (100.0%)	
Histamine				0.825[1]
No Reaction	2 (5.0%)	0 (0.0%)	2 (3.4%)	
Reaction	38 (95.0%)	19 (100.0%)	57 (96.6%)	
Hemp/Cannabis Sensitivity				0.001[1]
No Reaction	39 (97.5%)	13 (68.4%)	52 (88.1%)	
Reaction	1 (2.5%)	6 (31.6%)	7 (11.9%)	

Table 24: Skin Prick Testing sensitivity to cannabis or hemp, cannabis workers compared to recreational users without occupational exposure.

	Recreational Users without Occupational Exposure (N=20)	*Occupationally Exposed (N=19)*	*Total (N=39)*	*p value*
Saline				1.000[3]
No Reaction	20 (100.0%)	19 (100.0%)	39 (100.0%)	
Histamine				1.000[3]
No Reaction	1 (5.0%)	0 (0.0%)	1 (2.6%)	
Reaction	19 (95.0%)	19 (100.0%)	38 (97.4%)	
Hemp/Cannabis Sensitivity				0.044[3]
No Reaction	19 (95.0%)	13 (68.4%)	32 (82.1%)	
Reaction	1 (5.0%)	6 (31.6%)	7 (17.9%)	

Table 25: Skin Prick Testing sensitivity to cannabis or hemp, cannabis workers compared to those without occupational exposure who use recreationally or who do not use.

	Non-User (N=20)	*Occupationally Exposed (N=19)*	*Recreational Users (N=20)*	*Total (N=63)*	*p value*
Saline					0.983[1]
No Reaction	20 (100.0%)	19 (100.0%)	20 (100.0%)	59 (100.0%)	
Histamine					0.612[2]
No Reaction	1 (5.0%)	0 (0.0%)	1 (5.0%)	2 (3.4%)	
Reaction	19 (95.0%)	19 (100.0%)	19 (95.0%)	57 (96.6%)	
Hemp/Cannabis Sensitivity					0.005[2]
No Reaction	20 (100.0%)	13 (68.4%)	19 (95.0%)	52 (88.1%)	
Reaction	0 (0.0%)	6 (31.6%)	1 (5.0%)	7 (11.9%)	

Table 26: Crude odds ratios between groups of individual symptoms with handling or work-related cannabis tasks

	Non-User (N=20)	*Occupationally Exposed (N=42) [OR, CI, p]*	*Recreational (N=20) [OR, CI, p]*	*Total (N=82)*	*p value*
Red or watery eyes		[9.50 (1.15, 78.42), 0.01[3]]	[23.22 (2.59, 208.61), <0.001[3]]		0.003[1]
No	19 (95.0%)	28 (66.7%)	9 (45.0%)	56 (68.3%)	
Yes	1 (5.0%)	14 (33.3%)	11 (55.0%)	26 (31.7%)	
Nasal or sinus symptoms		[25.53 (1.44, 451.12), 0.002[3]]	[5.54 (0.25, 123.08), 0.549[6]]		0.001[1]
No	20 (100.0%)	26 (61.9%)	18 (90.0%)	64 (78.0%)	
Yes	0 (0.0%)	16 (38.1%)	2 (10.0%)	18 (22.0%)	
Shortness of breath		[16.80 (0.94, 299.82), 0.03[4]]	[5.54 (0.25, 123.08), 0.549[6]]		0.013[1]
No	20 (100.0%)	30 (71.4%)	18 (90.0%)	68 (82.9%)	
Yes	0 (0.0%)	12 (28.6%)	2 (10.0%)	14 (17.1%)	
Wheezing		[8.66 (0.47, 159.62), 0.191[5]]	[11.18 (0.56, 222.98), 0.153[7]]		0.121[1]
No	20 (100.0%)	35 (83.3%)	16 (80.0%)	71 (86.6%)	
Yes	0 (0.0%)	7 (16.7%)	4 (20.0%)	11 (13.4%)	
Cough or congestion		[7.43 (1.53, 36.17), 0.006[3]]	[6.00 (1.08, 33.27), 0.028[8]]		0.022[1]
No	18 (90.0%)	23 (54.8%)	12 (60.0%)	53 (64.6%)	
Yes	2 (10.0%)	19 (45.2%)	8 (40.0%)	29 (35.4%)	

