Methodological issues in the assessment of the safety of medical cannabis

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STATEMENT OF ORIGINALITY

This thesis is aimed at improving information regarding the safety of medical cannabis use. To the best of my knowledge, the meta-analysis is the first study to examine the safety of pharmaceutical cannabinoid products by assessing adverse events reporting in all randomized controlled trials. Our systematic review of safety studies of recreational cannabis use provides complementary safety information on herbal cannabis.

Secondly, the Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS) is the first observational cohort study ever conducted to address the safety of medical herbal cannabis use, with a median follow-up of one year.

Lastly, this thesis also includes a study of comparing the statistical efficiency of the estimated Ln(RR) in matched and unmatched cohort designs, given a fixed number of subjects. In light of the findings, a refinement of the existing guidelines regarding choosing a matching strategy to improve efficiency in cohort studies is proposed.

AUTHORSHIP

The thesis described herein contains four projects: assessing the safety of pharmaceutical cannabinoid products in a meta-analysis (thesis project #1), studying the safety of recreational cannabis use in a systematic review (thesis project #2), assessing the safety of Health Canada herbal cannabis products in the management of chronic pain in a prospective cohort study, *Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS) (thesis project #3)*, and investigating the impact of matching on statistical efficiency in cohort studies (thesis project #4). The meta-analysis (thesis project #1), the systematic review (project #2), and the methodology development project (thesis project #4), which I developed under the supervision of my thesis committee, arose during the execution of the COMASS study (thesis project #3). I joined the COMPASS research team after funding for the first submission of this protocol was denied by the Canadian Institutes of Health Research (CIHR). I then started working towards the submission of the second version. My personal contributions to this specific study are related to the selection of the appropriate study design and the development of safety data analysis. I was also responsible for conducting all of the statistical analyses required for the execution of COMPASS project including data verification and validation.

The first thesis project has been published in the Canadian Medical Association Journal (CMAJ) [Wang T, Collet J-P, Shapiro S, and Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008; 178 (13): 1669-1678]. I was responsible for designing the study, obtaining the data, analyzing and interpreting the data, and preparing the manuscript. All co-authors were involved in providing me with methodological and clinical advice throughout the execution of this manuscript. They also provided critical revisions and approval of the final version of the manuscript. Chapter 3 includes the text of this manuscript.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AIDS	acquired immunodeficiency syndrome
CB	cannabinoid receptor
CBD	cannabidiol
CBN	cannabinol
CDSA	Controlled Drugs and Substances Act
CI	confidence interval
CIHR	Canadian Institutes of Health Research
COMPASS	Cannabis for the Management of Pain: Assessment of Safety Study
CONSORT	Consolidated Standards of Reporting Trials
DAST	Drug Abuse Screening Test
DL_{CO}	diffusing capacity for carbon monoxide
FDA	Food and Drug Administration
$FEF_{25-75\%}$	forced expiratory flow over the middle half of the forced vital capacity
FEV_1	forced expired volume in one second
FRC	functional residual capacity
FVC	forced vital capacity
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IRR	incidence rate ratio
Ln (RR)	logarithm of the risk ratio
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMAR	Marihuana Medical Access Regulations
MMRP	Medical Marijuana Research Program
NCR	Narcotic Control Regulations
NRS	numerical rating scale
OR	odds ratio
PCS	Physical Component Summary
PFT	pulmonary function tests
PPS	Prairie Plant Systems Inc.
PT	Preferred Term
RCT	randomized controlled trial
REB	Research Ethics Board
RR	rate ratio
RV	residual volume
SAE	serious adverse event
SD	standard deviation
SE	standard error
SMAC	Safety Monitoring Advisory Committee
SOC	System Organ Class
SVC	slow vital capacity
THC	tetrahydrocannabinol
TLC	total lung capacity
UDT	urine drug testing
VAS	visual analogue scale
WAIS®-III	Wechsler Adult Intelligence Scale—Third Edition
WMS®-III	Wechsler Memory Scale—Third Edition

ABSTRACT

Increasing use of cannabis for therapeutic purposes raises safety concerns; however, epidemiological studies have not been conducted to specifically evaluate the safety of herbal cannabis used for medical purposes. Available safety information comes primarily from either observational studies that focus on recreational use or from randomized controlled trials (RCTs) that emphasize efficacy as the primary study objective.

This thesis seeks to improve our understanding of the safety of medical cannabis use. Existing safety information was first assessed in a meta-analysis of all cannabinoid RCTs and a separate systematic review of recreational cannabis. Following this, a prospective cohort study [Cannabis for the Management of Pain, Assessment of Safety Study (COMPASS)] was then conducted. A total of 215 subjects (chronic pain patients who used cannabis provided by Health Canada in the study) and 216 controls (who did not use cannabis) were recruited from across Canada. Adverse events were collected over a one-year period to assess the safety of herbal cannabis for the treatment of chronic pain. In considering the most efficient strategy to control for potential confounders in the development of COMPASS, the statistical efficiency of matching and a multiple model with an adjustment for confounders were compared in a separate project.

This thesis improves our knowledge about adverse events associated with medical cannabis (pharmaceutical cannabinoid products and herbal cannabis), and contributes to the discussion concerning its therapeutic uses from a safety point of view. The consistency of results from our meta-analysis and the COMPASS study allows us to more firmly conclude that medical cannabis was associated with an increased risk of non-serious adverse events (AEs), in particular in relation to the nervous system and psychiatric disorders, compared to controls. However, the evidence regarding the presence or absence of a potential risk of serious adverse

events, among patients on cannabis compared with controls, is inconclusive because the study lacks power.

In conclusion, the results suggest the adverse effects of medical cannabis among experienced users are modest. Further studies with systematic long-term follow-up are required to characterize safety issues among new cannabis users and the risk of serious adverse events.

RÉSUMÉ

L'utilisation accrue du cannabis pour des besoins thérapeutiques soulève des questions sur son innocuité; et pourtant, aucune étude épidémiologique n'a été conduite pour évaluer cette innocuité. L'information disponible vient essentiellement, d'études observationnelles d'utilisation du cannabis dans le cadre d'un usage récréatif, ou d'essais cliniques randomisés qui ont comme principal objectif l'évaluation de l'efficacité d'un produit.

Cette thèse cherche à améliorer notre connaissance sur l'innocuité du cannabis pour usage médical. L'information disponible a été initialement utilisée dans le cadre d'une méta-analyse des essais cliniques randomisés sur les cannabinoïdes et ensuite dans le cadre d'une revue systématique des études observationnelles sur l'utilisation du cannabis dans le cadre d'un usage récréatif. Par la suite, une étude de cohorte prospective [Cannabis for the Management of Pain, Assessment of Safety Study (COMPASS)] a été menée. Dans le cadre de cette étude, un total de 215 sujets (des patients ayant une douleur chronique et qui ont utilisé le cannabis fourni dans le cadre du programme de Santé Canada) ainsi que 216 contrôles (des gens avec douleur chrnonique qui n'ont pas utilisé de cannabis) ont été recrutés à travers tout le Canada. Les effets indésirables ont été collectés sur une période d'une année pour évaluer l'innocuité du cannabis. En cherchant la meilleure stratégie pour contrôler les facteurs confondants, dans le cadre de l'étude COMPASS, l'efficience statistique de l'appariement (matching) et du modèle multiple (multiple model) avec ajustement pour les facteurs confondants a été examinée dans un projet séparé.

Cette thèse améliore nos connaissances concernant les effets indésirables associés à l'utilisation du cannabis à des fins médicales (cannabinoïdes pharmaceutiques et les feuilles de cannabis), et contribue à la discussion concernant l'usage thérapeutique du cannabis d'un point de vue de son innocuité. La concordance des

résultats de notre méta-analyse et de ceux de l'étude COMPASS nous permet de conclure, en comparaison avec le groupe contrôle, l'utilisation du cannabis pour des besoins thérapeutiques est associée à un risque accrue d'effets indésirables moins sévères, en particulier ceux relatifs au système nerveux et aux désordres psychiatriques. Cependant, comparativement au groupe de contrôle, les résultats relatifs au risque potentiel d'effets indésirables sérieux chez les patients exposés au cannabis sont non concluants.

En conclusion, les résultats de notre étude suggèrent que les effets indésirables sont minimes parmi les utilisateurs de longue durée du cannabis. D'autres études ayant une période de suivi plus longue sont nécessaires pour déterminer l'innocuité du cannabis parmi les nouveaux utilisateurs et le risque d'effets indésirables graves.

CHAPTER 1: INTRODUCTION

1.1 Medicinal cannabis use

1.1.1 Pharmaceutical cannabinoid products

Cannabis preparations have been used as a medicine for thousands of years. However, much evidence for their safety and efficacy came from anecdotal suggestion, rather than from controlled clinical trials. Modern scientific investigation into the potential therapeutic uses of cannabis began with the isolation and synthesis of delta-9-tetrahydrocannabinol (Δ^9-THC), the primary psychoactive cannabinoid in cannabis. The Israeli scientists Raphael Mechoulam, Yuval Shvo, and Yehiel Gaoni determined the structure and stereochemistry of the first cannabinol in 1963,[1] and purified Δ^9-THC, its main psychoactive constituent in 1964.[2] This became the pharmacological basis for assessing the activity of cannabis.

In the 1990s, two types of cannabinoid receptors (CB_1 and CB_2) and natural cannabinoid molecules in the body that bind to and activate these receptors (endogenous cannabinoids) were identified. These discoveries provided key evidence that explained the reported therapeutic effects of cannabis, and helped to understand the mechanisms of action of cannabinoids.

In the past 20-30 years the active ingredients of cannabis, THC and cannabidiol (CBD), and their derivatives have been evaluated in a multitude of medical conditions.[3] Several forms of cannabinoids are currently used for medical purposes, including a synthetic THC (e.g. dronabinol), a synthetic THC analog (e.g. nabilone), and a standardized non-smoked cannabis extract (e.g. Sativex®,

including THC and CBD). Randomized controlled trials (RCTs) of these pharmaceutical cannabinoid products are being conducted internationally. These trials involved subjects with various medical conditions, such as cancer or multiple sclerosis, and use of cannabinoids was intended to address symptoms such as nausea and vomiting induced by chemotherapy or pain. However, no systematic review of these RCTs has ever been conducted to evaluate the safety of pharmaceutical cannabinoid products.

1.1.2 Herbal cannabis

Although the emphasis of medical cannabis research has shifted to include pharmaceutical cannabinoid products, there is still widespread use of herbal cannabis for various medicinal purposes. In a survey of medicinal cannabis use among 2969 people with chronic medical conditions in the United Kingdom (UK), 947 (32%) stated that they had used cannabis for symptom relief.[4] The most common conditions examined in such surveys are multiple sclerosis, neuropathy and other chronic pain conditions, arthritis, and depression.[4,5]

Unlike pharmaceutical cannabinoid products, which usually contain only one or two active compounds, herbal cannabis contains cannabinoids, which are a range of over 60 terpenophenolic compounds found exclusively in cannabis, as well as other non-cannabinoid components such as limonenes, terpenes and flavones. Many cannabinoid compounds may interact, and create additional synergistic or antagonistic effects.[6] Therefore, it is reasonable to consider that the safety profile of medical herbal cannabis may be different from that of pharmaceutical cannabinoid products. In particular, the potential adverse effects of cannabis on the lungs is specifically related to the use of smoking as the predominant route of delivery.[7]

Medical herbal cannabis refers to the use of cannabis for medical purposes. The difference between medical cannabis and recreational cannabis is not in the cannabis products or the way that it is grown, but in the reasons it is used. Information from recreational use of cannabis may then provide useful information regarding the possible adverse effects of herbal cannabis. Cannabis sativa is one of the most widely known of all psychoactive plants. It is widely used recreationally with an estimated annual prevalence of 160 million users worldwide.[8] Observational studies have made significant contributions to our understanding of the risks associated with recreational cannabis use. However, validity of observational studies has been the source of considerable controversy, in part due to their limited ability to control some potential bias and confounding.[9-12] It is well acknowledged that some potential confounders including tobacco use,[13-17] alcohol use,[18-21] other recreational drug use,[22-28] and drug-cannabis interactions[29-32] make it difficult to ascertain the true adverse effects of herbal cannabis.

More recently, small clinical trials of the efficacy of medicinal herbal cannabis have been conducted, but to date have provided no safety data.[33-36] There is a need for further epidemiological studies in order to address the safety of medical herbal cannabis.

1.2 Medicinal cannabis use in Canada

Recent legislative changes legalized herbal cannabis for medical use in Canada.[37,38] The Marihuana Medical Access Regulations (MMAR), enacted in 2001 and amended in 2005, allow patients with pain, nausea, loss of appetite associated with cancer, acquired immunodeficiency syndrome (AIDS), and other serious illnesses, who are unable to find relief from conventional therapies, to use cannabis.[37,38] Health Canada started to provide a quality–controlled cannabis product, obtained from Prairie Plant Systems Inc., for medical use.[39] Family

physicians and specialists are asked to support patients' applications for authorization to possess or grow cannabis for medicinal use. Physicians need to provide an attestation of diagnosis and indicate the failure of conventional therapies in order to support the patient's request to use medical cannabis.[38] Since 2001, an increasing number of patients in Canada have legally used cannabis for medical purposes under the new federal access regulations, and the rate of medical cannabis use is still rising.[40] An estimated 40% of patients with HIV/AIDS,[41] and 10% of patients with chronic pain currently use cannabis to relieve their symptoms.[16]

With increasing therapeutic use of cannabis, the safety of medical cannabis is an emerging source of concern for many physicians and patients. Even after Health Canada legalized a medical cannabis-production program, the safety of medical cannabis has not yet been evaluated in a prospective epidemiological study. To date, most of the safety information about cannabis use still comes from either observational studies that focus on recreational cannabis use[42-50] or from short-term RCTs that emphasize efficacy as their primary study objective.[51-60]

1.3 Medical cannabis research in Canada

As part of Health Canada's strategy to address the safety and efficacy of medical cannabis, the Medical Marijuana Research Program (MMRP) was created in 1999.[61] The use of standardized legal cannabis by Canadian patients under medical supervision provided a unique opportunity for the collection of data on the safety of herbal cannabis use in a prospective cohort study that would enable controlling for previous limitations. Health Canada decided to conduct such a study through the Canadian Institutes of Health Research (CIHR) peer review application process.[61] *The Cannabis for the Management of Pain, Assessment of Safety Study* (COMPASS) study was then developed with Drs Ware and Collet as co-Principal Investigators.[62]

1.4 Methodological challenges

The methodological challenges in a prospective cohort study stem from the strategies to remove bias and confounding. Multiple regression analysis and matching are the two major methods for confounding adjustment. When considering the most efficient strategy for use in the COMPASS study, we found that the statistical efficiency of matching in a case-control study had been extensively studied.[63-69] However, little attention had been paid to the impact of matching on efficiency in a cohort study. Most discussions about choosing an unmatched cohort design over a matched design were primarily focused on the potential difficulty and increased cost of identifying matched subjects.[70-72] The impact on statistical efficiency was usually neglected. This specific aspect needs to be addressed.

1.5 Thesis objectives

1.5.1 General objective

My thesis aimed at improving information regarding the safety of medical use of cannabis, and more specifically the safety of cannabis provided by Health Canada.

1.5.2 Specific objectives

The thesis work contains four objectives.

The first objective was to examine the safety of *pharmaceutical cannabinoid products* by assessing adverse events reporting in all RCTs and conducting a meta-analysis of safety results.

The second objective was to provide complementary safety information of *herbal cannabis* by conducting a systematic review of recreational cannabis safety using observational studies and case reports.

The third objective was to assess the risk of adverse events associated with cannabis when used in the treatment of chronic pain in the prospective cohort study (COMPASS).

The fourth objective was to address specific design issues related to the development of the COMPASS cohort safety study. In particular, the respective statistical efficiency of matching and multiple regression model adjustment for confounders was compared in a separate project. A refinement of the existing guidelines regarding when a matching strategy is likely to improve efficiency in cohort studies was also proposed.

1.6 Thesis Structure

This thesis is organized as follows:

Chapter 2 presents the history of cannabis as a form of medicine followed by the development of pharmaceutical cannabinoid products and herbal cannabis products. It then outlines the regulatory framework of the use of medical herbal cannabis in Canada.

Chapter 3 presents the review of existing information in the literature regarding cannabis safety with a clear separation between pharmaceutical cannabinoid products and recreational use of herbal products. Two different reviews are presented in this chapter. One review is focused on collecting the adverse events of pharmaceutical cannabinoid products (thesis project #1). The results of a meta-analysis are first presented in this chapter. The other review is focused on

examining the safety of recreational cannabis in order to provide complementary information about safety of herbal cannabis, in particular, the safety information that was not evaluated in clinical trials, including driving, prenatal exposure, and long-term use (thesis project #2). The results of a systematic review of observational studies and case reports of recreational cannabis use are then presented.

Chapter 4 presents a prospective cohort study—COMPASS, which was conducted to determine the association of the risk of adverse event with the use of herbal cannabis for the treatment of chronic pain disorders (thesis project #3). A total of 215 subjects (patients with pain who used cannabis in the study) and 216 controls (patients with pain who did not use cannabis) were recruited from 7 clinics across Canada. A standardized quality-controlled herbal cannabis product supplied by Health Canada to the site pharmacies was dispensed to subjects for a one-year period. Data on adverse events were collected during clinic visits and telephone interviews. The safety profile of Health Canada's herbal cannabis is assessed and the association between the use of medical cannabis and its rate of adverse events is determined in this chapter.

Chapter 5 focuses on the issue of statistical efficiency in the choice of matched and unmatched cohort study design (thesis project #4). This issue is firstly addressed by directly looking into the mathematic formula on statistical efficiency in a simple situation. Then, the statistical efficiency is computed on each set of assigned parameter values to further investigate the extent to which matching may improve the efficiency in estimating the parameter of interest in a cohort study. Finally, examples are provided to compare the statistical efficiency of matched cohort studies with unmatched cohort studies, and how revised guidelines may help decide when matching is likely to improve efficiency is further discussed.

Finally, chapter 6 summarizes the main findings, makes overall conclusions and recommendations.

CHAPTER 2: BACKGROUND

This chapter consists of five sections. The first section briefly reviews the history of cannabis as a source of medicine. The next two sections provide an overview of various pharmaceutical cannabinoid products and herbal cannabis products in Canada. This is followed by the review of their effects on pain management. The final section of chapter two focuses mainly on the current legal framework of medical herbal cannabis in Canada.