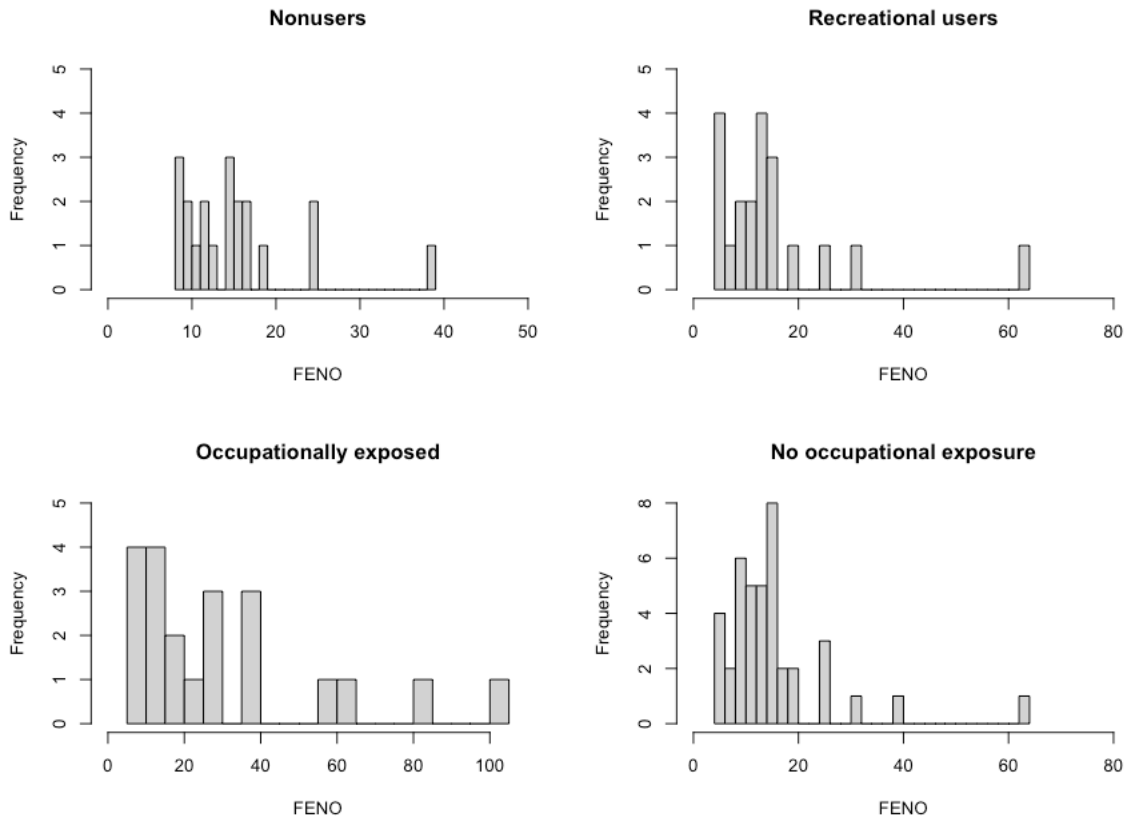
Appendix 5: Modeling

Analysis of FeNO

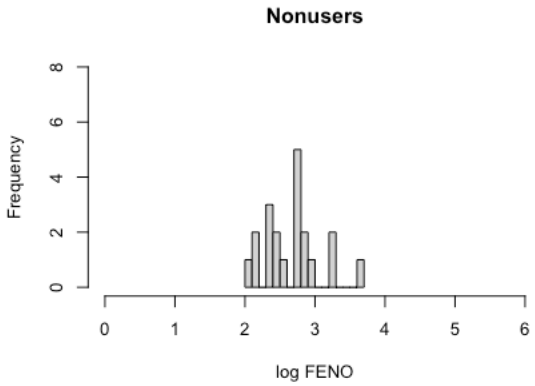
To perform regression analysis, we must satisfy the following assumptions:

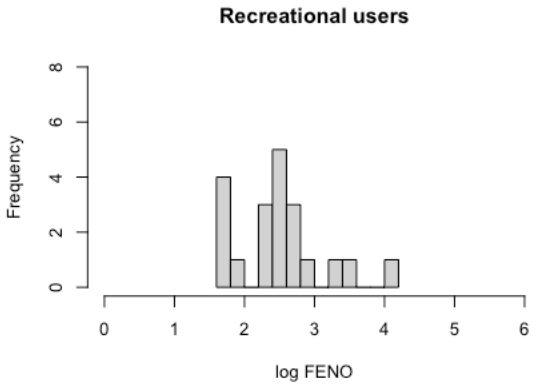
Linearity, Independence, Normality, and Equal Variance

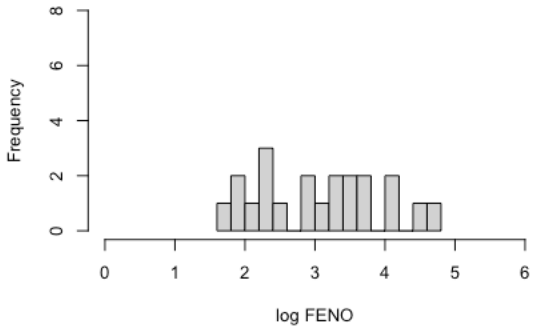
Initial analysis of FENO between groups demonstrates right skew data:

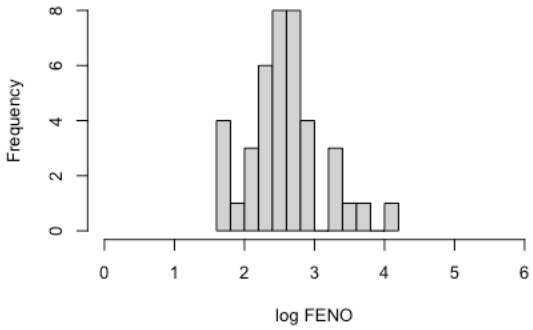


Log transformation of these gives us a more normal looking result.