2.1 History of cannabis as a medicine

Cannabis products have been consumed for thousands of years.[73] *Cannabis* is obtained from *Cannabis sativa*. Its aromatic resin contained compounds that were of recreational and medicinal value. *Cannabis* is also known as *hemp*. *Marijuana* describes the dried cannabis flowers and leaves which are smoked, while *hashish* refers to blocks of cannabis resin which can be smoked and eaten.[74] We use the word "*cannabis*" in this thesis to stand for all these different expressions.

Although cannabis has been used for medicinal and recreational purposes for thousands of years, it was not until the middle of the 19th century when the Irish physician Sir William O'Shaughnessy (1809-1889) made the first scientific study of cannabis.[75] By the end of the 19th century, over 100 scientific publications in Europe and the United States had declared the therapeutic value of cannabis, and it had become a widespread prescription medicine.[76]

At the beginning of the 20th century, the medical indications of cannabis were summarized in the following areas: sedative or hypnotic, analgesic and others (for example, to improve appetite).[77] Cannabis has appeared in many forms such as solid extracts and tinctures. Its leaves have been rolled into cigarettes for the treatment of asthma and even made into corn plasters. Cannabis has been used as an ingredient in a large array of patent medicines and has been marketed by many laboratories in different countries.[78]

Scientific interest in cannabis and its related properties increased substantially due to the rapid rise of recreational cannabis use among youth and young adults. Cannabinol (CBN) was isolated in 1895 and cannabidiol (CBD) was identified in 1934.[79] The most significant discovery was that of the primary psychoactive ingredient in cannabis, delta-9-tetrahydrocannabinol (Δ^9-THC), which was isolated and synthesized in 1964.[2,80,81]

So far, 66 cannabinoids have been isolated from cannabis plants.[82] Cannabinoids refer to a group of C_{21} terpenophenolic compounds uniquely and naturally present in *Cannabis sativa*.[83] Among them, THC and CBD are the most prevalent natural cannabinoids and have been extensively studied through many perspectives. The potency of cannabis is determined by the percentage of Δ^9-THC. CBD is not psychoactive; however it has been found that CBD can antagonize many of the pharmacological effects of THC, including tachycardia and the perception of the "high".[73]

In 1988, a cannabinoid receptor (CB_1) was identified in the brain,[84] and in 1993, a second cannabinoid receptor (CB_2) was discovered on rat immune cells.[85] The successful cloning of cannabis receptors prompted the discovery of the endocannabinoids which are naturally occurring cannabinoid receptor ligands in the body.[86] The cloning also revealed the existence of the whole endocannabinoid system which consists of endocannabinoids (e.g. anandamide and 2-arachidonoyl glycerol), multiple enzymes involved in the biosynthesis and degradation of these

lipids, and CB_1 and CB_2 receptors.[87] The discovery of the endocannabinoid system provided a scientific rationale for therapeutic effects of natural cannabinoids.

2.2 Pharmaceutical cannabinoid products

The discoveries of cannabinoid compounds, specific receptors and endogenous cannabinoids have allowed for remarkable advances toward our understanding of the biochemical basis of cannabis therapeutics and have generated more research on the safety and efficacy of cannabis for therapeutic use. Indeed, considerable research on the short and long-term effects of cannabis in humans has been conducted since these discoveries were made. However, research on medical herbal cannabis use faced a significant decline in the early twentieth century. Many factors contributed to this decrease including the difficulty of obtaining replicable effects, the failure to isolate the active principle of cannabis, the development of other medications with known efficacy for the treatment of the main indications of cannabis use, and prohibitive legislation.[88]

The emphasis of medical cannabis research shifted to synthetic cannabinoids from that of the plant or plant extracts. A few medical cannabinoid products have been synthesized in the laboratory, including a synthetic THC, a synthetic THC analog, a selective CB_1 receptor antagonist, CB_2 receptor agonist, CB_2 receptor antagonist, and a cannabinoid extract.

In Canada at present there are three cannabinoid products that are available for medical use. These products include dronabinol (Marinol®, which is synthetic THC), nabilone (Cesamet®, a synthetic derivative of THC), and an herbal cannabis extract (Sativex®, which contains THC and CBD in an oromucosal spray).

2.2.1 Synthetic THC

There were many clinical studies conducted in the 1970s that evaluated the therapeutic effects of THC as an antiemetic agent and as an appetite stimulant. These efforts resulted in the approval of dronabinol (Marinol®), a synthetic THC. Dronabinol preparations do not contain the other significant chemical constituents present in cannabis. It is a Schedule III controlled substance currently marketed by Solvay Pharmaceuticals.

Dronabinol is used to treat nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments. Dronabinol is also used to treat appetite loss associated with weight loss in people who have acquired immunodeficiency syndrome (AIDS).

2.2.2 Synthetic cannabinoids

Nabilone is a synthetic cannabinoid that is not derived from the cannabis plant. It was found to have anxiolytic and antiemetic properties and was approved by the Food and Drug Administration (FDA) in 1985. Nabilone is a Schedule II controlled substance currently marketed by Valeant Pharmaceuticals. Between 1975 and 1997, 16 randomized controlled trials were reported using nabilone to control or prevent chemotherapy-induced nausea and vomiting.[89] There were very few trials reported thereafter although a recent trial of nabilone has shown efficacy in the treatment of pain associated with fibromyalgia.[90]

At present, nabilone is marketed as Cesamet® in Canada, the United States, the United Kingdom and Mexico. It is approved for treatment of chemotherapy-induced nausea and vomiting and for use in the treatment of anorexia and weight loss in patients with AIDS. It is also widely used off-label as an adjunct analgesic for neuropathic pain.

2.2.3 Cannabis extracts

Oral administration of synthetic THC has some pharmacokinetic drawbacks as it requires a long time to reach maximum plasma concentration and there is a long decay rate. Using novel drug delivery methods such as a smokeless inhaler device provides faster absorption.[91]

Sativex® is derived from botanical material and is available in a pump–spray format for self-administration and titration via the oromucosal route. It contains THC (27mg/ml from Tetranabinex®) and CBD (25mg/ml from Nabidiolex®). It is formulated in an ethanol:propylene glycol vehicle with peppermint flavouring.[92]

In Canada, Sativex® is approved for neuropathic pain associated with multiple sclerosis and for intractable cancer-related pain. It is available in the UK as an unlicensed medicine which enables UK doctors to prescribe the product to individual patients who they consider may benefit from using this medication. Sativex® is in pivotal Phase III clinical trials in the US. The first large scale US trial for cancer patients started in the summer of 2007.

2.3 Medical herbal cannabis

In Canada, other than the above-mentioned three pharmaceutical cannabinoid products, the herbal form of cannabis is also available legally through the Marihuana Medical Access Regulations (MMAR).[37,38] Under this federal regulation, patients have the option of purchasing dried marihuana and/or seeds from Health Canada in order to grow their own cannabis with approval from Health Canada. Since the drug is not "approved" there are no formal indications but rather symptom/disease complexes for which patients report benefit. These include spasticity associated with multiple sclerosis, epileptic seizures, severe

pain associated with arthritis, spasticity and pain associated with spinal cord injury and disease, and for end of life symptom control (see section 2.5).

Health Canada obtains dried marihuana and seeds for medical use from Prairie Plant Systems Inc. (PPS). The dried cannabis is standardized on total tetrahydrocannabinol content [Δ^9-THC and Tetrahydrocannabinolic acid (THCA)] (12.5 ± 2%) and cannabinolic acid content (CBNA) (0.25 % - 0.35%). Good Manufacturing Practices (GMPs) guidelines are applied to ensure that drugs are consistently produced and controlled to maintain the quality standards appropriate for their intended medical use.

2.4 Role of pharmaceutical cannabinoid products and herbal cannabis products in the management of pain

The efficacy of these cannabinoid medicines has been evaluated in randomized controlled trials. The use of cannabinoids as antiemetics has been systematically reviewed and suggests potential efficacy.[89, 93] There has also been considerable interest in the use of cannabinoids as adjunctive therapy for pain management as the recent publication of several small randomized controlled trials reveals. However, the therapeutic benefits of cannabinoids or cannabis as analgesics remain controversial. A qualitative systematic review conducted in 2001 that included nine randomized controlled trials did not find any evidence supporting the role of cannabinoids in the relief of pain.[46] This review did not include trials evaluating the analgesic effect of medical herbal cannabis. Since this review was published, a number of clinical trials that showed encouraging results have been reported, especially in investigating the efficacy of cannabinoids in the management of chronic pain. [33,34,51,52,54,56,58-60, 90,94-98] The cannabinoid products examined in these trials included oral synthetic THC, oral synthetic THC analogs, oral cannabis extracts (2.5mg THC, 2.5mg THC plus 1.25mg CBD), sublingual cannabis extracts (THC/CBD), and herbal cannabis.

Dronabinol and oromucosal THC/CBD have been shown to be effective for central neuropathic pain associated with multiple sclerosis.[51,52,54,58,59] Oromucosal THC/CBD also reduces pain in rheumatoid arthritis.[56] Nabilone has been found to be effective for pain associated with fibromyalgia.[90]

A number of comprehensive literature reviews have been recently conducted that discuss the efficacy of medical cannabinoid products as an analgesic agent.[99-103] A recent review supports further consideration of cannabinoids in the management of chronic pain but there is little evidence to support their use in the management of acute pain conditions.[99] One meta-analysis of seven clinical trials that examined the efficacy of cannabis-based treatments for neuropathic and multiple sclerosis-related pain found that cannabinoids were effective in pain relief.[100] Two reviews were also conducted that examined the effectiveness of Sativex® on pain and sleep. After reviewing all the randomized controlled trials of Sativex®, the researchers found sufficient evidence to support the clinical benefits of cannabinoids as a novel class of agents in the management of chronic pain and sleep disturbance associated with chronic pain.[101-103] In addition, smoked cannabis has been found to be effective in the management of neuropathic pain.[34,35,36]

2.5 Legal framework of medical herbal cannabis in Canada

It has been reported that an estimated 40% of patients with HIV/AIDS [104] and 10% of patients with chronic pain[16] currently use cannabis to relieve their symptoms. However, herbal cannabis is legal for medical use in only a few countries including Canada[37,38] and the Netherlands[5], while Belgium, Australia, the United Kingdom, Spain and some U.S. states have made attempts at making cannabis products available.

Although Health Canada has approved the marketing of nabilone since 1982 and the marketing of dronabinol since 1995,[105] herbal cannabis is still scheduled under

the Narcotic Control Regulations (NCR) of the Controlled Drugs and Substances Act (CDSA) of Health Canada[106] and the Food and Drugs Act.[107]

In June 1999, the Minister of Health allowed the legal possession of cannabis for medical purposes by exemption under section 56 of the CDSA. In June 2000, the Court of Appeal of Ontario ruled that withholding cannabis from patients for whom medical necessity could be demonstrated was unconstitutional.[108] In July 2001, Health Canada amended the NCR and released the Marihuana Medical Access Regulations (MMAR) which legalized the cultivation, possession and use of cannabis by patients whose physicians supported its medical application.[37]

Cannabis remains an illegal and controlled substance. However, under the MMAR, Health Canada allows for medical access to cannabis for people who are suffering from grave and debilitating illnesses. The herbal form of cannabis has been available legally through these federal regulations.[37,38]

The original MMAR allowed patients with pain, nausea, loss of appetite associated with cancer, AIDS, and other serious illnesses who were unable to find relief from conventional therapies to use cannabis.[37] Patients applying under the original MMAR had to classify their diseases into one of three broad categories. Category 1 included the terminally ill who had a life expectancy of less than 12 months, category 2 included patients diagnosed with "serious medical conditions," and category 3 covered those who exhibited symptoms associated with all "other" medical conditions. For patients in the first two categories, Health Canada allowed cannabis to be used to treat the symptoms of nausea, chronic pain, depressed appetite associated with cancer, AIDS, and other serious illnesses when conventional treatments had little or no effect. The third category included patients who had tried standard therapies to treat their symptoms but who were convinced that only cannabis could provide adequate relief.

The amended MMAR—Regulations Amending the Marihuana Medical Access Regulations—were introduced in 2005. Under the amended MMAR, physicians' responsibility on declaring the need for and dose of cannabis was reduced. Instead, the regulations mainly focused on providing an attestation of diagnosis and failure of conventional therapies to manage pain and other serious symptoms listed in the amended regulations.[38] The amended regulations also reduced the number of categories of symptoms from three to two by merging the previous categories one and two. Category 1 now lists individuals who suffer from "acute pain, violent nausea and/or other serious symptoms caused by the following conditions: multiple sclerosis, spinal cord injury, disease of the spinal cord, cancer, AIDS/HIV infection, severe forms of arthritis and/or epilepsy".[38] Category 2 includes "key applicants who have serious pathological symptoms other than those described in category 1".[38]

As of June 2009, 4029 patients in Canada were authorized to use herbal cannabis for medical purposes under the MMAR.[40] Pain is an important feature of many of the conditions that necessitate cannabis use, although data on reasons for use in the MMAR are unavailable.

In conclusion, it is clear that our understanding of cannabis pharmacology has increased in recent years, and with this the medical use of several standardized pharmaceutical cannabinoid products has been explored. In the next chapter we explore some of the major safety considerations concerning the use of cannabis for medical purposes.

CHAPTER 3: SYSTEMATIC REVIEWS OF ADVERSE EFFECTS OF CANNABIS

This chapter is concerned primarily with a review of published scientific literature regarding cannabis safety. Included in the chapter is a meta-analysis of randomized controlled trials (RCTs) to examine adverse events of pharmaceutical cannabis products, a systematic review of observational studies and case reports to investigate safety of recreational use of herbal cannabis, and conclusions and recommendations.

3.1 Introduction

The distribution of herbal cannabis to Canadian patients under the new regulations, the Medical Marihuana Access Regulations (MMAR), has generated concern among provincial medical licensing authorities, physician advocacy groups and medico-legal advisory groups. The safety of cannabis is also a source of concern for many physicians considering the use of this class of products and for the federal government with responsibility for the supply of cannabis to the patients.

The safety of cannabis may be approached in two parts: safety of pharmaceutical cannabinoid products which contain the main active compound(s) — tetrahydrocannabinol (THC) and/or cannabidiol (CBD) – and the safety of herbal cannabis itself.

As with other marketed therapeutic agents, the safety of pharmaceutical cannabinoid products may be studied using a variety of methodological approaches including RCTs, observational studies, and the spontaneous reporting of adverse events.[109,110] A meta-analysis of all the adverse events reported in RCTs is important in evaluating the safety of pharmaceutical cannabinoids and may also inform attempts to assess the safety of herbal cannabis when used for medical purposes.

The adverse effects of medical herbal cannabis have not been systematically reviewed, although the medical use of herbal cannabis is substantial. Reports of adverse effects of herbal cannabis have all focused on recreational cannabis use. Information from recreational use of cannabis may provide useful information regarding the possible adverse effects of herbal cannabis when used for medical purposes. More importantly, it may also provide information on safety that is not usually evaluated in clinical trials (e.g. driving, prenatal exposure, cancer, or long-term use). However, one may not assume that all risks associated with recreational cannabis use may be applied to medical use, as the user population is very different (chronically ill vs. healthy), doses used and modes of administration may be different, and side effects such as drowsiness may in fact be beneficial in patients who are deprived of sleep because of their illness.

Therefore, in this chapter we systematically review the adverse effects of cannabis in two separate parts. Part 1 contains a meta-analysis of the safety of pharmaceutical cannabinoid products. Data were taken from RCTs, observational studies and published case reports of pharmaceutical cannabinoid products. A meta-analysis of RCTs examining the adverse events of pharmaceutical cannabinoid products was reported as the main focus of this chapter. Part 2 contains a systematic review of the published adverse events of recreational cannabis use. This review was conducted in an effort to provide information on safety of herbal cannabis that has not been evaluated in clinical trials of

pharmaceutical cannabinoid products (e.g. driving, prenatal exposure, cancer and long-term use).

3.2 Part 1: Adverse events of pharmaceutical cannabinoid products—a meta-analysis[i]

3.2.1 Objectives

The primary objective of conducting a meta-analysis was to examine the adverse events of pharmaceutical cannabinoid products, and to create a database of known cannabinoid-related adverse events to inform physicians, policymakers and the public. Additionally, we sought to critically evaluate the quality of published studies to guide future studies on the safety of medical cannabis use.

3.2.2 Methods

Search strategy and study selection

A comprehensive search was conducted in MEDLINE (1966-October week 5, 2007), PsycINFO (1967- October week 5, 2007), and EMBASE (1980-week 42, 2007). The keywords used in the search strategies were "bhang", "charas", "cannabis", "cannabinoids", "dagga", "ganja", "hashish", "hemp", "marijuana", "marihuana", and "tetrahydrocannabinol or THC". Studies were required to specify "human", "safety", "case report", "case-control", "cohort", "cross-sectional", "crossover", "randomized controlled trial", "longitudinal" or "epidemiological" in their titles or keywords.

[i] This part includes the text of the manuscript, which was published in the Canadian Medical Association Journal (CMAJ). [Wang T, Collet J-P, Shapiro S, and Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008; 178(13): 1669-1678 by permission of the publisher. © 2008 Canadian Medical Association.]

Articles' titles and abstracts were reviewed for relevance by two independent reviewers (MW, TW) based on the following criteria. RCTs evaluating the safety and efficacy of cannabis were included if adverse events were quantified; observational studies using cannabis as main exposure were included if safety was one of the main outcomes of interest; and case reports were included if they described adverse events in subjects exposed to cannabis. Observational studies in which driving outcomes were evaluated were included.

Studies were excluded if they focused on adverse effects of cannabis occurring in combination with other agents; involved synthetic cannabinoids (e.g. nabilone, levonantradol); studied treatment of cannabis dependence or cannabis cessation; or focused on effects of cannabis on school achievements, marriage, criminal behavior (e.g. homicide, violent crimes) or hormone levels. Studies of the mechanisms of action, pharmacodynamic or pharmacokinetic effects or other basic experimental designs were excluded. Studies that were not published in English, French, Spanish or German were excluded.

Additional studies were identified from the reference lists of selected articles or review articles. Disagreements regarding study selection were resolved through discussion between primary reviewers. The full text reports of selected papers were obtained, and further selection was conducted according to the above criteria.

Assessment of study quality

Two raters (TW, AL[i]) independently assessed study quality. All included RCTs were assessed for methodological quality using the Jadad scale,[111] while the Downs and Black checklist was used to assess the quality of all included

[i] Aihua Liu, MSc, Department of Epidemiology, Biostatistics and Occupational Health, McGill University.

observational studies involving a control group.[112] Disagreements regarding quality assessment were resolved through discussion.

Data extraction

Articles regarding the safety of cannabis were classified based on the reason for cannabis use in the populations studied (medical or recreational) and the study design used. Serious adverse events (SAEs) and non-serious adverse events (AEs) were then identified following definitions recommended by the International Conference on Harmonization (ICH).[113] Under these guidelines, a "serious adverse event" is defined as any untoward medical occurrence that requires in-patient hospitalization or prolongation of existing hospitalization, which causes congenital malformation, that results in persistent or significant disability or incapacity, which is life-threatening or that results in death. A "non-serious adverse event" is defined as any untoward medical occurrence in a patient or subject; this does not necessarily have to have a causal relationship with the treatment. The expectedness of an adverse event was also defined following ICH guidelines, in which an "unexpected" adverse event is identified when "the nature or severity of this event is not consistent with the applicable product information".[113] All identified adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA v10.0) headings "System Organ Class (SOC)" and "Preferred Term (PT)".[114] Data extraction and MedDRA coding were performed by one reviewer (TW), and verified by a second medically qualified reviewer (MW).

Data analysis

Serious and non-serious adverse events identified from clinical trials were tabulated by study design and by MedDRA coding. For descriptive purposes,

incidence rates of serious and non-serious adverse events within RCTs were estimated by using the number of events divided by corresponding cumulative person-years. We combined the person-years from all subjects exposed to cannabis to generate a cumulative person-year estimate. The same logic was applied to the calculation of total person-years exposed to control. When the duration of exposure of a subject withdrawn from an RCT was unclear, the person-year contribution of this subject was estimated as half of the complete follow-up time per subject in the trial.

A meta-analysis was then conducted using a random effects model to assess the occurrence of adverse events, serious or non-serious, in subjects assigned to cannabis versus control. Rate ratios and variances were derived for each trial. A correction of 0.5 was added to each count in the case of zero events. A point estimate with corresponding 95% confidence interval (CI) was computed for pooled rate ratios (RR), using the generic inverse variance function in RevMan 4.2.10.[115] All pooled estimates were assessed for heterogeneity, using heterogeneity X^2 test and the I^2 statistic, which is the percentage of variation across studies that is due to heterogeneity.[116] We also prospectively studied adverse events based on type of cannabis preparations (oromucosal spray, oral THC, and oral THC/CBD), and pre-defined subgroup analyses on different duration of exposure (>2weeks and <=2 weeks), study design (parallel and crossover) and study population (cancer and non-cancer subjects) were further carried out within each medical cannabis preparation. For non-serious adverse events, we also estimated pooled RRs and corresponding 95% CIs for each system organ class.

3.2.3 Results

A total of 1720 articles were found under the initial search strategy (Figure 3-1). We excluded 1456 articles that did not satisfy the inclusion and exclusion criteria,

including 28 RCTs which failed to report quantifiable adverse event data, 94 studies which focused on adverse effects of cannabis occurring in combination with other agents, 30 trials which investigated synthetic cannabinoids, 347 studies which focused on cannabis dependence, cannabis cessation or cannabis abuse, 364 studies which were not RCTs, observational studies or case reports, 345 which studied mechanism of action, pharmacodynamic or pharmacokinetic effects or other basic experimental designs, and 41 studies which focused on effects of cannabis on school achievements, marriage, criminal behavior or hormone levels. We also excluded 38 studies which were not published in English, French, Spanish or German. One trial was presented in 2 separate publications: one with safety data reported up to 15th week,[51] and the other with safety data collected from 16th week to 52nd week.[52] We counted those 2 articles as 1 single trial.

An additional 57 studies, including 49 case reports and 8 observational studies, were identified from the reference lists of review articles. One in-press RCT was also included.[58]

Therefore, a total of 321 studies regarding safety issues of cannabis were identified during the period 1966 to October 2007. Thirty-one (9.7%) studies, incuding 23 RCTs and 8 observational studies, focused on pharmaceutical cannabinoid products, and 290 (90.3%) studies, including 92 observational studies and 198 case reports, focused on the safety issues of recreational cannabis.

The meta-analysis (part 1) presented in section 3.2 focused on the 23 RCTs and 8 obervational studies in which the safety of pharmaceutical cannabinoid products could be evaluated. The systematic review (part 2) of the 290 studies focusing on the safety of recreational cannabis use will be presented in section 3.3.

Randomized controlled trials

In the 23 RCTs of pharmaceutical cannabinoid products, the median Jadad score was 4 (out of 5), with a range from 2 to 5. Four trials did not provide information on the number and reasons of withdrawn subjects.[117-120] Detailed information of each included trial is summarized in Table 3-1. Seventeen (73.9%) trials had a sample size less than 100, and 11 (47.8%) of these had less than 50 subjects. The median duration of exposure was 2 weeks (range 8 hours-12 months). The total number of subjects exposed to medical cannabinoids was 1932, yielding 445 person-years of cannabinoid exposure. There were 239 person-years of exposure among 1209 subjects included in the control group (placebo or standard care), of whom 1121 were exposed to placebo (236 person-years).

Except for one trial conducted among 12 healthy cannabis-naïve volunteers,[121] all trials involved subjects with medical conditions, such as cancer or multiple sclerosis, and use of cannabinoids was intended to address symptoms such as nausea and vomiting induced by chemotherapy or pain (see Table 3-1). Oral capsules/tablets of THC or cannabis extracts (15 trials) and sublingual cannabis extracts (8 trials) were the methods of administration studied. No trial of smoked medical cannabis was included in the review as adverse events were not quantified.

Serious adverse events

Our review identified 164 SAEs among subjects assigned to pharmaceutical cannabinoid products and 60 among subjects assigned to control. The rates of serious adverse events did not differ significantly between these 2 groups (RR=1.04; 95% CI=0.78-1.39). SAEs are categorized in Table 3-2. Respiratory (16.5%), gastrointestinal (16.5%), and nervous system disorders (15.2%) were the most commonly reported SAE category among subjects assigned to pharmaceutical cannabinoid products, while nervous system disorders (30.0%) were the most frequently reported category among control subjects. Multiple sclerosis relapse (n=21, 12.8%), vomiting (n=16, 9.8%) and urinary tract infection

(n=15, 9.1%) were the most commonly reported events among subjects assigned to medical cannabinoids. The majority of SAEs (99%) were identified from 2 trials, [51,52,122] which contributed 88.8% of person-years of medical cannabis exposure and 84.1% of exposure to control.

Fifteen deaths (3.4 per 100 person-years) were reported among cannabis users (3 because of pneumonia, 1 because of cervix carcinoma, 1 because of convulsion, 10 non-specified), and 3 (1.3 deaths per 100 person-years) deaths were reported among control subjects (1 pneumonia, 1 myocardial ischaemia, 1 non-specified). No statistical difference was found between these two groups (RR=2.66; 95% CI=0.77-9.28). The mortality rate ratio was mainly influenced by one RCT studying the effects of THC on cancer-related anorexia-cachexia syndrome (RR=2.61; 95% CI=0.33-20.37).[122]

Non-serious adverse events

There were 4615 non-serious AEs among subjects assigned to pharmaceutical cannabinoid products (incidence rate 10.37 events/person-year) and 1641 events among control subjects (incidence rate 6.87 events/person-year) in the 23 RCTs reviewed (Table 3-3). Nervous system disorders were the most frequently reported in both groups (36.7% for medical cannabinoids and 31.3% for control). Dizziness was the most commonly reported AE among cannabinoid-exposed participants; details of other non-serious AEs are shown in Table 3-4.

The incidence rate for AEs was significantly higher among subjects assigned to pharmaceutical cannabinoid products than placebo (RR=1.86; 95% CI=1.57-2.21) (Figure 3-2). A high degree of variance between studies was found (heterogeneity X^2=187.42, P<0.001; I^2=86.7%). Further subgroup analysis by different type of cannabis preparations reduced the heterogeneity (Table 3-5). The average rate of a non-serious AE was significantly higher for oromucosal delivery (RR=1.88; 95% CI=1.48-2.39) and oral THC (RR=2.18; 95% CI=1.59-2.99) compared to placebo.

No difference was found when comparing oral THC/CBD with placebo (RR=1.31; 95% CI=0.88-1.96). One study with a different duration of exposure between oral THC/CBD (2 weeks) and placebo (1 week) reported a significant lower incidence rate among subjects assigned to THC/CBD than controls.[55] Exclusion of this study increased the pooled rate ratio for oral THC/CBD from 1.31(0.88-1.96) to 1.54(1.14-2.08). Further subgroup analysis by study design and study population did not significantly alter the pooled rate ratio of non-serious adverse events for each pharmaceutical cannabinoid product (Table 3-5).

Observational studies

Eight observational studies were found which focused on safety issues of pharmaceutical cannabinoid products,[95, 98,123-128] in which 39 serious AEs and 3553 non-serious AEs were reported (Tables 3-6 and 3-7). None of these studies had a control group. Nervous system disorders were the most frequently reported category for both serious (n=9, 23.1%) and non-serious AEs (n=1412, 39.8%). Psychiatric disorders were the second frequently reported category in both serious (n=4, 10.3%) and non-serous adverse events (n=1265, 35.6%). All non-serious adverse events reported in observational studies are summarized in Table 3-8.

3.2.4 Discussion of the meta-analysis

Our review identified 8371 adverse events related to medical cannabinoid use, including 4779 events in 23 RCTs and 3592 events in 8 observational studies, and most of them were not serious. We found that pharmaceutical cannabinoid product users have a 1.9-fold higher rate of non-serious AEs compared to control subjects (RR=1.86; 95% CI=1.57-2.21). However, the evidence regarding a potential risk of serious adverse events of subjects on cannabinoids compared

with that of subjects in the control group is inconclusive (RR=1.04; 95% CI=0.78-1.39) because the study lacks power.

Although the RCT is a powerful study design due to its ability to reduce bias and confounding, the quality of reporting of AEs in published trials limited our results. First, not all published cannabis trials provided safety information; we excluded 28 RCTs, including 2 trials regarding smoked cannabis in HIV patients,[33,34] because they did not quantify adverse events or only reported events in one intervention group. Despite poor safety reporting, these excluded trials have good methodological quality as judged by the Jadad scale. Thus we believe that the Jadad score does not adequately reflect the quality of safety reporting in RCTs. Second, most of the trials selected did not provide both the absolute number of AEs and the number of subjects reporting at least 1 event, as recommended by the Consolidated Standards of Reporting Trials (CONSORT) statement.[129] This is why our results only focus on the incidence of adverse events, rather than having both incidence rates of events and risks of subjects who had reported at least 1 event analyzed. Third, our results may be influenced by the fact that we assumed that the occurrence of AEs was independent, which would not be valid if one patient developed more than 1 event (a very likely scenario for non-serious AEs). Therefore, our analysis may report narrower 95% CIs than reality, which may affect the results of significance testing.

Despite these limitations, we still identified 4779 adverse events in the 23 RCTs, and most of them (4615 [96.6%]) were not serious. As compared with placebo, use of pharmaceutical cannabinoid products was associated with an increased risk of non-serious AEs, in particular, nervous system disorders, gastrointestinal disorders and psychiatric disorders. Moreover, the finding that adverse events identified within RCTs are similar in nature to those observed in epidemiological studies suggests that unexpected adverse events are unlikely.

Our review did not include data concerning the synthetic cannabinoid nabilone since it has different pharmacokinetic and pharmacodynamic properties and may have a different safety profile than THC. While the drug is being used for medical purposes, we caution that our safety data cannot be extended to nabilone. The safety of nabilone should be studied separately.

3.3 Part 2: Safety of recreational herbal cannabis use—a systematic review

The meta-analysis presented in section 3.2 did not explore the safety of herbal cannabis due to a lack of quantifiable adverse event data. Unlike pharmaceutical cannabinoid products, which usually contain only one or two active compounds, herbal cannabis contains many other cannabinoids and other compounds which may interact and create additional synergistic or antagonistic effects.[6] Therefore, it is reasonable to consider that the safety profile of medical herbal cannabis may be different from that of pharmaceutical cannabinoid products. In particular, the potential adverse effects of cannabis on the lungs are specifically related to the use of smoking as the route of delivery.[7]

Given the extent of legal medical cannabis use and the potential risks of the smoked route of delivery, good quality safety data on herbal cannabis remain urgently needed. There was virtually no information on risks associated with medical herbal cannabis use. However, the adverse effects of recreational cannabis use have been studied in observational studies or case reports. Information from recreational use of cannabis may then provide useful information regarding the possible adverse effects of the medical use of herbal cannabis. Therefore, we conducted a systematic review of 92 observational studies and 198 case reports focusing on the safety of recreational cannabis use as the second part of our reviews of cannabis safety. The purpose was to provide complementary safety information on medical herbal cannabis.

3.3.1 Methods

By using the same inclusion and exclusion criteria described in 3.2.2 ("search strategy and study selection"), we identified 290 observational studies, including 92 observational studies and 198 case reports, focusing on safety of recreational cannabis use. Detailed results have been presented in section 3.2.3.

The Downs and Black checklist was used to assess the quality of all included observational studies by two independent raters (TW, AL).[112] This checklist assigns a score of up to 32 based on the presence of specific parts of the study report including reporting, external validity, bias, confounding and power.[112] Disagreements regarding quality assessment were resolved through discussion. All identified adverse events in case reports were coded and tabulated using the Medical Dictionary for Regulatory Activities (MedDRA v10.0) headings "System Organ Classes (SOC)".[114] All safety outcomes in observational studies were grouped into MedDRA SOC category as well.

3.3.2 Results

Observational studies

Ninety-two observational studies (Table 3-9) were identified in which the adverse events of recreational cannabis were addressed. The AEs were distributed among nine categories: psychiatric disorders (37 studies),[130-166] prenatal cannabis exposure (19),[167-185] injury, poisoning and procedural complications (including driving accidents) (13),[186-198] neoplasms (7),[199-205] nervous system disorders (7),[206-212] respiratory disorders (3),[213-215] cardiac disorders (2),[216,217] hepatobiliary disorders (1)[218] and reproductive system and breast disorders (1)[219]. In addition, two retrospective cohort studies explored the association between cannabis consumption and mortality.[220,221]

The median quality score was 16 (out of 32), ranging from 7 to 21. The scores on two internal validity subscales, including bias and confounding, were all low (bias: 3.7/7 points; confounding: 2.7/6 points). With the exception of one study,[130] information on power and sample size estimation was not reported. Self-report was the main method used to capture information on cannabis exposure.

Psychiatric disorders as an outcome: Of the 37 psychiatric studies, 21 prospective cohort studies,[131-151] 10 cross-sectional studies,[152-161] 2 case-control studies[162, 163] and 4 retrospective cohort studies[130,164-166] were identified. The outcomes examined included psychosis, schizophrenia, depression, psychotic symptoms, anxiety, suicide attempt, and mental disorders. Despite variations in study location, study population, assessments of cannabis exposure and determinations of outcomes, observational studies reported a consistent association between cannabis consumption and psychiatric disorders, even after adjusting for potential confounders considered in each study. Only one study failed to show this association in a high-risk population.[149]

Prenatal cannabis exposure: Of 19 epidemiological studies examining the effects of prenatal cannabis exposure, 16 showed statistically significant impacts of maternal cannabis use during pregnancy on growth,[167-171] behavior,[172] depressive symptoms,[173] rhabdomyosarcoma,[174] sudden infant death syndrome,[175] impairment of cognitive development,[176-181] and acute nonlymphoblastic leukemia[182] among offspring. Three studies found no association between maternal cannabis use and low birth weight,[183] acute myeloid leukemia,[184] or reading or language development at age 9-12 years.[185]

Injury, poisoning and procedural complications (including driving accidents) as an outcome: Thirteen studies explored the association between cannabis use and car accidents, including 4 cohort studies, 3 cross-sectional studies and 6 case-control studies. Statistically significant associations between current cannabis use and car accidents were reported in nine studies in the US,[186-188] New

Zealand,[189,190] Canada,[191] Australia[192] and France,[193, 194] while 3 studies found that cannabis use had no effects on the drivers' ability to operate safely.[195-197] One observational study from Norway found that impaired drivers had higher blood THC concentration than drivers who were considered not impaired.[198]

Neoplasms as an outcome: The carcinogenic effect of cannabis was examined in 7 studies, including 5 case-control studies[199-203] and 2 cohort studies[204,205] with inconsistent results. Three hospital-based studies found an association between cannabis use and increased risk of cancer, including two lung cancer studies[201,202] and one head and neck cancer study.[203] In addition, one cohort study found that smoking cannabis at least once a month was associated with a 2.8-fold increase in the risk of malignant primary adult-onset glioma.[204] On the other hand, 2 population-based case-control studies and one retrospective cohort study found no association between cannabis uses and increase risk of oral cancer[200] and lung and upper aerodigestive tract cancers.[199] A cohort study of 64,855 members of the US Kaiser Permanente Medical Care Program with a mean follow-up time of 8.6 years found no association between cannabis-ever users or current users and tobacco-related cancers, after adjusting for tobacco smoking, but did report an increased risk of developing prostate cancer and cervical cancer.[205]

Nervous system disorders as an outcome: Six cohort studies and one cross-sectional study were conducted to explore the effect of cannabis on cognitive decline. One 12-year follow-up study, conducted in persons under age 65 years in Maryland, reported no significant association between cognitive decline and cannabis use.[206] Six studies have shown significant impairment on measures of verbal memory and attention, in long-term or heavy cannabis users, whereas late-onset users (who began smoking at age 17 or later) or short-term users did not show a significant cognitive impairment.[207-212]

Respiratory symptoms as an outcome: Three cohort studies, aiming to evaluate the relationship between cannabis and respiratory symptoms, revealed the use of

cannabis was associated with higher risk of developing respiratory symptoms, including chronic cough, chronic bronchitis, wheeze, or sputum production, than controls.[213-215] Three studies all controlled for the potential effects of tobacco smoking by classifying subjects into the following 4 groups: cannabis and tobacco smokers, cannabis smokers alone, tobacco smokers alone, and controls.