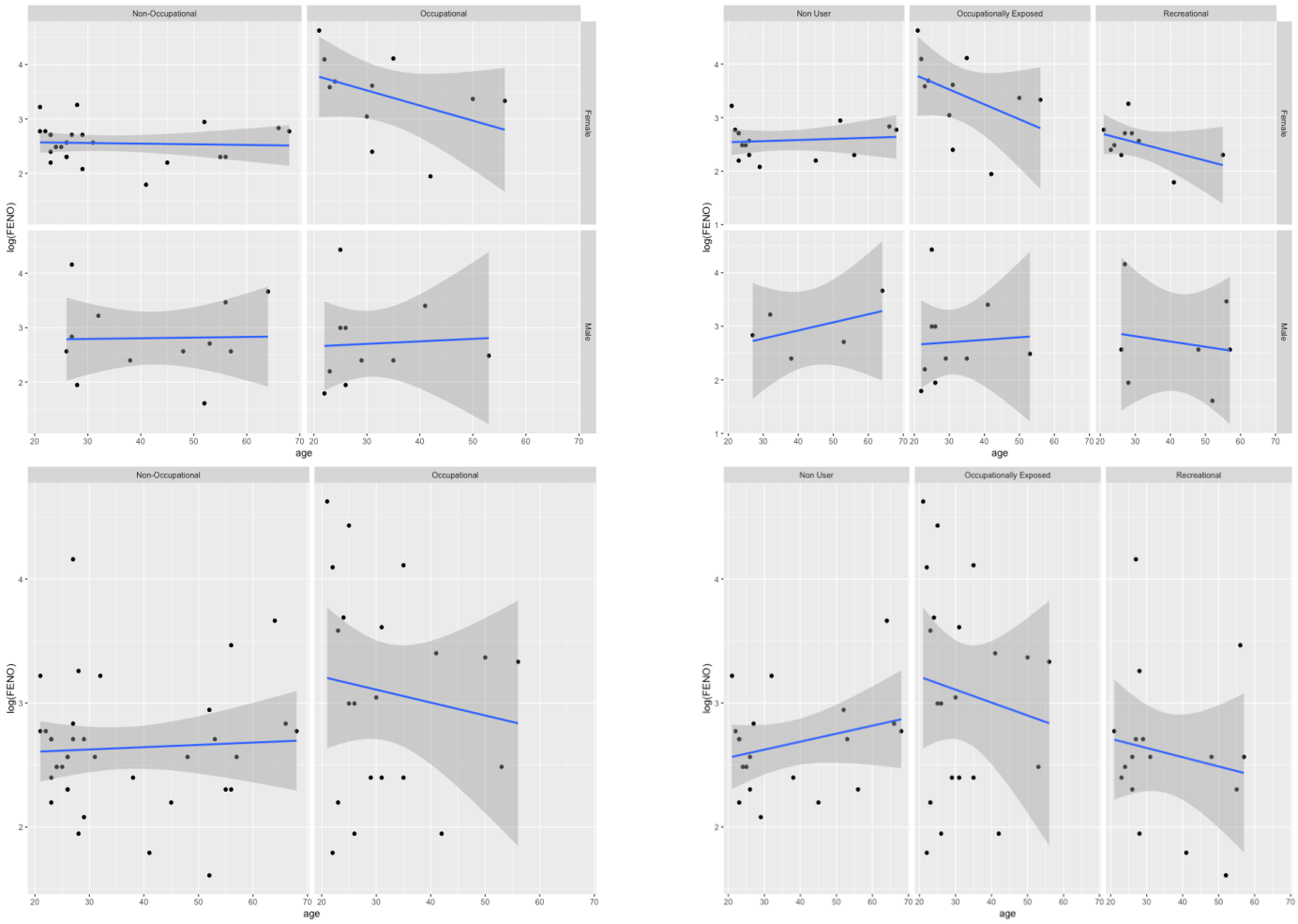

Nonusers
Frequency
log FENO


Recreational users
Frequency
log FENO

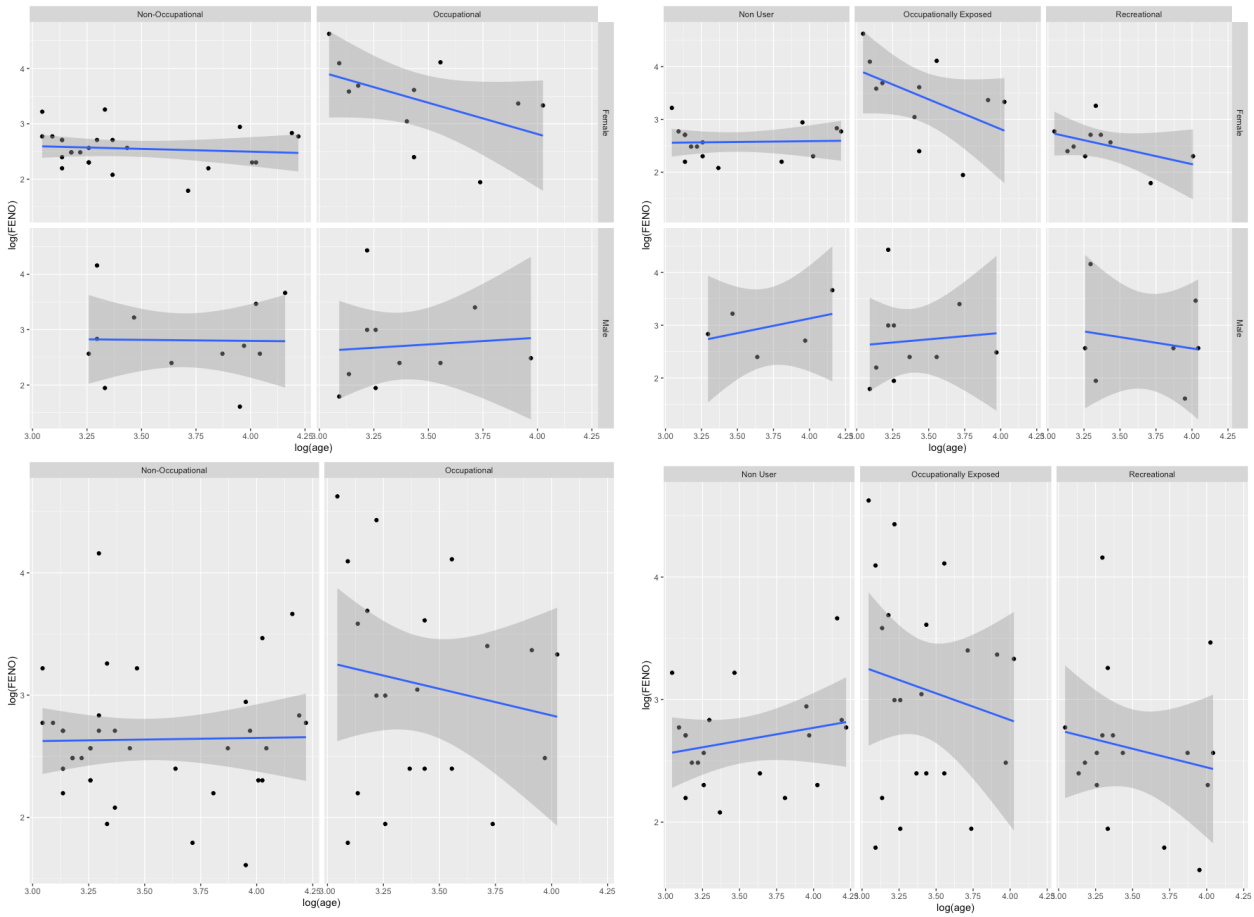

Occupationally exposed
Frequency
log FENO


No occupational exposure
Frequency
log FENO

Next, the log-transformed data was examined for evidence of linear relationships between exposure groups by age and by age, subdivided by sex.



The same comparison using log-Age was also examined

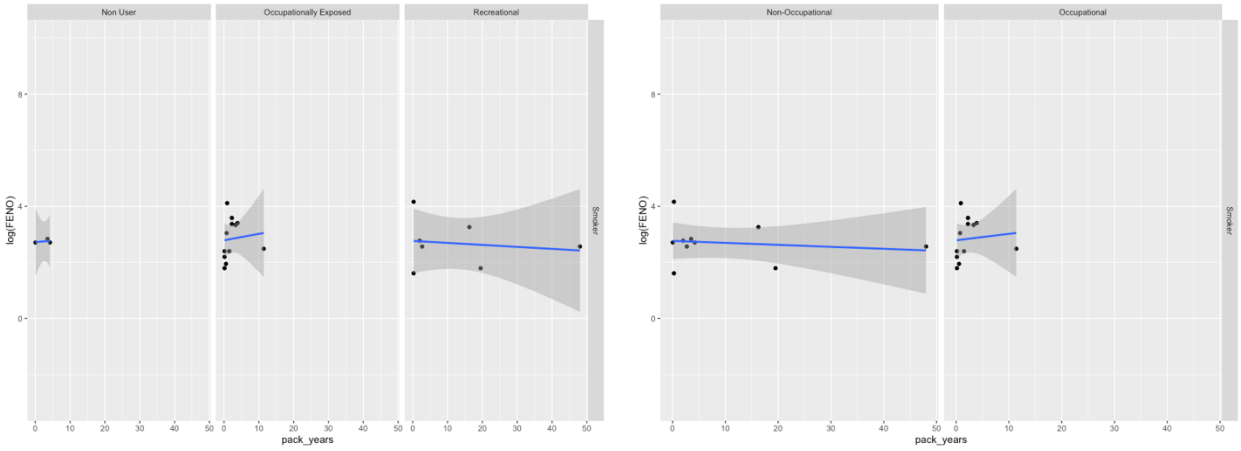


Shaded areas represent 95% confidence interval for the data based on standard error calculation. We see a decreasing trend in log FENO with both age and log age in male Occupational and Recreational groups of both sexes with an increasing trend with age in non-users, and the female occupational group. This is the same as the trend of just FENO with age (not shown).

Pack years and log-pack-years of smoking was also investigated. There appeared to be something of a relationship with pack years. Log pack years shows this a little better.