Case reports

The 198 case reports identified during this study reported 357 adverse events. Of these events, 18 cases (5.0% of the total) died of the reported events. The most frequently reported events were in the psychiatric (n=107, 30.0%), nervous system (n=56, 15.7%) and respiratory system (n=43, 12.0%) categories. All adverse events, categorized by SOC and PT, in published case reports are summarized in Tables 3-10, 3-11 and 3-12.

3.3.3 Discussions of the systematic review of recreational cannabis safety

We found a contrast between the low number of cases reporting cannabis adverse events (n=357) for recreational cannabis use over a 40-year period and the relatively large number of adverse events identified for pharmaceutical cannabinoid products (n=8371). This difference is likely due to a large underreporting of cases in the context of recreational use, a well-recognized phenomenon in pharmacovigilance.[222-225] A high detection of non-serious AEs in RCTs is likely due to more detailed follow-up.[226] In addition, the illegal status of recreational cannabis gives rise to the possibility of a "prosecution" bias that would reduce accurate reporting of cannabis use. Therefore a true denominator is extremely difficult to identify in calculating risks. Moreover, unlike the adverse events collected in cannabinoid RCTs, information on severity and seriousness was not usually provided in the safety studies of recreational cannabis use.

Both case reports and observational studies were affected by other biases that limit the interpretation of the results. For example, the time sequence between drug exposure and event occurrence, or information about confounders was often missing. Recall bias arising from the reliance on self-reporting, inability to track changes in terms of cannabis-use status and amount of consumption before the event, and the quality of cannabis were other limitations. There was no information on comorbidities of the study population. All studies were limited by the special nature of the exposed population (mainly recreational drug users), the selection of the control groups and controlling for potential confounders including tobacco use,[13-17] alcohol use, [18-21] other recreational drug use,[22-28] and drug-cannabis interactions.[29-32] For example, the effect of cannabis on head and neck cancer as addressed in one case-control study[203] may have been overestimated because the controls in this study were blood donors with a lower prevalence of lifetime cannabis use (9%) than the age-matched population at that time (30%). In this study, the error in estimating the prevalence of cannabis use could change the direction of the effect.

Despite these limitations, we still observed from published case reports that psychiatric and nervous system disorders were the most frequently reported adverse events among recreational cannabis users. This is consistent with the safety profile of pharmaceutical cannabinoid products identified in the meta-analysis. Moreover, our findings regarding psychiatric adverse effects are consistent with those published in a recent systematic review of longitudinal studies of psychosis and recreational cannabis use,[48] so our conclusion is likely to be valid. Furthermore, our review of observational studies has hinted that recreational cannabis use may be associated with an increased risk of car accidents and congenital abnormalities. These are two important risks which need to be considered when considering medical use of cannabis. On the other hand, the associations between long-term use of cannabis and the risk of cancer or neurocognitive function decline are less consistent.

3.4 Conclusions and recommendations of this chapter

After systematically evaluating the safety of cannabis used recreationally and medicinally, we found that pharmaceutical cannabinoid users had an average 1.9-fold increase in non-serious adverse events compared to controls. However, our results are inconclusive regarding the risk of serious adverse events because the study lacks power.

Moreover, results of the systematic review reinforce advice not to use cannabis during pregnancy. With respect to driving a vehicle, our systematic review attests a significant association between car accidents and the use of cannabis. This reinforces the warning to patients about not to drive while under the effects of cannabis.

The findings in this chapter form the basis for future controlled observational studies and clinical trials to describe the safety of medical cannabis use. The finding that 99% of SAEs were reported in only 2 trials suggests that more studies with long-term exposure are required to further characterize safety issues. Such studies are crucial to detect rare adverse events and to address specific concerns regarding the development of tolerance and the development of cognitive effects of medical cannabinoid use. We believe that adverse events of cannabis use should continue to be systematically collected, and results should be publicly available, to assist in clinical, regulatory and political decision-making. Our research is a step in this direction. A prospective cohort study designed to assess the safety of Health Canada herbal cannabis products among chronic pain patients is presented in the next chapter.

3.5 Tables and Figures

Figure 3-1: Retrieval and selection of studies of safety of cannabis

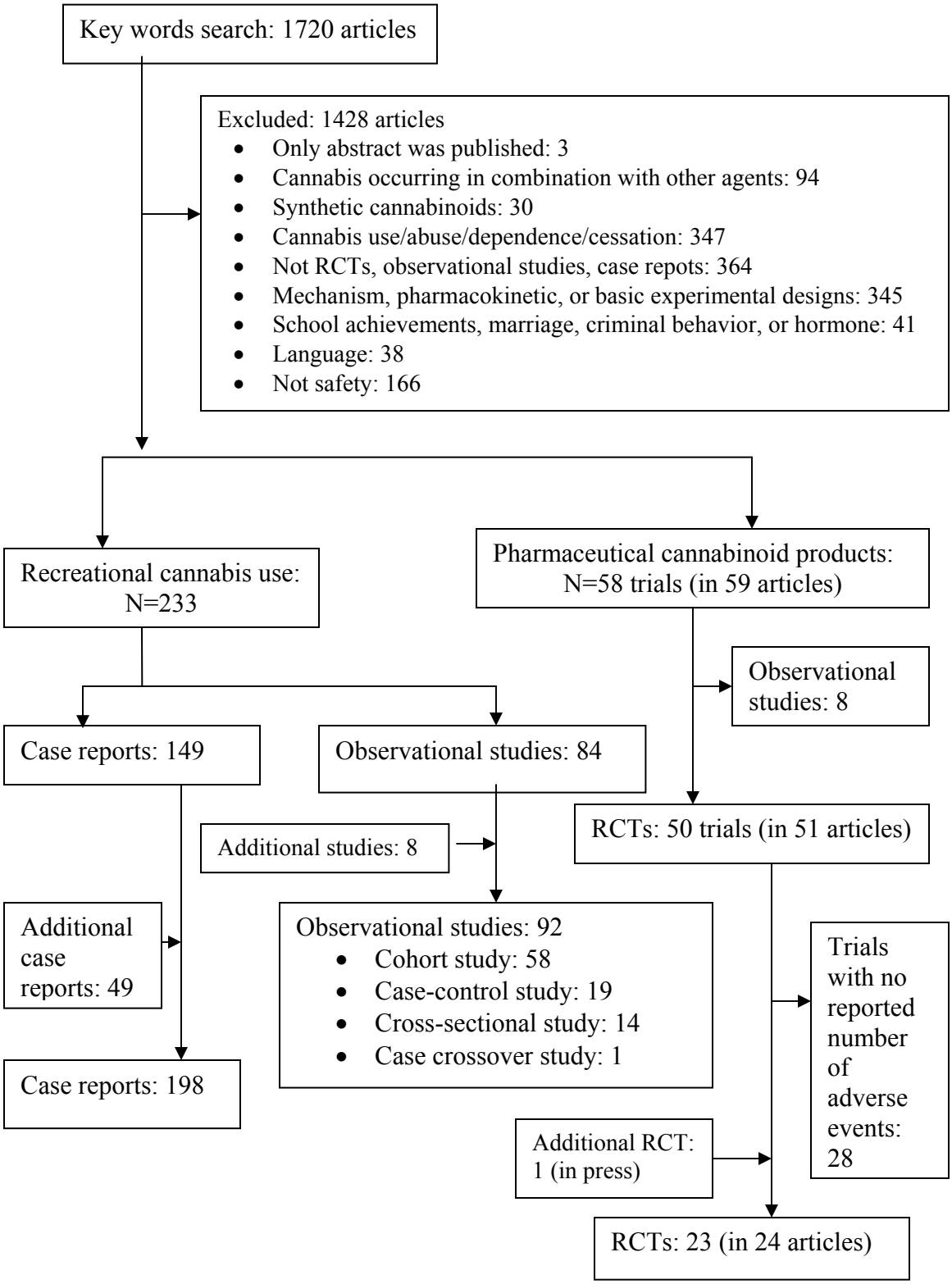

Table 3-1: Randomized controlled trials of pharmaceutical cannabinoid products which report detailed adverse event data (1966- 2007), by mode of administration

1. Oromucosal spray (THC/CBD)

Study design	Study population	Sample size	Age, yr Mean (range)	Gender, % male	Duration of exposure	Most frequently reported adverse event: n/N (%)
RCTs; Parallel	Multiple sclerosis[57]	189	49.1	40	6 weeks	Nervous system disorders: 68/169 (40.2%)
	Multiple sclerosis[59]	66	49 (27-72)	21	4 weeks	Nervous system disorders: 22/56 (39.3%)
	Multiple sclerosis[60]	160	51 (27-74)	38	6 weeks	Nervous system disorders: 45/112 (40.2%)
	Neuropathic pain[58]	125	53	41	5 weeks	Gastrointestinal disorders: 40/101 (39.6%)
	Rheumatoid arthritis[56]	58	62.8	21	5 weeks	Nervous system disorders: 13/23 (56.5%)
RCTs; Cross-over	Brachial plexus avulsion [94]	48	39 (23-63)	96	2 weeks	Nervous system disorders: 48/62 (77.4%)
	Glaucoma[120]	6	55	100	18 hours	Gastrointestinal disorders: 5/18 (27.8%)
	Neuropathic pain[97]	21	48	50	2 weeks	Nervous system disorders: 11/36 (30.6%)

b. Oral THC or oral THC/CBD

Study design	Study population	Sample size	Age, yr Mean (range)	Gender, % male	Duration of exposure	Most frequently reported adverse event: n/N(%)
RCTs; Parallel	Cancer-related anorexia-achexia syndrome[122]	243	61	54	6 weeks	Gastrointestinal disorders: 70/187 (37.4%)
	Chemotherapy induced nausea[227]	116	61	60	4 days	Nervous system disorders: 56/78 (71.8%)
	HIV wasting syndrome[228]	50	40	88	12 weeks	Nervous system disorders: 3/11 (27.3%)
	Multiple sclerosis [51]	630	50 (18-64)	34	15 weeks	Nervous system disorders: 834/2594 (33.3%)
	Multiple sclerosis [52]	611	50 (18-64)	34	37 weeks	
	Postoperative pain[229]	40	44.8	0	24 hours	Nervous system disorders: 34/82 (41.5%)

Study design	Study population	Sample size	Age, yr Mean (range)	Gender, % male	Duration of exposure	Most frequently reported adverse event: n/N(%)
RCTs; Cross-over	Cancer patients with pain[118]	10	51	20	3 days	Nervous system disorders: 112/218 (51.4%)
	Cancer patients with pain[230]	36	51	28	1 day	Nervous system disorders: 173/430 (40.2%)
	Chemotherapy induced nausea[119]	79	46 (22-71)	35	1 day	Psychiatric disorders: 49/76 (64.5%)
	Chemotherapy induced vomiting[117]	73	43	58	2 days	Nervous system disorders: 60/106 (56.6%)
	Healthy, volunteers[121]	12	Female: 25; Male: 27	50	8 hours	Psychiatric disorders: 60/123 (48.8%)
	Idiopathic Parkinson's Disease[231]	19	67 (51-78)	63	4 weeks	Nervous system disorders: 17/38 (44.7%)
	Multiple sclerosis[53]	16	46	NR[1]	4 weeks	Nervous system disorders: 23/39 (59.0%)
	Multiple sclerosis[54]	24	50 (23-55)	42	3 weeks	Nervous system disorders: 53/100 (53.0%)
	Multiple sclerosis[55]	57	54.9	49	2 weeks	Psychiatric disorders: 21/45 (46.7%)
	Multiple sclerosis[232]	9	NR[1]	NR[1]	1 day	Psychiatric disorders: 1/1 (100%)

1. NR=not reported.

Table 3-2: Serious adverse events (fatal and non-fatal) reported in randomized controlled trials of pharmaceutical cannabinoid products

Serious adverse event	**Cannabinoid exposure**		**Control**	
	N (%)	**Rate [1]**	**N (%)**	**Rate [1]**
Respiratory, thoracic and mediastinal disorders	*27(16.5%)*	*0.06*	*7 (11.7%)*	*0.03*
Dyspnoea	13		3	
Pneumonia	11(3 death)		3 (1 death)	
Pleural effusion	2		0	
Lower respiratory tract infection	1		0	
Pulmonary embolism	0		1	
Gastrointestinal disorders	*27(16.5%)*	*0.06*	*4 (6.7%)*	*0.02*
Vomiting	16		1	
Diarrhea	6		0	
Gastroenteritis	2		0	
Abdominal pain	1		0	
Constipation	1		3	
Duodenal ulcer	1		0	
Nervous system disorders	*25(15.2%)*	*0.06*	*18(30.0%)*	*0.08*
MS relapse	21		11	
Convulsion	2 (1 death)		4	
Dizziness	1		0	
Multiple sclerosis	1		1	
Cerebrovascular disorder	0		2	
General disorders and administration site conditions	*21(12.8%)*	*0.05*	*8 (13.3%)*	*0.03*
Death	10		1	
Pain	6		4	
Pyrexia	5		2	
Chest pain	0		1	

1. Incidence rate = events/person-year

Serious adverse event	Cannabinoid exposure		Control	
	N (%)	Rate [1]	N (%)	Rate [1]
Renal and urinary disorders	*16 (9.8%)*	*0.04*	*8 (13.3%)*	*0.03*
Urinary tract infection	15		8	
Haematuria	1		0	
Neoplasm, benign and malignant	*14 (8.5%)*	*0.03*	*2 (3.3%)*	*0.01*
Neoplasm progression	13		2	
Cervix carcinoma	1 (1 death)		0	
Psychiatric disorders	*11 (6.7%)*	*0.03*	*1(1.7%)*	*0.00*
Mood altered	11		1	
Surgical and medical procedures	*6 (3.7%)*	*0.01*	*3 (5.0%)*	*0.01*
Suprapubic catheter insertion	3		2	
Insertion of baclofen bump	2		0	
Hip arthroplasty	1		0	
Physiotherapy	0		1	
Metabolism and nutrition disorders	*4 (2.4%)*	*0.01*	*1 (1.7%)*	*<0.01*
Dehydration	4		1	
Vascular disorders	*3 (1.8%)*	*<0.01*	*1 (1.7%)*	*<0.01*
Transient ischaemic attack	2		0	
Circulatory collapse	1		0	
Cardiac disorders	*2 (1.2%)*	*<0.01*	*1 (1.7%)*	*0.01*
Bradycardia	1		0	
Syncope	1		0	
Myocardial ischaemia	0		1 (1 death)	

1. Incidence rate = events/person-year

Serious adverse event	Cannabinoid exposure		Control	
	N (%)	Rate [1]	N (%)	Rate [1]
Musculoskeletal and connective tissue disorders	*2 (1.2%)*	*<0.01*	*1 (1.7%)*	*<0.01*
Back pain	1		0	
Limb fracture	1		1	
Skin and subcutaneous tissue disorders	*2 (1.2%)*	*<0.01*	*1 (1.7%)*	*<0.01*
Cellulites	2		1	
Hepatobiliary disorders	*1 (0.6%)*	*<0.01*	*0 (0%)*	*0*
Cholestasis	1		0	
Infections and infestations	*1(0.6%)*	*<0.01*	*0(0%)*	*0*
Groin abscess	1		0	
Injury, poisoning and procedural complications	*1(0.6%)*	*<0.01*	*1 (1.7%)*	*<0.01*
Fall	1		0	
Overdose	0		1	
Investigations	*1 (0.6%)*	*<0.01*	*0(0%)*	*0*
Biopsy lymph gland	1		0	
Social circumstances	*0 (0%)*	*0*	*1 (1.7%)*	*<0.01*
Unspecified	*0 (0%)*	*0*	*2(3.3%)*	*0.01*
Total	164	0.37	60	0.25

1. Incidence rate = events/person-year

Table 3-3: Non-serious adverse events reported in randomized controlled trials of pharmaceutical cannabinoid products, categorized by system organ class

System Organ Class (MedDRA)	Cannabinoid exposure		Control		Pooled rate ratio (95% CI)
	N (%)	Rate [1]	N (%)	Rate [1]	
Nervous system disorders	1695 (36.7%)	3.81	513 (31.3%)	2.15	1.87 (1.53-2.30)
Gastrointestinal disorders	758 (16.4%)	1.70	246 (15.0%)	1.03	1.52 (1.19-1.93)
General disorders and administration site conditions	651 (14.1%)	1.46	294 (17.9%)	1.23	1.15 (1.00-1.32)
Psychiatric disorders	512 (11.1%)	1.15	122 (7.4%)	0.51	2.73 (1.69-4.41)
Musculoskeletal and connective tissue disorders	331 (7.2%)	0.74	174 (10.6%)	0.73	1.01 (0.84-1.21)
Renal and urinary disorders	236 (5.1%)	0.53	134 (8.2%)	0.56	0.91 (0.77-1.07)
Infections and infestations	134 (2.9%)	0.30	70 (4.3%)	0.29	0.96 (0.73-1.26)
Eye disorders	106 (2.3%)	0.24	16 (1.0%)	0.07	1.97 (1.23-3.17)
Injury, poisoning and procedural complications	37 (0.8%)	0.08	11 (0.7%)	0.05	1.25 (0.73-2.14)
Metabolism and nutrition disorders	37 (0.8%)	0.08	4 (0.2%)	0.02	1.47 (0.75-2.86)

1. Incidence rate=events/person-year

System Organ Class (MedDRA)	Cannabinoid exposure		Control		Pooled rate ratio (95% CI)
	N (%)	Rate [1]	N (%)	Rate [1]	
Respiratory, thoracic and mediastinal disorders	36 (0.8%)	0.08	7 (0.4%)	0.03	1.42 (0.77-2.62)
Skin and subcutaneous tissue disorders	30 (0.7%)	0.07	27 (1.6%)	0.11	0.60 (0.38-0.94)
Blood and lymphatic system disorders	26 (0.6%)	0.06	8 (0.5%)	0.03	0.90 (0.50-1.60)
Cardiac disorders	22 (0.5%)	0.05	12 (0.7%)	0.05	1.12 (0.63-2.00)
Vascular disorders	3 (0.1%)	0.01	2 (0.1%)	0.01	0.69 (0.32-1.51)
Investigations	1 (<0.1%)	<0.01	1 (0.1%)	<0.01	0.68 (0.31-1.35)
Total	4615	10.37	1641	6.87	1.86 (1.57-2.21)

1. Incidence rate = events/person-year

Table 3-4: Frequency of non-serious adverse events reported in randomized controlled trials of pharmaceutical cannabinoid products

Adverse event	**Number of events**	**Percentage (%)**
Nervous system disorders	*1695*	*36.7%*
Dizziness	714	
Somnolence	377	
Sedation	100	
Headache	79	
Coordination abnormal	73	
Tremor	71	
Paraesthesia	63	
Multiple sclerosis	31	
Memory impairment	29	
Syncope	29	
Tinnitus	29	
Hypoaesthesia	28	
Dysgeusia	22	
Dreamy state	16	
Vertigo	16	
Balance disorder	13	
Abnormal dreams	2	
Nervous system disorder	2	
Migraine	1	
Gastrointestinal disorders	*758*	*16.4%*
Other Gastrointestinal tract	285	
Dry mouth	239	
Nausea	117	
Diarrhoea	45	
Constipation	23	

Adverse event	Number of events	Percentage (%)
Vomiting	15	
Dysphagia	13	
Oral pain	12	
Mouth ulceration	5	
Abdominal pain	3	
Glossodynia	1	
General disorders and administration site conditions	*651*	*14.1%*
Pain	278	
Asthenia	198	
Fatigue	109	
Feeling drunk	24	
Application site irritation	21	
Hyperhidrosis	10	
Thirst	3	
Hot flush	2	
Influenza	2	
Chills	1	
Feeling abnormal	1	
Feeling hot	1	
Tenderness	1	
Psychiatric disorders	*512*	*11.1%*
Euphoric mood	127	
Depression	93	
Mental disorder	51	
Speech disorders	45	
Dissociation	34	
Disorientation	28	
Disturbance in attention	28	
Mood altered	24	
Delusional perception	18	

Adverse event	Number of events	Percentage (%)
Hallucinations	15	
Confusional state	14	
Feeling of despair	7	
Irritability	5	
Aggression	4	
Anxiety	4	
Nervousness	4	
Indifference	4	
Affect liability	3	
Inappropriate affect	1	
Panic attack	1	
Paranoia	1	
Psychomotor hyperactivity	1	
Musculoskeletal and connective tissue disorders	*331*	*7.2%*
Muscle spasms	289	
Muscle twitching	21	
Myalgia	7	
Muscle spasticity	5	
Muscle weakness	4	
Musculoskeletal pain	2	
Sensation of heaviness	2	
Arthralgia	1	
Renal and urinary disorders	*236*	*5.1%*
Bladder disorders	222	
Urinary tract infection	14	
Infection and infestations	*134*	*2.9%*
Infection	134	
Eye disorders	*106*	*2.3%*
Vision Blurred	105	

Adverse event	Number of events	Percentage (%)
Photopsia	1	
Injury, poisoning and procedural complications	*37*	*0.8%*
Fall	34	
Drug toxicity	2	
Joint injury	1	
Metabolism and nutrition disorders	*37*	*0.8%*
Increased appetite	32	
Anorexia	5	
Respiratory, thoracic and mediastinal disorders	*36*	*0.8%*
Dyspoea	22	
Nasopharyngitis	4	
Pharyngitis	4	
Cough	2	
Throat irritation	2	
Dysphonia	1	
Upper respiratory tract infection	1	
Skin and subcutaneous tissue disorders	*30*	*0.7%*
Skin problem	15	
Pruritus	11	
Decubitus ulcer	4	
Blood and lymphatic system disorders	*26*	*0.6%*
Anemia	24	
Leukopenia	2	

Adverse event	Number of events	Percentage (%)
Cardiac disorders	*22*	*0.5%*
Palpitations	16	
Tachycardia	6	
Vascular disorders	*3*	*0.1%*
Hypertension	2	
Hypotension	1	
Investigations	*1*	*0.0%*
Weight decrease	1	
Total	4615	100.0%

Figure 3-2: Incidence rates and rate ratios of non-serious adverse events among subjects exposed to pharmaceutical cannabinoid products versus controls in 23 randomized controlled trials

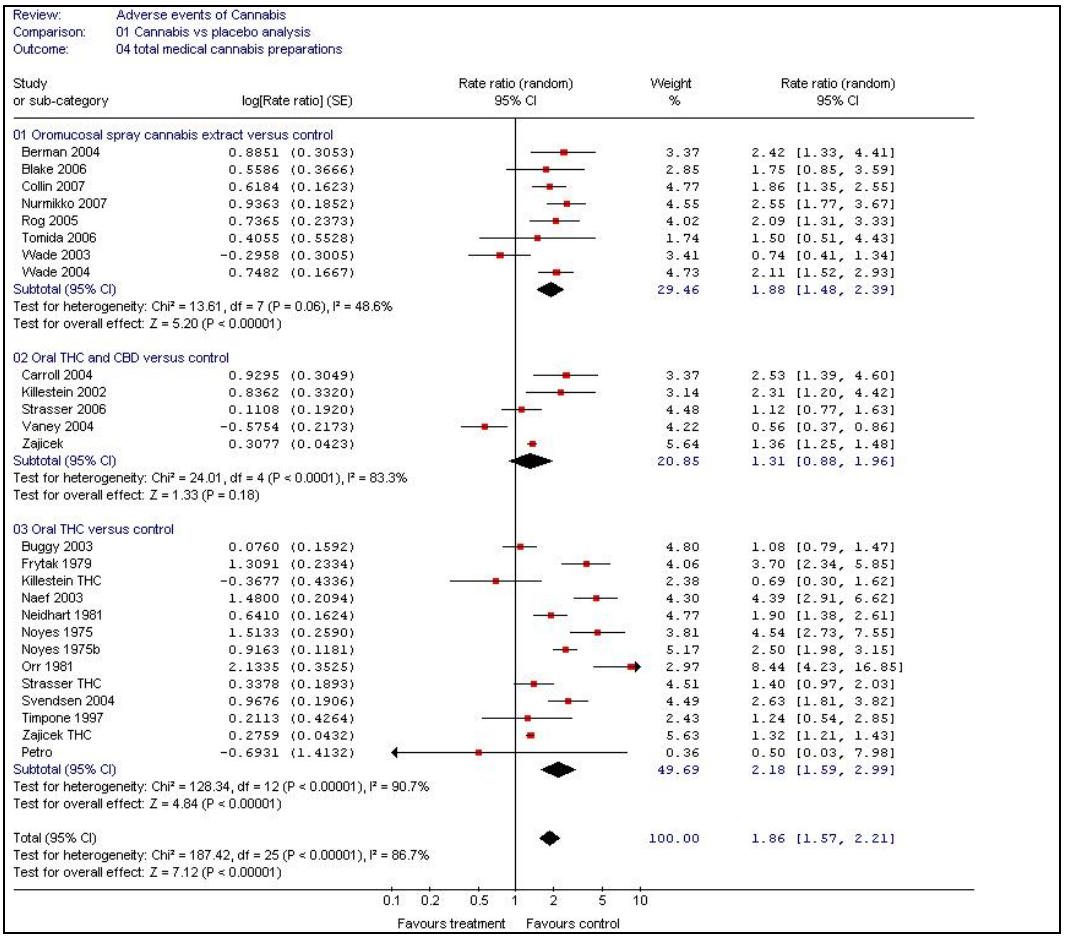

Table 3-5: Incidence rates of non-serious adverse events among pharmaceutical cannabinoid subjects and controls in randomized controlled trials: subgroup analysis

Group/Subgroup	No. of trials	Pooled rate ratio (95%CI)	Heterogeneity		
			X^2	P value	I^2 (%)
All studies	23	1.86 (1.57-2.21)	187.42	<0.001	86.7
Oromucosal spray versus control	*8*	*1.88 (1.48-2.39)*	*13.61*	*0.06*	*48.6*
Duration of exposure					
>2 weeks	5	2.10 (1.76-2.49)	1.93	0.75	0
<=2 weeks	3	1.38 (0.61-3.11)	7.64	0.02	73.8
Study design					
RCT parallel	5	2.10 (1.76-2.49)	1.93	0.75	0
RCT crossover	3	1.38 (0.61-3.11)	7.64	0.02	73.8
Study population					
With cancer	0	NA[1]	NA[1]	NA[1]	NA[1]
Without cancer	8	1.88 (1.48-2.39)	13.61	0.06	48.6
Oral THC versus control	*13*	*2.18 (1.59-2.99)*	*128.34*	*<0.001*	*90.7*
Duration of exposure					
>2 weeks	5	1.46 (1.04-2.04)	15.02	0.005	73.4
<=2 weeks	8	2.91 (1.88-4.50)	59.20	<0.001	88.2
Study design					
RCT parallel	5	1.53 (1.10-2.17)	21.05	<0.001	81.0
RCT crossover	8	2.82 (1.94-4.11)	36.19	<0.001	80.7
Study population					
With cancer	6	2.93 (1.96-4.39)	32.28	<0.001	84.5
Without cancer	7	1.60 (1.04-2.47)	48.62	<0.001	87.7
Oral THC and CBD versus control	*5*	*1.31 (0.88-1.96)*	*24.01*	*<0.001*	*83.3*
Duration of exposure					
>2 weeks	4	1.54 (1.14-2.08)	7.68	0.05	60.9
<=2weeks	1	0.56 (0.37-0.86)	NA[1]	NA[1]	NA[1]
Study design					
RCT parallel	2	1.35 (1.24-1.46)	1	0.32	0.3
RCT crossover	3	1.46 (0.51-4.19)	21.94	<0.001	90.9
Study population					
With cancer	1	1.13 (0.77-1.64)	NA[1]	NA[1]	NA[1]
Without cancer	4	1.39 (0.80-2.42)	23.12	<0.001	87.0

1. NA=not applicable

Table 3-6: Serious adverse events reported in observational studies of pharmaceutical cannabinoid products

Serious adverse event	Number of events	Percentage (%)
Nervous system disorders	*9*	*23.1%*
Convulsion	3	
Multiple sclerosis relapse	2	
Myoclonus	2	
Balance disorder	1	
Circulatory collapse	1	
Psychiatric disorders	*4*	*10.3%*
Mental disorder	4	
Respiratory, thoracic and mediastinal disorders	*4*	*10.3%*
Pneumonia	2	
Lung neoplasm malignant	1	
Pleurisy	1	
Gastrointestinal disorders	*3*	*7.7%*
Diarrhoea	2	
Vomiting	1	
Musculoskeletal and connective tissue disorders	*3*	*7.7%*
Muscle spasms	1	
Muscular weakness	1	
Osteomyelitis	1	
Renal and urinary disorders	*3*	*7.7%*
Urinary tract infection	3	
Vascular disorders	*3*	*7.7%*
Deep vein thrombosis	1	

Serious adverse event	Number of events	Percentage (%)
Orthostatic hypotension	1	
Syncope vasovagal	1	
Neoplasm benign, malignant and unspecified	*2*	*5.1%*
Breast cancer	2	
Skin and subcutaneous tissue disorders	*2*	*5.1%*
Cellulitis	1	
Decubitus ulcer	1	
Blood and lymphatic system disorders	*1*	*2.6%*
Lymphadenopathy	1	
Cardiac disorders	*1*	*2.6%*
Ventricular extrasystoles	1	
Hepatobiliary disorders	*1*	*2.6%*
Biliary cirrhosis	1	
Infections and infestations	*1*	*2.6%*
Sepsis	1	
Investigations	*1*	*2.6%*
Liver function test abnormal	1	
Metabolism and nutrition disorders	*1*	*2.6%*
Dehydration	1	
Total	39	100.0%

Table 3-7: Non-serious adverse events reported in observational studies of pharmaceutical cannabinoid products

System Organ Class (MedDRA)	Number of events	Percentage (%)
Nervous system disorders	1412	39.8%
Psychiatric disorders	1265	35.6%
Gastrointestinal disorders	558	15.7%
Vascular disorders	141	4.0%
Cardiac disorders	107	3.0%
General disorders and administration site conditions	42	1.2%
Investigations	13	0.4%
Injury, poisoning and procedural complication	7	0.2%
Eye disorders	6	0.2%
Respiratory, thoracic and mediastinal disorders	2	0.1%
Total	3553	100.0%

Table 3-8: Summary of non-serious adverse events reported in observational studies of pharmaceutical cannabinoid products

Adverse event	Number of events	Percentage (%)
Nervous system disorders	*1412*	*39.8%*
Sedation	517	
Dizziness	393	
Neurologic visual problems NEC	224	
Coordination abnormal	185	
Somnolence	23	
Headache	21	
Balance disorder	12	
Dysgeusia	11	
Lethargy	6	
Memory impairment	5	
Multiple sclerosis	5	
Hypotonia	4	
Paralysis	2	
Cholinergic syndrome	1	
Dysarthria	1	
Sensory disturbance	1	
Spasticity	1	
Psychiatric disorders	*1265*	*35.6%*
Confusional state	308	
Mood altered	290	
Anxiety	214	
Depression	193	
Abnormal dreams	149	
Panic attack	95	
Disturbance in attention	12	

Adverse event	Number of events	Percentage (%)
Paranoia	2	
Euphoric mood	1	
Sleep disorder	1	
Gastrointestinal disorders	*558*	*15.7%*
Dry mouth	405	
Diarrhoea	29	
Nausea	29	
Oral pain	28	
Constipation	14	
Vomiting	14	
Oral mucosal disorder	12	
Tooth discolouration	11	
Mouth plaque	6	
Mouth ulceration	4	
Pharyngitis	4	
Abdominal pain	2	
Vascular disorders	*141*	*4.0%*
Hypotension	141	
Cardiac disorders	*107*	*3.0%*
Tachycardia	107	
General disorders and administration site conditions	*42*	*1.2%*
Fatigue	19	
Oedema	6	
Asthenia	5	
Pain	5	
Instillation site foreign body sensation	3	
Loss of control of legs	2	
Pallor	1	
Pyrexia	1	

Adverse event	Number of events	Percentage (%)
Investigations	*13*	*0.4%*
Weight decreased	7	
Gamma-glutamyltransferase increased	6	
Injury, poisoning and procedural complications	*7*	*0.2%*
Poisoning	7	
Eye disorders	*6*	*0.2%*
Vision blurred	6	
Respiratory, thoracic and mediastinal disorders	*2*	*0.1%*
Hypoxia	1	
Pulmonary embolism	1	
Total	3553	100.0%

Table 3-9: Published observational epidemiological studies of the safety of recreational cannabis, by system studied

Observational Studies	**Number of publications**	**Percentage (%)**
Psychiatric disorders	37	40.2%
Prenatal cannabis exposure	19	20.7%
Injury, poisoning and procedural complications	13	14.1%
Neoplasm, benign and malignant	7	7.6%
Nervous system disorders	7	7.6%
Respiratory, thoracic and mediastinal disorders	3	3.3%
Cardiac disorders	2	2.2%
Hepatobiliary disorders	1	1.1%
Reproductive system and breast Disorders	1	1.1%
Others	2	2.2%
Total	92	100.0%

Table 3-10: Adverse events in published case reports of recreational cannabis, categorized by system organ class

System Organ Class (MedDRA)	Number of events	Percentage (%)
Psychiatric disorders	107	30.0%
Nervous system disorders	56	15.7%
Respiratory, thoracic and mediastinal disorders	43	12.0%
Vascular disorders	32	9.0%
Cardiac disorders	31	8.7%
Neoplasms benign, malignant and unspecified	21	5.9%
Gastrointestinal disorders	12	3.4%
Injury, poisoning and procedural complications	11	3.1%
Eye disorders	9	2.5%
Endocrine disorders	6	1.7%
Congenital, familial and genetic disorders	5	1.4%
Pregnancy, puerperium and perinatal conditions	5	1.4%
Ear and labyrinth disorders	4	1.1%
Musculoskeletal and connective tissue disorders	4	1.1%
General disorders and administration site conditions	3	0.8%
Blood and lymphatic system disorders	2	0.6%
Immune system disorders	2	0.6%
Renal and urinary disorders	2	0.6%
Skin and subcutaneous tissue disorders	1	0.3%
Investigations	1	0.3%
Total	357	100.0%

Table 3-11: Most commonly reported adverse events in published case reports of recreational cannabis

Adverse event	Number of events	Percentage (%)
Psychotic disorder	40	11.2%
Arteritis	27	7.6%
Cerebrovascular accident	15	4.2%
Schizophrenia	15	4.2%
Bullous lung disease	12	3.4%
Depersonalization	12	3.4%
Drug toxicity	11	3.1%
Cerebral atrophy	10	2.8%
Myocardial infarction	9	2.5%
Panic attack	9	2.5%
Coordination abnormal	8	2.2%
Hallucination	8	2.2%

Table 3-12: Summary of adverse events in published case reports of recreational cannabis

Adverse event	Number of events	Percentage (%)
Psychiatric disorders	*107*	*30.0%*
Psychotic disorder	40	
Schizophrenia	15	
Depersonalization	12	
Panic attack	9	
Hallucination	8	
Flashback	5	
Confusional state	2	
Delirium	2	
Delusion of grandeur	2	
Euphoric mood	2	
Panic disorder	2	
Body dysmorphic disorder	1	
Catatonia	1	
Completed suicide	1	
Conduct disorder	1	
Delusion of replacement	1	
Hypomania	1	
Paranoia	1	
Psychomotor retardation	1	
Nervous system disorders	*56*	*15.7%*
Cerebrovascular accident	15	
Cerebral atrophy	10	
Coordination abnormal	8	
Coma	7	
Transient ischaemic attack	4	
Convulsion	3	
Amnesia	2	
Memory impairment	2	
Stupor	2	
Grand mal convulsion	1	

Adverse event	Number of events	Percentage (%)
Migraine	1	
Myoclonus	1	
Respiratory, thoracic and mediastinal disorders	*43*	*12.0%*
Bullous lung disease	12	
Pneumothorax	7	
Pneumomediastinum	6	
Bronchopulmonary aspergillosis	3	
Bronchopulmonary aspergillosis allergic	3	
Obstructive airways disorder	2	
Alveolar proteinosis	1	
Asthma	1	
Bronchial carcinoma	1	
Bronchitis	1	
Epiglottitis	1	
Hypopharyngeal cancer	1	
Laryngitis	1	
Laryngospasm	1	
Pulmonary granuloma	1	
Respiratory failure	1	
Vascular disorders	*32*	*9.0%*
Arteritis	27	
Thromboangiitis obliterans	4	
Hypertension	1	
Cardiac disorders	*31*	*8.7%*
Myocardial infarction	9	
Cardiac death	7	
Atrial fibrillation	5	
Tachycardia	4	
Cardiomyopathy	2	
Arrhythmia	1	
Atrioventricular block second degree	1	
Coronary artery thrombosis	1	
Dyspnoea	1	