It was the basis of this analysis that justified combination of past smokers vs never smokers in terms of pack years. Again, this is a valid approach based on our small cohort and was the previous approach used by Toren et, al.

Never smokers obviously has nothing to show.



An increase in log-FeNO with increasing PY in the non-users, a decrease in the recreational group and a paradoxical increase in the occupationally exposed group. In just the groups separated by work exposure you see this hold up.

The following model was defined based on this analysis:

$$\log(FeNO) = \beta_0 + \beta_{1a}X + \beta_{1b}X + \beta_2X + \beta_3X + \beta_4X + \beta_5X + \beta_6X$$

Where:

β_0 is the intercept

β_1 is the coefficient for either occupational exposure or recreational use

β_2 is the sex coefficient

β_3 is the age coefficient

β_4 is the height coefficient

β_5 is the coefficient for positive report of work or handling related atopic symptoms

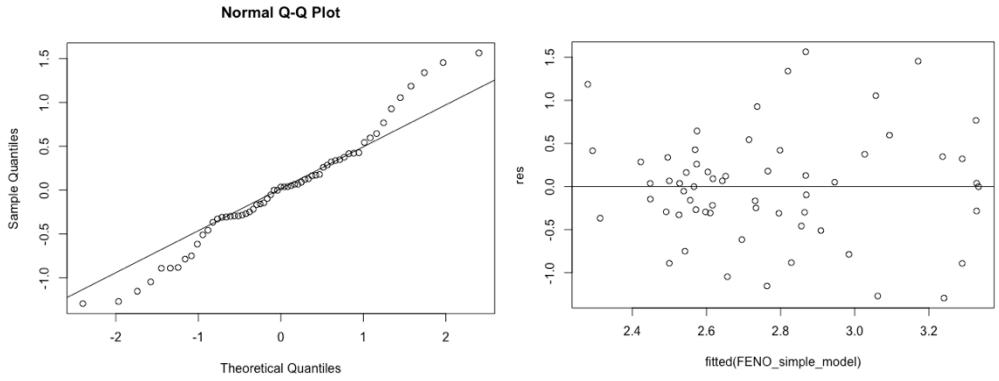
β_6 is the coefficient for smoking status

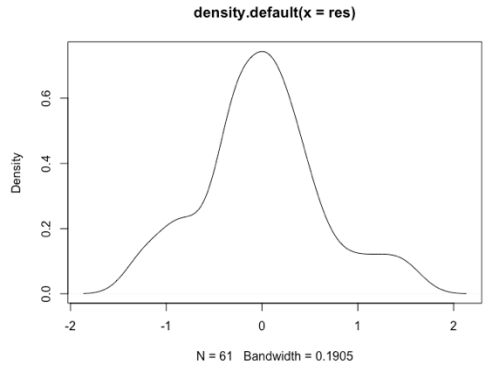
For the case where smoking is not considered ($\beta_6 = 0$) a basic model for occupational exposure is defined.

```
Residuals:
     Min       1Q   Median       3Q      Max
-1.29477 -0.30774  0.03661  0.33762  1.56308

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.0818349  1.5170861  -0.054   0.9572
EXP          0.3991054  0.2036531   1.960   0.0551 .
SEX          0.1481151  0.1785581   0.830   0.4104
AGE          0.0001983  0.0067598   0.029   0.9767
HEIGHT       0.0153431  0.0090966   1.687   0.0973 .
ATOPY        0.0513419  0.1931786   0.266   0.7914
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6584 on 55 degrees of freedom
Multiple R-squared:   0.17, Adjusted R-squared:  0.09454
F-statistic: 2.253 on 5 and 55 DF,  p-value: 0.06177
```