Adverse event	Number of events	Percentage (%)
Neoplasms benign, malignant and unspecified	*21*	*5.9%*
Squamous cell carcinoma	6	
Lip and/or oral cavity cancer	5	
Tongue neoplasm malignant stage unspecified	4	
Bladder transitional cell carcinoma	1	
Lung neoplasm malignant	1	
Nasopharyngeal cancer	1	
Non-small cell lung cancer	1	
Renal cell carcinoma stage unspecified	1	
Seminoma	1	
Gastrointestinal disorders	*12*	*3.4%*
Vomiting	6	
Uvulitis	3	
Abdominal pain	1	
Gingival hyperplasia	1	
Pancreatitis acute	1	
Injury, poisoning and procedural complications	*11*	*3.1%*
Drug toxicity	11	
Eye disorders	*9*	*2.5%*
Visual disturbance	7	
Conjunctivitis allergic	1	
Glaucoma	1	
Endocrine disorders	*6*	*1.7%*
Gynaecomastia	3	
Delayed puberty	1	
Diabetic ketoacidosis	1	
Hyperprolactinaemia	1	
Congenital, familial and genetic disorders	*5*	*1.4%*
Amniotic band syndrome	3	
Porencephaly	1	
Skull malformation	1	

Adverse event	Number of events	Percentage (%)
Pregnancy, puerperium and perinatal conditions	*5*	*1.4%*
Foetal growth retardation	5	
Ear and labyrinth disorders	*4*	*1.1%*
Ear congestion	4	
Musculoskeletal and connective tissue disorders	*4*	*1.1%*
Clubbing	4	
General disorders and administration site conditions	*3*	*0.8%*
Malaise	2	
Hyperthermia	1	
Blood and lymphatic system disorders	*2*	*0.6%*
Anaemia	1	
Coagulopathy	1	
Immune system disorders	*2*	*0.6%*
Hypersensitivity	1	
Urticaria contact	1	
Renal and urinary disorders	*2*	*0.6%*
Renal infarct	1	
Urinary retention	1	
Skin and subcutaneous tissue disorders	*1*	*0.3%*
Pruritus generalized	1	
Investigations	*1*	*0.3%*
Electrocardiogram ST segment depression	1	
Total	357	*100.0%*

CHAPTER 4: SAFETY OF HERBAL CANNABIS FOR MEDICAL USE

4.1 Introduction

Chapter 3 presented a review of existing safety information on cannabis. The meta-analysis of randomized controlled trials (RCTs) suggested that short-term use of pharmaceutical cannabinoid products only increased the risk of non-serious adverse events. However, this meta-analysis was inconclusive regarding the risk of serious adverse events. Furthermore, it did not provide information on the long-term safety because the median duration of follow up from available trials was only 2 weeks. Moreover, none of the trials involved the use of herbal cannabis, in particular, the use of smoking as the route of delivery.

The systematic review of observational studies and case reports of recreational cannabis use provided complementary information on the adverse effects of herbal cannabis. However, the methodological limitations identified in existing observational studies with respect to cannabis exposure, potential confounders and the choice of control groups raised doubts about their conclusions. It is also not clear whether the use of medicinal cannabis has similar safety concerns as recreational use, as the quality and amounts used and existence of co-morbidities are different in the two populations. Moreover, medical cannabis users have entirely different expectations regarding the adverse events from those of the recreational users. Hence, caution must be exercised when assuming that adverse effects of recreational cannabis use may be translated to medical cannabis use.

An increasing number of Canadian patients are using cannabis for medical purposes under the Marihuana Medical Access Regulations (MMAR) or through support of medicinal cannabis compassion clubs in Canada. The risks of herbal cannabis use among healthy populations have been widely studied, but the risk of adverse events associated with medical use of cannabis has not yet been evaluated in a prospective epidemiological study. Studies on the effects of cannabis smoking on the neurocognitive function and pulmonary function in patients with chronic pain are scarce. Given the extent of medicinal cannabis use (and with this, with involvement of physicians) and the potential risks of the use of smoking as the route of delivery, there is an urgent need for safety data on herbal cannabis when used for medical purposes. Therefore, a multicenter cohort study was conducted to compare the adverse event profile of patients with chronic pain who reported using cannabis as part of their pain management regimen with a group of chronic pain patients who were not cannabis users.

The results of a CIHR-funded study entitled *Cannabis for the Management of Pain: Assessment of Safety Study* (COMPASS) are presented in this chapter. The safety profile of herbal cannabis among chronic pain patients is assessed and the association between the use of medical cannabis and its incident rate of adverse events is determined. The effects of medical cannabis on pulmonary and neurocognitive function are also examined.

4.2 Methods

4.2.1 Summary of the study design

A prospective cohort study with a one-year follow-up was conducted in seven clinic centers across Canada (Vancouver, BC; London, ON; Toronto, ON; 2 centers in Montreal, QC; Fredericton, NB; and Halifax, NS) between January 2004 and April 2008 (Principal investigators: Drs. Mark A. Ware and Jean-Paul

Collet). Initial plans were to recruit 350 subjects in the cannabis group and 1050 subjects in the control group. A standardized herbal cannabis product (12.5% THC) was dispensed to eligible subjects for a one-year period. The primary outcome was adverse events, consisting of serious adverse events (SAEs) and non-serious adverse events (AEs). Secondary outcomes included changes in pulmonary function, neurocognitive function, pain intensity and quality of life.

Standardized procedures were utilized to obtain data on adverse events during clinic visits and telephone interviews. The data were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 11.0). The causality and severity of the adverse event were first assessed by physicians at study sites, and then were adjudicated by a committee of clinical reviewers using the WHO-UMC causality assessment system[233] and Common Terminology Criteria for Adverse Events v3.0 (CTCAE)[234].

The study was approved by the ethics committee of each participating hospital. An independent Safety Monitoring Advisory Committee (SMAC) oversaw the safety results over the course of the study.

4.2.2 Objectives

The primary objective was to assess the risk of adverse events associated with cannabis when used in the treatment of chronic pain up to a suggested maximum daily dosage of 4-5 grams. The secondary objective was to examine the effects of medical cannabis on pulmonary and neurocognitive function. The third objective was to explore the effectiveness of cannabis in patients with chronic pain, including the change of pain intensity and the change of quality of life.

4.2.3 Study population

Patients 18 years of age or older were eligible for the trial if they were experiencing chronic non-cancer pain, and they were diagnosed with moderate to severe pain in which conventional treatments had been considered medically inappropriate or inadequate. Other requirements for inclusion were a willingness to participate for the duration of the trial, and provision of written informed consent. Patients who were pregnant or breast-feeding, who had a history of drug dependency, who exhibited significant and unstable ischemic heart disease or arrhythmia, who had a history of psychosis, or who suffered from significant and unstable broncho-pulmonary disease were excluded.

Subjects were recruited from the regions served by the seven study sites. Subjects were advised that cannabis use might reduce their ability to perform hazardous tasks such as operating heavy machinery, and were recommended not to drive while under the effects of cannabis. The study was publicized through the media. The control subjects were recruited consecutively from the participating clinics from among the routine patients attending. Written informed consent was obtained from participants according to protocol.

4.2.4 Main outcome measures

4.2.4.1 Primary outcomes

Definitions

The primary outcome of this study was adverse events, including SAEs and non-serious AEs which were identified using definitions recommended by the International Conference on Harmonization (ICH).[113] Under the ICH guidelines, a SAE is defined as any untoward medical occurrence that requires hospitalization or prolongation of existing hospitalization, that causes congenital malformation,

or that results in persistent or significant disability or incapacity that is life-threatening or that results in death. A non-serious AE is defined as any untoward medical occurrence in a patient or subject that does not necessarily have a causal relationship with treatment. The expectedness of an AE was also defined following ICH guidelines, in which an "unexpected" AE is identified when "the nature or severity of this event is not consistent with the applicable product information".[113]

Reporting of serious and non-serious adverse events

The flow chart in Appendix 1 shows how reported adverse events were collected and transmitted among the study sites, the study coordinating center, the SMAC and the regulatory and research ethics boards.

Serious and unexpected adverse events were reported by the study physician to the regulatory agency at Health Canada within the reporting time frames as recommended under ICH guidelines and to the investigators.[113] The investigators were responsible for ensuring that their respective ethics committee is informed of any serious and unexpected adverse events reported. The death of a subject was reported on a Death Report Form. In addition, during periodic site visits, the study monitor reviewed the subjects' hospital charts to ensure that serious adverse events were not missed by the site physicians.

Non-serious adverse events were reported by the participants during interviews at clinic visits, during telephone interviews, or at any time by calling the local study nurse. Specific questions about adverse events were asked at each visit or subject contact.

Interpretations of serious and non-serious adverse events: causality and severity

The causality of an event was evaluated using the causality algorithm defined by the WHO.[233] The severity of a non-serious AE was classified as "mild" (transient or mild discomfort that lasts less than 48 hours and in which no medical intervention/therapy is required), "moderate" (mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy is required), and "severe" (marked limitation in activity, some assistance is usually required and in which medical intervention/therapy and/or possible hospitalization are required).

Adjudication

The causality and severity of adverse events were classified initially by the attending physician in each site. To identify and address any differences in the way study sites classified the causality and severity of adverse events, an Adjudication Committee was established. Two clinical reviewers (Drs. Mark Ware and Mary Lynch), who were unaware of cannabis exposure status, assessed independently the severity and causality of the event, and created their own assignments for these variables for each event. The committee then met to discuss the discrepancies and means to resolve them. Suggestions for amendments to the database were passed on to the Steering Committee for approval and any necessary database changes made.

4.2.4.2 Secondary outcomes

Neurocognitive tests

The neurocognitive tests comprised two subtests of the Wechsler Memory Scale—Third Edition (WMS®-III) (Verbal Paired Associates I—recall and Verbal

Paired Associates II, including recall and recognition) and two subtests of the Wechsler Adult Intelligence Scale—Third Edition (WAIS®-III) (digit symbol-coding, picture arrangement). These tests have been previously used in studies of the neurocognitive effects of cannabis.[36, 50, 235] Psychometric properties have been well documented. The WMS®-III subtests have been shown to have very good internal consistency (range 0.74-0.93) and acceptable test-retest coefficients (range 0.62-0.82) for all age groups.[236] With regard to the WAIS®-III subtests, test-retest reliabilities across all age groups indicated the good reliability of digit symbol-coding (range 0.86-0.93), however, test-retest reliability coefficients tended to be lower for picture arrangement, which ranged between 0.57 and 0.83.[237, 238]

Pulmonary function tests

The following pulmonary function tests were performed: slow vital capacity (SVC), functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC), diffusing capacity for carbon monoxide (DL_{CO}), forced expired volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and forced expiratory flow over the middle half of the forced vital capacity ($FEF_{25-75\%}$).

Pain intensity

Pain intensity was measured to assess the effectiveness of medical cannabis. At each clinic visit, patients were asked to rate their average, worst, least pain, as well as their current pain, on an 11-point numerical rating scale (NRS), with "no pain (0)" and "worst pain possible (10)" as anchors.[239] This questionnaire is short, easy to administer, and has been validated as a measure of pain intensity. The correlation between the NRS and the visual analog scale (VAS) was 0.85,

indicating the strong construct validity of the NRS.[240] The NRS has also been shown to have an adequate internal consistency (Cronbach's $\alpha > 0.80$), and good test-retest coefficients (range 0.70-0.88). [241, 242]

Quality of life

The Short Form 36 (SF-36v2®) questionnaires were administered to assess quality of life. The SF-36v2® is a multi-purpose, short-form health survey with 36 questions, and yields information on physical health (comprising physical functioning, role limitations due to physical problems, bodily pain, and general health perceptions) and mental health (comprising vitality, social functioning, role limitations due to emotional problems, and mental health). [243] The median reliability coefficients for each of the eight scales were equal or greater than 0.80 except for social functioning, which had a median reliability across studies of 0.76.[244] Two summary scores, Physical Component Summary (PCS) and Mental Component Summary (MCS), were generated. Internal consistency reliability estimates for physical and mental summary scores were 0.95 and 0.93, respectively.[243] The content validity of the SF-36 has been compared with that of seven other widely used generic health surveys. Comparisons supported that the SF-36v2® included eight of the most frequently measured health concepts.[244]

4.2.5 Procedures

4.2.5.1 Baseline assessments

Baseline assessments are outlined in Appendix 2. An interview was carried out to capture demographic characteristics, tobacco use history, alcohol use history, past cannabis use, and medical data. A patient's disability status was recorded during the baseline interview. "Short-term disability" was considered as being "off-work" but with plans to return to work eventually, and "disability" was

considered as being recognized by the government as no longer being able to work. Before the study cannabis was dispensed, neurocognitive function tests were administered along with a short-form health survey—SF-36v2®, pain intensity scale, Drug Abuse Screening Test (DAST) and Urine drug testing (UDT) in both groups. Pulmonary function tests were carried out in the cannabis group only.

4.2.5.2 Intervention

Supply

Only cannabis (12.5% ± 2% Δ^9–THC) grown under contract to Health Canada, by Prairie Plant Systems Inc., was used in this study. Cannabis was packaged and distributed in foil packets, each containing 30 grams of dried herbal material. The product was shipped to participating pharmacies for dispensing to patients.

Mode of administration

Participants were able to use the delivery system with which they were most comfortable, and the investigators and physicians did not recommend any particular mode. They could use cannabis by smoking, vaporizers (inhalation) and oral administration such as baked in cookies or brownies.

Dosing and dispensing

Subjects were advised to begin with low doses and were then titrated upwards to the effective dose with experience of the material. Subjects were recommended to take the first dose in the evening in a relaxed and comfortable environment, and to repeat subsequent doses up to four times daily, though more frequent dosing might be required. Changes in dose size and frequency were made only once the

subject felt comfortable with the material. The dose was titrated gradually upward until either symptom relief was satisfactory or side effects became intolerable.

An upper limit recommendation was made to advise prescribing patterns to minimize possible adverse effects of cannabis and to reduce risk of diversion. The total recommended daily dosage of cannabis in this study should not exceed 4-5 grams per day but might do so under exceptional circumstances when deemed appropriate by the prescribing physician. Cannabis was dispensed by the site pharmacy at weekly intervals for the first month and then monthly thereafter for the remainder of the study. Prior to dispensing, subjects were to return unused cannabis for weighing and destruction.

4.2.5.3 Follow-up

The schedule of visits and assessments is summarized in Appendix 2. Adverse events were collected over one year of follow-up. Six clinic visits (at 1, 2, 3, 6, 9 and 12 months after baseline) and three telephone interviews (1, 2, and 3 weeks after baseline visit) were scheduled for subjects in the cannabis group; while two follow-up clinic visits (6 and 12 months after baseline) and five telephone interviews (1, 2, and 3 weeks, and then 3 and 9 months after baseline visit) were scheduled for control subjects. Adverse events were collects at each clinic visit and each telephone interview.

Assessments of neurocognitive function and quality of life were scheduled at baseline (prior to using the study cannabis) and then at 6 and 12 months after baseline in all patients. Pain intensity numerical rating scale was administered at baseline, 3, 6, 9 and 12 months after baseline in all patients. Pulmonary function tests were conducted in the cannabis group at baseline (before they started the study cannabis) and 12 months after baseline.

Self-reported drug use was verified using urine drug testing (UDT) consisting of a semi-quantitative immunoassay panel that measures THC, opiates, cocaine metabolites, benzodiazepines, and amphetamines. UDT was conducted in both groups during all clinic visits. Positive results indicated recent use of the drug. Discordance between self-reported drug use and UDT was considered as non-compliance with the protocol.

4.2.6 Sample size and power considerations

In preliminary planning, a cohort of 350 chronic pain cannabis-using subjects was targeted. Failure to observe a particular side effect with a sample size of 350 subjects would be consistent with a conclusion that the maximum risk was not greater than 0.9%.[245,246] A decision to seek to enroll 3 controls for each case was made in an effort to increase the power and statistical efficiency of the study. It was assumed that adverse events follow Poisson distributions in the two study groups. For a proposed sample size of 1400 (350 cannabis-using subjects and 1050 control subjects, all followed for one year), at a 5% level of statistical significance, a rate ratio of 1.5 can be detected at powers above 80% for SAEs with incidence rate in the control group above 0.15 cases/person-year (i.e. 158 events in the control group).[247-249] Power was higher for analysis of non-serious AEs, due to the higher incidence rate for the control population. (Appendix 3)

4.2.7 Statistical analysis

Primary analysis

Baseline demographic and clinical characteristics between cannabis and control groups were first compared, and reasons for withdrawals in both groups were tabulated. All patients recruited to the study were included in the primary safety analysis.

We coded and tabulated all recorded AEs using the Medical Dictionary for Regulatory Activities (MedDRA version 11.0) under the headings "System Organ Class" (SOC) and "Preferred Term (PT)".[114] We characterized all AEs by severity and causality. The total numbers of AEs were summarized and analyzed descriptively.

We estimated the incidence rates of serious and non-serious adverse events in both cannabis and control groups by dividing the number of events by the corresponding cumulative person-years of follow-up. The cumulative person-years were calculated from the date of the baseline visit until the date of discontinuation, death, or completion of the study, whichever came first.

A separate Poisson regression was used to compute incidence rate ratios (IRRs) for SAEs and non-serious AEs among cannabis users compared with controls. The Goodness of Fit was assessed to evaluate overdispersion; if evidence of overdispersion was found, we fitted an overdispersed Poisson regression model to assess the occurrence of SAEs, non-serious AEs, and AEs categorized into each MedDRA SOC among cannabis users or controls.[250-252]

Multiple Poisson regression models for the outcomes of SAEs and all non-serious AEs were adjusted for age, gender, disability status, past cannabis use (ever vs. never), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), average pain intensity, and concomitant medication use (i.e. whether used opioids, antidepressants, or anticonvulsants) at baseline interview, and study sites. We investigated the use of concomitant pain medications throughout the study, and found that 90% of patients did not change their use of opioid, antidepressant or anticonvulsant medications. As the number of patients who changed their use of concomitant pain medications throughout the study was considered to be small and the pattern of change was similar between the cannabis and control groups, only baseline data were included in the final data analysis.