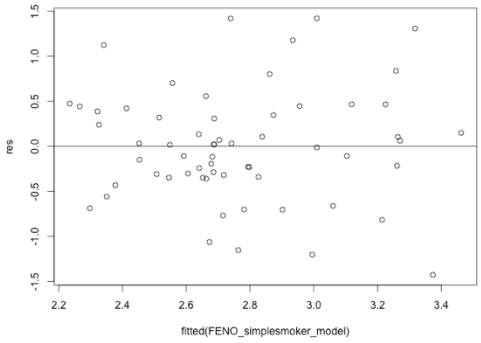


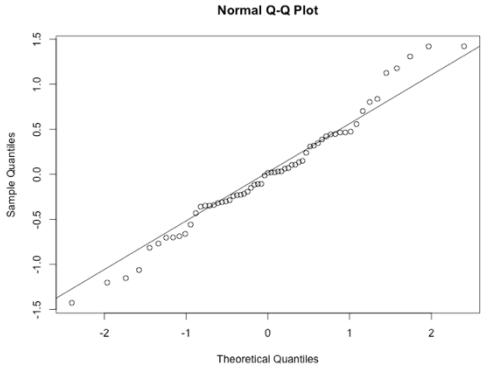
The intercept coefficient in this model ceases to be significant and analysis of the Q-Q plot showed concerning evidence of violating normality assumptions. When smoking status is appropriately included in the model the fit improves.

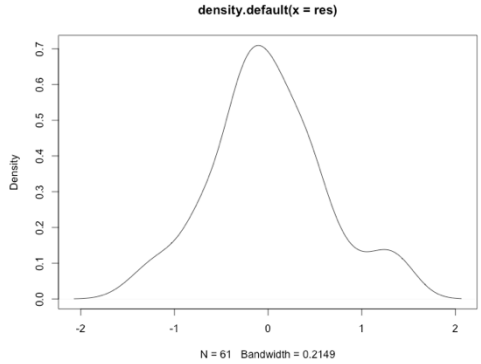
```
Residuals:
     Min       1Q   Median       3Q      Max
-1.42754 -0.34134  0.01632  0.38679  1.42148

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.540856   1.550203  -0.349   0.7285
EXP          0.445325   0.205657   2.165   0.0348 *
SEX          0.121849   0.178701   0.682   0.4982
AGE          0.000375   0.006722   0.056   0.9557
ATOPY        0.092561   0.194731   0.475   0.6365
HEIGHT       0.018473   0.009368   1.972   0.0537 .
SMOKE       -0.247832   0.193315  -1.282   0.2053
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6546 on 54 degrees of freedom
Multiple R-squared:  0.1945,    Adjusted R-squared:  0.105
F-statistic: 2.173 on 6 and 54 DF,  p-value: 0.05977
```







Appendix 6: Quantile Regression Model

To address the limitations of the linear regression a quantile regression model could be developed the predicts FeNO in cannabis workers.

$$Q_\tau(FeNO) = \beta_0(\tau) + \beta_{1a}(\tau)X + \beta_{1b}(\tau)X + \beta_2(\tau)X + \beta_3(\tau)X + \beta_4(\tau)X + \beta_5(\tau)X + \beta_6(\tau)X$$

Table 8 presents coefficients for a reference equation that predicts FeNO in workers with exposure to cannabis in an indoor grow facility that includes mean and median values and the 10th and 90th percentiles by quantile regression. These values reject the null hypothesis at the alpha = 0.1 level.

As an example, a 40-year-old female cannabis worker standing 140cm, smoker, reporting work associated symptoms in the 90th%ile for predicted FeNO would be:

FeNO = 39.6-17.46-40*.11+140*.28+1.4-5.11 = 53.23 ppb

her predicted FeNO if she were representative of the mean:

FeNO = -33.4+1.4-40*.12+140*.41-.73-5.94 = 13.93 ppb

Multiple R-squared was 0.195 and F-test p value 0.06 for this best accepted model.

Table 27: Reference equation coefficients for estimating FeNO in an occupationally exposed indoor cannabis grower.

Coefficients	*10th %ile*	*Mean*	*Median*	*90th %ile*
Intercept + Occupational Exposure	14.533	-33.378	-30.912	39.575
Female	1.39	1.412	2.08	-17.464
Age	-0.127	-0.121	-0.102	-0.114
Height	-0.005	0.415	0.363	0.282
Handling Atopy	-2.78	-0.737	-5.673	1.401
Tobacco smoking	-0.725	-5.941	-3.289	-5.113