We further categorized the average daily dose into the following groups: 0 (the control group), <1, 1-1.99, 2-2.99, or ≥3 grams/day. The incidence rates for the specific dosage group were calculated and compared with the rate for the control group to obtain the incidence rate ratios.

We also calculated the proportion of patients who experienced at least one event, serious, and non-serious adverse events in both groups. Logistic regression analysis was performed to explore the association between the risk of having AEs and medical cannabis use. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Subgroup analysis

To further control for confounding by past cannabis use, we estimated the stratified incidence rate of adverse events by past cannabis use in both cannabis and control groups. We grouped the past cannabis use into three categories. "Current cannabis users" were those who reported using cannabis at baseline interview; "ex cannabis users" were those who reported having used cannabis but were not using at baseline interview; "naïve users" were those who reported never using cannabis prior to baseline interview. We also carried out a Poisson regression within "ex cannabis users" and "naïve users" to validate the association between adverse events and cannabis.

Secondary analysis

Neurocognitive function tests: Raw scores and scaled scores of each subtest of neurocognitive functions were considered as continuous measures to compare their changes over time. Only subjects with complete raw scores of each subtest at both time points were included in each analysis. A random effects model with a random intercept for patient was used to model neurocognitive function. The main

effect of cannabis, time as well as cannabis by time interaction effects were considered in the model. A separate analysis was performed for each of the neurocognitive subtests, except for Verbal Paired Associates II—recognition test since 95% of participants obtained a maximum score of 24 on this test. Multiple regression analyses were adjusted for age, gender, education (college/university vs. high school/elementary), disability status, alcohol use (current vs. former or never users), past cannabis use (ever vs. never), and average pain intensity, quality of life [measured by Physical Component Summary (PCS) and Mental Component Summary (MCS)] at each time point and study sites. As analysis of both raw and scaled scores gave virtually identical results only the raw scores are presented in the tables.

Pulmonary function tests: Since the respiratory risk could be mainly influenced by smoked cannabis, we performed analyses in which we excluded 24 subjects who had never smoked cannabis in the study. A random effects model with a random intercept for patient was fitted to examine possible effect of cannabis and potential interactive effects of tobacco and cannabis on each pulmonary function measure, with age, gender, tobacco use (current vs. former or never users), past cannabis use (current vs. ex or naïve users) and study sites as the covariates.

Average pain intensity and quality of life: This study focused on analyzing and reporting average pain intensity, and 2 summary scores of SF-36v2®. Only subjects with complete pain intensity or quality of life scores at both time points were included in the analysis. A random effects model with a random intercept for patient was used to model average pain intensity scale, and PCS and MCS of the quality of life. The main effect of cannabis, time as well as cannabis by time interaction effects were considered in the model. Multiple regression analyses were adjusted for age, gender, disability status, concomitant pain medication use at baseline interview, alcohol use (current vs. former or never users), tobacco use (current vs. former or never users), past cannabis use (ever vs. never) and study sites.

Statistical analyses were undertaken with SAS software (version 9.1).

4.2.8 Protocol modifications

To explore the association between adverse events and medical cannabis use, a target sample of 350 cannabis exposed subjects and 1050 control subjects was proposed in the original protocol. However, early in the implementation of the study, the feasibility of recruiting 1050 controls (an average of 150 controls per clinic) was questioned. In addition, tight clinic visit scheduling was perceived to be too much of a burden for the patients. So an amendment to the number of controls and the number of clinic visits was made. The protocol was revised and approved by all regulatory and ethics committees with respect to the following points: remove the requirement for baseline and follow-up neurocognitive testing in all participants recruited after March 1st 2006 in both the cannabis users and the control group; decrease the number of control participants from 1050 to 350; and switch the 2-, 3- and 9-month clinic visits for participants in the cannabis group recruited after March 1st 2006 to telephone interviews instead.

Given the revised sample size of this study (350 cannabis-using subjects and 350 subjects in the control group, all followed for one year), we estimated that a rate ratio of 1.5 can be detected with power above 60% for the incidence rate of SAEs in the control group above 0.15 cases/person-year (i.e. 53 events in the control group) and with power above 70% for the incidence rate of serious adverse event in the control group above 0.20 cases/person-year (i.e. 70 events in the control group).

4.3 Results

From January 2004 to April 2008, a total of 431 patients with chronic pain were recruited to the study, 215 in the cannabis group and 216 in the control group. The cumulative person-years of follow up were 177 in the cannabis group and 204 in the control group (Table 4-1).

Sixty-seven patients receiving the study cannabis and 34 control patients discontinued the study before its intended completion, but all of these patients were included in the safety analysis. The most common reasons for early discontinuation of study drug in the cannabis group were lack of efficacy (18 patients), adverse events (10 patients), non-compliance with the protocol (6),[i] lack of efficacy and adverse effects (5 patients), dislike of the study product (4), and not specified (8). Sixteen patients discontinued the study due to non-medical reasons, for example, moving to other cities and family reasons. The most common reasons for early discontinuation among control patients were non-compliance with the study protocol (7),[ii] becoming pregnant (2), other personal reasons (8), and not specified (15). Two control patients died over the course of the trial, with 1 patient suicide and the other a death in the operating room during surgery.

As can be seen in Table 4-2, there were no significant differences in baseline measures between patients who completed the study and those who did not. However, in the cannabis group, "naïve users" [9 (56%)] or "ex cannabis users" [26 (45%)] were more likely to withdraw from the study cannabis exposure, compared with "current cannabis users" [32 (23%)]. ($X^2_{df=2}$ =14.46, P<0.001)

[i] Non-compliance with the protocol in the cannabis group included 2 patients who had discordance between UDT and self-reported drug use, 3 patients with drug or alcohol abuse, and 1 patient participating in another trial at the same time.
[ii] Non-compliance with the protocol in the control group included 6 patients who used external cannabinoid products and 1 patient who had discordance between urine drug test and self-reported drug use.

4.3.1 Baseline characteristics

Baseline characteristics for both groups are presented in Table 4-3. Subjects in the cannabis group were younger, with a larger percentage of male, more disabled, and more tobacco or alcohol users than the control group. Other socioeconomic status did not differ between the cannabis and control groups. Neurocognitive function was similar between the two groups at baseline. The average pain intensity was significantly higher in the cannabis group than the control group, and the Physical Component Summary score of the quality of life assessment was significantly lower in the cannabis group. On the other hand, more control patients were using opioids (66.2% in the control group vs. 54.9% in the cannabis group), antidepressants (59.3% vs. 47.0%), and anticonvulsants (54.6% vs. 43.7%) at baseline presentation. The cannabis group included 141 (65.6%) "current cannabis users", 58 (27.0%) "ex cannabis users", and 16 (7.4%) "naïve users". Controls included 70 (32.4%) "ex cannabis users" and 146 (67.6%) "naïve users".

4.3.2 Study intervention

Except for one patient without daily dosage data, the median daily dosage among 214 subjects was 2.5 grams, ranging 0.1-13.4 grams (interquartile range: 1.5-3.0 grams). On average, "current cannabis users" (median: 2.8 grams/day; range: 0.2-13.4 grams/day) consumed more cannabis than "ex cannabis users" (median: 1.8 grams/day; range: 0.1-3.7 grams/day) or "naïve users" (2.0 grams/day; range: 0.1-3.4 grams/day) over the course of the study ($P<0.001$, the Wilcoxon rank sum test).

Three subjects failed to report modes of administration data. Of 212 subjects exposed to cannabis, 188 (88.7%) used smoking as one of routes of administration, and 24 (11.3%) had never smoked in the study. "Current cannabis

users" (132/139, 95.0%) were more likely to smoke the study cannabis than "ex cannabis users" and "naïve users" (56/73, 76.7%).

4.3.3 Adverse events

4.3.3.1 Serious Adverse Events

Twenty-eight (13.0%) subjects in the cannabis group reported at least 1 SAE, compared with 42 (19.4%) in the control group. The risk of at least 1 SAE was not significantly different between the two groups (unadjusted OR=0.64; 95% CI=0.38-1.04).

A total of 40 SAEs were reported in the cannabis and 56 in the control group. The rates of SAEs were 22.61 and 27.45 events per 100 person-years of follow-up in the cannabis and control groups, respectively (unadjusted IRR=0.82; 95% CI=0.46-1.46).

SAEs were first summarized by SOC categories in Table 4-4. The most common categories were surgical and medical procedures and gastrointestinal disorders in the cannabis (n=10, 25% and n=10, 25% respectively) and control groups (n=11, 20%, and n=7, 13% respectively). SAEs were then summarized by preferred terms in Table 4-5. The most common events in the cannabis group were abdominal pain (3 events), intestinal obstruction (3) and nephrolithiasis (3). None of the SAEs were "certainly" related to the study cannabis. One convulsion was considered "probably/likely" related to the study cannabis.

Drug reactions led to treatment interruptions in 24 (60%) events, among which 22 were temporary suspensions with a median of 3 days (range 1-37 days). Treatment was permanently stopped for 2 patients due to serious adverse events

(1 convulsion and 1 alcohol problem). At the end of the trial, 31 (77.5%) serious adverse events in the cannabis group had been fully resolved.

4.3.3.2 Non-serious adverse events

Most patients [190/215 in the cannabis group (88.4%); 184/216 in the control group (85.2%)] experienced at least 1 non-serious adverse event, with a median of 3 events per patient (range 0-16; interquartile range 2-5) among cannabis users and a median of 2 events per patient (range 0-14, interquartile range 1-4) among controls. The risk of having at least 1 adverse event did not differ significantly between cannabis users and controls (unadjusted OR=1.32; 95% CI=0.75-2.32).

1) Non-serious AE in cannabis group

A total of 816 non-serious adverse events were reported in the cannabis group, resulting in an incidence rate of 4.61 events/person-year. This rate was significantly higher than that in the control group (unadjusted IRR=1.64; 95% CI=1.35-1.99).

The number of patients, the occurrence of events, and corresponding rates within each MedDRA SOC category are shown in Table 4-6. The most common AE categories in the cannabis group were nervous system disorders (n=163, 20.0%), gastrointestinal disorders (n=109, 13.4%) and respiratory disorders (n=103, 12.6%). Compared with controls, the rates of nervous system disorders (unadjusted IRR=2.02; 95% CI=1.45-2.82), respiratory disorders (unadjusted IRR=1.80; 95% CI=1.18-2.75), and psychiatric disorders (unadjusted IRR=2.74; 95% CI=1.45- 5.18) were significantly higher in the cannabis group (Figure 4-1).

Non-serious adverse events were also summarized by PT in Table 4-7. The most common AEs in the cannabis group were headache (n=40, 4.9%), nasopharyngitis

(n=37, 4.5%), nausea (n=36, 4.4%), somnolence (n=29, 3.6%) and dizziness (n=27, 3.3%).

Regarding severity, mild (n=420, 51.5%) or moderate (n=383, 46.9%) events were more common than severe ones (n=13, 1.6%) in the cannabis group. Severe adverse events were diverticulitis, fatigue (3), haematemesis, mania, motor dysfunction, movement disorder, multiple sclerosis, muscle spasms, nausea, convulsion, and vomiting. Among them, only mania was considered as "certainly" related to the study cannabis.

Table 4-8 summarizes the causality for non-serious AEs. Three hundred and six non-serious AEs, considered as "certainly", "probably/likely" or "possibly" related to the study cannabis, were reported by 126 patients. Among these, the non-serious AEs "certainly" related to the study cannabis were somnolence (5), amnesia (4), cough (4), nausea (4), dizziness (3), euphoric mood (3), hyperhidrosis (2), paranoia (2), anxiety (1), cognitive disorder (1), confusional state (1), decreased appetite (1), headache (1), increased appetite (1), lethargy (1), mania (1), oral discomfort (1), rash (1), sedation (1), vision blurred (1), and vomiting (1).

2) Non-serious AE in the control group

In total, 574 non-serious adverse events were reported in the control group, with an incidence rate of 2.81 events/person-year. Gastrointestinal disorders (n=99, 17.2%) and nervous system disorders (n=93, 16.2%) were the most frequently reported (Table 4-6). The majority of adverse events among controls were mild (n=330, 57.5%) or moderate (n=241, 42.0%), while 3 events (1 pulmonary embolism and 2 somnolence) were categorized as "severe".

4.3.3.3 Comparison of adjusted adverse event rates

Table 4-9 summarizes the associations between the use of medical cannabis and the rate of adverse events. Compared with control subjects, medical cannabis users were at increased risk of non-serious AEs (adjusted IRR=1.74; 95% CI=1.42-2.14). However, this increased risk was not identified with SAEs (adjusted IRR=1.08; 95% CI=0.57-2.04).

Table 4-10 shows the risks by the daily dose for adverse events associated with medical cannabis use. Increasing the daily dose of cannabis did not lead to higher risks of adverse events.

4.3.3.4 Subgroup analysis by past cannabis use

We observed that, in the cannabis group, "ex cannabis users" and "naïve users" reported more AEs than "current cannabis users", especially in the following MedDRA SOC categories: nervous system disorders, gastrointestinal disorders, psychiatric disorders, and general disorders and administration site conditions (Table 4-11). We combined "ex cannabis users" and "naïve users" as "ex cannabis and naïve users", and found that the rate of non-serious AEs in the cannabis group was approximately twice as much as that in the control group (adjusted IRR=2.07; 95% CI=1.59-2.70) (Table 4-9).

4.3.4 Neurocognitive tests

Detailed results of mean values at baseline and follow-up periods for the raw scores on each subtest by month of treatment among cannabis-exposed patients are reported in Table 4-12. To determine whether neurocognitive function changed over time, we examined changes from the individual patient's baseline performance after 6, and 12 months. A significant improvement was observed in

all four subtests after 6, and 12 months of the study cannabis use. Control subjects also performed better at the 6-, and 12-months follow-up examination. There were no significant differences in four measures between cannabis and control patients at baseline or at any given point during the follow-up period, after adjusting for age, gender, education, past cannabis use, alcohol history, disability status, concurrent average pain intensity, concurrent quality of life (measured by PCS and MCS), and study sites (Table 4-13).

4.3.5 Pulmonary function tests

Pulmonary function tests were conducted in the cannabis group only. Mean values are presented for "current tobacco smokers" and "never or former tobacco smokers" separately in Table 4-14.

No significant interaction between cannabis and tobacco smoking was noted for all pulmonary function measures. After adjusting for tobacco smoking and all other covariates, our analysis failed to reveal a significant effect of cannabis on lung volumes indices, including SVC, FRC, and TLC. However, residual volume was significantly reduced after having used the study cannabis for one year, with an average of 142 ml. (Table 4-15)

An average decline of 54 ml in FEV_1 (P=0.010) and a 0.78% decrease in the FEV_1/FVC ratio was observed after one-year of using the study cannabis (P=0.045). $FEF_{25-75\%}$ was lower after using the study cannabis, with an average decrease of 0.200 (P=0.011). (Table 4-15)

4.3.6 Pain intensity

Mean pain intensity scores are shown in Table 4-16. A total of 145 subjects in the cannabis group and 157 in the control group completed all pain intensity assessments over 1 year. Compared to baseline, a significant reduction in the average pain intensity was observed in the cannabis group, with 0.92 points decreasing in one year (95% CI=0.62, 1.23); while the average pain intensity in the control group remained at the same level throughout the study (0.18 points per year; 95% CI=-0.13, 0.49). The significant interaction between Cannabis and Time in the linear mixed model indicated greater reduction of pain with the use of cannabis than with control (1.10 points greater reduction in one year, 95% CI=0.72, 1.56).

4.3.7 Quality of life

Results of the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36v2® questionnaire are detailed in Table 4-17. With regard to the change of PCS score, a significant improvement was observed in both groups at 6, and 12 months of clinic visits. The analysis of the change in the PCS indicated greater improvement of physical function with the use of cannabis than with control (2.36 points greater improvement at 6-month, 95% CI=0.84, 3.88; and 1.62 points at 1-year, 95% CI= 0.10, 3.14). Neither within-group nor between-group differences for the Mental Component Summary (MCS) were observed.

4.4 Discussion

We identified 40 SAEs from 28 subjects and 816 non-serious AEs from 190 subjects using medical cannabis in the study. Nervous system and gastrointestinal disorders were the most common categories. Headache, nasopharyngitis, nausea,

somnolence, and dizziness were the five most common events in the cannabis group. Medical cannabis was associated with an increased risk of non-serious AEs (adjusted IRR=1.74; 95% CI=1.42-2.14), in particular in relation to the nervous system and psychiatric disorders, compared to controls. The adverse event profile is in accordance with results of the meta-analysis of cannabinoid RCTs in Chapter 3. As for SAEs, our study gave rise to an adjusted IRR of 1.08 with a wide CI (95% CI=0.57-2.04), which was not statistically significant. Therefore, the evidence regarding a potential risk of serious adverse events of patients on medical cannabis compared with that of controls is inconclusive.

The respiratory risk associated with smoked cannabis is often used as a reason not to consider herbal cannabis (smoked) for medicinal purposes. We identified 1 serious respiratory event (pulmonary embolism) and 103 mild or moderate non-serious respiratory events in the cannabis group. Medical cannabis use was associated with an increased risk of non-serious respiratory system disorders (unadjusted IRR=1.80; 95% CI=1.18-2.75). This is consistent with findings in the systematic review of recreational cannabis use conducted in Chapter 3, which suggested that long-term cannabis smoking was associated with an increased risk of developing respiratory complications such as coughing, sputum production, and wheezing.[7, 213-215, 253, 254]

The use of pulmonary function tests allows us to quantitatively measure the impact of smoked medical herbal cannabis on lung function over one year of use. Our study did not find any clinically significant reduction in lung volume indices. However, cannabis smokers experienced on average an FEV_1 decline of 54ml in one year, an excess of the normal annual value of 20 ml per year due to ageing. The association between long-term cannabis smoking and the FEV_1/FVC ratio, DLco, or airway hyperreactivity remains controversial.[254] Tashkin et al did not find any association,[255] while Taylor et al revealed evidence of mild airflow obstruction in association with cannabis use and, in particular, the combination of cannabis and tobacco use.[213,256] One recently published population-based study

suggests that the increased risk of chronic obstructive pulmonary disease (COPD), identified by the abnormal FEV_1/FVC, may be caused by the synergistic effect of smoking both tobacco and cannabis, not smoking only cannabis.[257] However, in the absence of pulmonary function data in control group, we were unable to assess the differences among cannabis alone, tobacco alone, and the combination of cannabis and tobacco smoking for the effect on pulmonary function over time.

There is little data on the non-acute effects of medical herbal cannabis use on neurocognitive function in chronic pain populations. Our study attempted to address the issue. The results did not reveal any substantial neurocognitive impact related to one-year of cannabis use (Tables 4-12 and 4-13). The systematic review presented in Chapter 3 and a previous published meta-analysis[50] have reviewed the non-acute effects of recreational cannabis use on the neurocognitive performance, suggesting the short-term use may not be associated with a significant cognitive impairment. However, there is an additional problem with the long-term cannabis use. As in the systematic review in Chapter 3, the significant impairment on measures of neurocognitive function was noted only among cannabis users with an average more than ten or twenty years of regular use.[212,258] A retrospective cross-sectional study found that long-term cannabis users (mean: 24 years, range: 17-32 years) performed significantly poorer on tests of memory and attention than shorter-term users (mean: 10 years, range 3-17 years). Both groups consumed similar amounts of cannabis (median: 7 grams per week, range: 0.28-57 grams per week). They did not find any difference on memory and attention between shorter-term users and non-cannabis users.[212] However, the impacts of such long-term medical cannabis on neurocognitive function cannot be addressed in our study.

Our results also found that the use of herbal cannabis reduced average pain intensity and improved the physical component score of the quality of life assessment. However, reports of benefit from cannabis in observational studies require careful interpretation. First, unmeasured confounders may distort the

results in observational studies, despite our efforts to control for potential confounders in our analyses. For example, unmeasured reasons for choice of various treatments could be related to better outcome. Second, the patients in the cannabis group were seen by the physicians more often than the control group throughout the study. This might result in subjective feelings of improvement among subjects in the cannabis group, as pain perception and quality of life assessments are highly subjective. Third, it is well acknowledged that improvement in pain status subsequent to entering treatment may be partially explained by the phenomenon of regression to the mean.[259, 260] This phenomenon might be more predominant in the cannabis group, as patients recruited to this group reported experiencing more severe pain and poorer quality of life than controls in the baseline interview. Bias introduced by this phenomenon should not be disregarded. Fourth, only subjects with complete scores of each test at both time points were included in each analysis. This would potentially affect the power of the multivariate models and, most importantly, might lead to biased results if the data were not missing at random in our study. For example, the rate of dropout due to "lack of efficacy" was much greater among subjects in the cannabis group (23 subjects in the cannabis group vs. 0 subjects in the control group). Ignoring informative dropouts might lead to overoptimistic statements about the effectiveness of medical cannabis. Therefore, the potential biases attributable to incomplete data require greater recognition. All these weaknesses have limited the interpretation of the effectiveness of cannabis in our study. Further randomized controlled trials are required to determine the long-term efficacy of cannabis in the management of chronic non-cancer pain.

We have identified five potential limitations of the study. First, the small sample size and short follow up time would have hampered our study from properly addressing SAEs. Our study involved 215 subjects (177 person-years) in the cannabis group and 216 controls (204 person-years). This sample size only enabled us to detect a rate ratio of 1.5 at powers above 50% for the incidence rate of SAEs in the control group above 0.20 cases/person-year. Furthermore, due to

the relatively short follow up time, the impacts of medical cannabis on pulmonary function and neurocognitive function cannot be completely addressed.

Second, we observed a significant dropout rate, which may be responsible for source of selection bias. In our study, losses to follow-up in the cannabis group were an estimated 30% over a median follow-up of 12 months, including 4% discontinued prior to 3-month visit, 5% between 3-month and 6-month visit, 13% between 6-month and 9-month visits, and 9% between 9-month and 12-month visit. Factors associated with dropout included AEs, perceived lack of efficacy, and/or a dislike of the study product. However, patients lost to follow-up were comparable with patients who finished the entire study (Table 4-2). This suggests that potential selection bias may be limited.

Third, it is worth noting that the large proportion of study participants in the cannabis group (66%) were experienced cannabis users. Due to the small number of cannabis-naïve patients in the study, the safety concerns in this group cannot be answered. However, our results indicated that the rate of non-serious AE among "current cannabis users" [4.01 (3.66-4.36) events/person-year] was lower than that among "ex cannabis users" [6.16 (5.40-6.92) events/person-year] or "naïve users" [5.65 (4.25-7.09) events/person-year]. We would have observed a higher RR of AE for cannabis if only new cannabis users had been included. However, the fact that the rate ratio in the subgroup analysis (adjusted IRR=2.07; 95% CI=1.59-2.70) was similar to that in the entire study population reinforces the validity of our results.

Fourth, observational bias could come from ascertainment of outcomes. Given the nature of observational studies and differential follow up schedules (9 visits after baseline in the cannabis group vs. 7 in the control group), subjects in the cannabis group may have reported mild or moderate AEs which have been otherwise neglected by controls. The effect of this limitation is likely to lead to more

exaggerated estimates when comparing the risk of AEs among medical cannabis users with that of the controls.

Finally, indication bias or confounding by indication due to selective prescribing was another source of bias. This bias arises when some characteristics such as disease severity, symptoms, predisposing and concomitant conditions, and concurrent therapies influence the decision to prescribe a drug class.[12,261] This bias existed in our study particularly as a result of the legal status of herbal cannabis. The MMAR allows patients with pain, nausea, loss of appetite associated with cancer, AIDS, and other serious illnesses who are unable to find relief from conventional therapies, to use cannabis.[37,38] The resulting lack of comparability of the treatment groups being studied threatens the validity of the results whenever information on important determinants of prescription choices is unmeasured or unavailable. In our study, average pain intensity scores and patients' disability status are considered as the two most important factors that influence the decision to use medical cannabis. Adjusting for these two variables in the final model of our study helped to control indication bias.

Even with these limitations in mind, however, this study improves our knowledge about adverse events associated with medical cannabis. Our study is the first observational cohort study ever conducted to address the safety of medical herbal cannabis use, with a median follow-up of one year. Our study used standardized herbal cannabis provided by Health Canada, with a THC potency of 12.5%. We chose an appropriate control group to compare the risk of AEs. In addition, information obtained from our control group provided an adverse event profile that has not been described elsewhere for chronic pain patients who follow routine treatments. Finally, our study provides an appropriate statistical strategy to comprehensively interpret AEs.

In conclusion, our results found that medical cannabis was associated with an increased risk of non-serious AEs among experienced users when used as part of

pain management regimen. These findings should be considered in the context of risk and benefit of medical cannabis. In the situation of conventional treatments considered not medically inappropriate or inadequate, cannabis can be used as part of pain management regimen for those patients who find it useful for their conditions. However, close monitoring of pulmonary function on a longitudinal basis would be necessary because the abnormal decline in the volume of airflow was observed after one year of cannabis use. Further vigilance is also warranted in the prescribing of medical cannabis to naïve cannabis individuals, as they appear to be more likely to develop adverse events compared with experienced users. However, due to the small number of cannabis-naïve patients in the study, the safety concerns in this group cannot be answered. Moreover, our study was inconclusive on the risk of serious adverse events. Therefore, more studies with larger sample size and systematic long-term follow-up are required to further characterize safety issues, including pulmonary and neurocognitive function, among medical cannabis users.

In the next chapter we consider some methodological challenges in designing prospective cohort safety studies that may be useful in conducting further research.

4.5 Tables and Figures

Table 4-1: Duration of follow up, according to study groups

Duration	**Cannabis (N=215)**	**Control (N=216)**
<30 days	3 (1.4%)	3 (1.4%)
30 days to <3 months	6 (2.8%)	0
3 months to <6 months	10 (4.6%)	3 (1.4%)
6 months to <9 months	28 (13.0%)	13 (6.0%)
9 months to <12 months	20 (9.3%)	15 (6.9%)
> 12 months	148 (68.8%)	182 (84.3%)
Range (days)	7-551	28-567
Total person-years (years)	176.9	204.1

Table 4-2: Baseline characteristics of the patients, according to discontinuation status[1]

Characteristics	Complete subjects (N=330)	Discontinued subjects (N=101)	P
Age at enrollment (years) [2]	49.5 (10.5)	47.2 (11.5)	0.09
Gender (% of male)	138 (41.8%)	48 (47.5%)	0.31
Education (% of University/College)[3]	171 (53.2%)	62 (63.2%)	0.08
N (%) of being married	211 (63.9%)	62 (61.4%)	0.64
N (%) of being disabled	178 (53.9%)	53 (52.5%)	0.80
Tobacco status			0.24
Current smokers	116 (35.2%)	42 (41.6%)	
Former/never smokers	214 (64.8%)	59 (58.4%)	
Alcohol status			0.07
Current drinking	234 (70.9%)	81 (80.2%)	
Former/never drinking	96 (29.1%)	20 (19.8%)	
Past cannabis use [4]			
Control group	N=182	N=34	0.05
Ex cannabis users	54 (29.7%)	16 (47.1%)	
Naïve users	128 (70.3%)	18 (52.9%)	
Cannabis group	N=148	N=67	<0.001
Current cannabis users	109 (73.6%)	32 (47.8%)	
Ex cannabis users	32 (21.6%)	26 (38.8%)	
Naïve users	7 (4.7%)	9 (13.4%)	
Average pain intensity [2]	6.4 (1.9)	6.3 (1.9)	0.72
Duration of pain (years) [5]	8 (0.5-82)	7 (1-51)	0.53
Type of pain			0.76
Nociceptive	55 (16.7%)	19 (18.8%)	
Neuropathic	120 (36.4%)	33 (32.7%)	
Both	154 (46.8%)	49 (48.5%)	

1. Data are presented as number (percentage) unless otherwise indicated.
2. Mean (SD)
3. Completed subjects=321; discontinued subjects=98
4. "Current cannabis users" were those who reported using cannabis and were still using at baseline interview; "Ex cannabis users" were those who reported having used

cannabis but were not using at baseline interview; “naïve users” were those who reported never using cannabis prior to baseline interview.

5. Median (range), the Wilcoxon Rank Sum Test

Table 4-3: Baseline characteristics of the patients, according to study groups[1]

Characteristics	Cannabis (N=215)	Control (N=216)	P
Age at enrollment [2]	45.5 (10.5)	52.4 (12.2)	<0.001
Gender (% of male)	110 (51.2%)	76 (35.2%)	<0.001
Education (% of University/College)	111 (51.6%)	122 (56.5%)	0.14
N (%) of being married	133 (61.9%)	140 (64.8%)	0.52
N (%) of being disabled	129 (60.0%)	102 (47.2%)	0.01
Tobacco status			0.01
Current smokers	91 (42.3%)	67 (31.0%)	
Former/never smokers	124 (57.7%)	149 (69.0%)	
Alcohol status			0.05
Currently drinking	166 (77.2%)	149 (69.0%)	
Former/never drinking	49 (22.8%)	67 (31.0%)	
Past cannabis use [3]			<0.001
Current cannabis users	141 (65.6%)	0	
Ex cannabis users	58 (27.0%)	70 (32.4%)	
Naïve users	16 (7.4%)	146 (67.6%)	
Type of pain			0.40
Nociceptive	35 (16.3%)	39 (18.1%)	
Neuropathic	83 (38.6%)	70 (32.4%)	
Both	97 (45.1%)	107 (49.5%)	
Average pain intensity [2]	6.6 (1.7)	6.1 (2.1)	0.002
Duration of pain (years) [4]	8.0 (0-54)	7.0 (0-82)	0.42
Medications			
Opioids	118 (54.9%)	143 (66.2%)	0.02
Antidepressants	101 (47.0%)	128 (59.3%)	0.01
Anticonvulsants	94 (43.7%)	118 (54.6%)	0.02

Characteristics	Cannabis (N=215)	Control (N=216)	P
Neurocognitive function [2,5]			
Verbal paired associates I	16.9 (8.2)	16.6 (7.9)	0.78
Verbal paired associates II (recall)	5.6 (2.4)	5.3 (2.4)	0.35
Verbal paired associated II (recognition)	23.7 (2.0)	23.7 (2.1)	0.91
Digit symbol-coding	52.5 (19.7)	48.5 (18.8)	0.11
Picture arrangement	11.5 (4.4)	11.3 (4.7)	0.71
Quality of life [2,6]			
Physical Component Summary	27.9 (7.4)	30.5 (8.4)	<0.001
Mental Component Summary	42.5 (12.0)	41.8 (12.6)	0.55

1. Data are presented as number (percentage) unless otherwise indicated.
2. Mean (SD), Student T-test
3. "Current cannabis users" were those who reported using cannabis and were still using at baseline interview; "Ex cannabis users" were those who reported using cannabis but were not using at baseline interview; "naïve users" were those who reported never using cannabis prior to baseline interview.
4. Median (range), the Wilcoxon Rank Sum Test
5. Verbal paired associates I: cannabis group=162, control group=92;
   Verbal paired associates II: cannabis group=160, control group=92;
   Digit symbol-coding: cannabis group=161, control group=92;
   Picture arrangement: cannabis group=160, control group=92.
6. Cannabis group=212, control group=204.

Table 4-4: Serious adverse events, categorized by system organ class

System Organ Class (MedDRA)[1]	Cannabis		Control	
	Number of events	Rate[2]	Number of events	Rate[2]
Surgical and medical procedures	10	5.65	11	5.39
Gastrointestinal disorders	10	5.65	7 [3]	3.43
Musculoskeletal and connective tissue disorders	5	2.82	6	2.94
Injury, poisoning and procedural complications	4	2.26	1	0.49
Renal and urinary disorders	3	1.69	1	0.49
Nervous system disorders	2	1.13	4	1.96
Respiratory, thoracic and mediastinal disorders	1	0.56	7	3.43
Infections and infestations	1	0.56	5	2.45
Vascular disorders	1	0.56	3	1.47
Metabolism and nutrition disorders	1	0.56	2	0.98
Psychiatric disorders	1	0.56	2 [4]	0.98
Investigations	1	0.56	0	0.00
General disorders and administration site conditions	0	0.00	3	1.47
Blood and lymphatic system disorders	0	0.00	1	0.49
Eye disorders	0	0.00	1	0.49
Hepatobiliary disorders	0	0.00	1	0.49
Immune system disorders	0	0.00	1	0.49
Total	**40**	**22.61** [5]	**56**	**27.45** [5]
Total number of patients	**28**	**13.02%** [6]	**42**	**19.44%** [6]

1. Ordered by rate of serious adverse events in the cannabis group
2. Incidence rate=events/ 100 person-years
3. One patient died in the operating room during surgery.
4. One patient committed suicide.
5. The rates of serious adverse events did not differ significantly between these two groups (Unadjusted incidence rate ratio=0.82; 95% CI=0.46-1.46).
6. The risk of having reported at least 1 SAE was not significantly different between two groups (Unadjusted odds ratio=0.64; 95% CI=0.38-1.04).

Table 4-5: Summary of serious adverse events

Serious adverse event[1]	Cannabis		Control	
	Number of events	Rate[2]	Number of events	Rate[2]
Surgical and medical procedures	*10*	*5.65*	*11*	*5.39*
Knee arthroplasty	2		1	
Surgery	1		3	
Hysterectomy	1		1	
Amputation	1		0	
Bilateral orchidectomy	1		0	
Cholecystectomy	1		0	
Elective procedure	1		0	
Joint arthroplasty	1		0	
Oophorectomy	1		0	
Colostomy	0		1	
Hip arthroplasty	0		1	
Mastectomy	0		1	
Medical device implantation	0		1	
Oesophagogastric fundoplasty	0		1	
Vaginal operation	0		1	
Gastrointestinal disorders	*10*	*5.65*	*7*	*3.43*
Abdominal pain	3		3 (1 died)	
Intestinal obstruction	3		0	
Rectal haemorrhage	1		1	
Gastrointestinal haemorrhage	1		0	
Nausea	1		0	
Vomiting	1		0	
Diarrhoea	0		2	
Pancreatitis	0		1	
Musculoskeletal and connective tissue disorders	*5*	*2.82*	*6*	*2.94*
Back pain	2		0	
Arthralgia	1		2	
Musculoskeletal pain	1		1	
Musculoskeletal chest pain	1		0	
Neck pain	0		2	
Fistula	0		1	

1. Ordered by the rate of serious adverse events in the cannabis group
2. Incidence rate=events/ 100 person-years

Serious adverse event[1]	Cannabis		Control	
	Number of events	Rate[2]	Number of events	Rate[2]
Injury, poisoning and procedural complications	*4*	*2.26*	*1*	*0.49*
Rib fracture	2		0	
Limb injury	1		0	
Patella fracture	1		0	
Pelvic fracture	0		1	
Renal and urinary disorders	*3*	*1.69*	*1*	*0.49*
Nephrolithiasis	3		0	
Urinary tract infection	0		1	
Nervous system disorders	*2*	*1.13*	*4*	*1.96*
Convulsion	1		0	
Multiple sclerosis	1		0	
Dizziness	0		2	
Headache	0		1	
Hypoaesthesia	0		1	
Respiratory, thoracic and mediastinal disorders	*1*	*0.56*	*7*	*3.43*
Pulmonary embolism	1		1	
Bronchospasm	0		3	
Pneumonia	0		3	
Infections and infestations	*1*	*0.56*	*5*	*2.45*
Post procedural infection	1		1	
Abscess	0		1	
Infection	0		1	
Joint abscess	0		1	
Sepsis	0		1	
Vascular disorders	*1*	*0.56*	*3*	*1.47*
Aneurysm arteriovenous	1		0	
Hypertension	0		1	
Hypovolaemic shock	0		1	
Syncope	0		1	

1. Ordered by the rate of serious adverse events in the cannabis group
2. Incidence rate=events/ 100 person-years

Serious adverse event[1]	Cannabis		Control	
	Number of events	Rate[2]	Number of events	Rate[2]
Metabolism and nutrition disorders	*1*	*0.56*	*2*	*0.98*
Dehydration	1		1	
Diabetic coma	0		1	
Psychiatric disorders	*1*	*0.56*	*2*	*0.98*
Alcohol problem	1		0	
Completed suicide	0		1 (died)	
Suicide attempt	0		1	
Investigations	*1*	*0.56*	*0*	*0.00*
Biopsy skin	1		0	
General disorders and administration site conditions	*0*	*0.00*	*3*	*1.47*
Pain	0		2	
Chest pain	0		1	
Blood and lymphatic system disorders	*0*	*0.00*	*1*	*0.49*
Lymphadenopathy	0		1	
Eye disorders	*0*	*0.00*	*1*	*0.49*
Vision blurred	0		1	
Hepatobiliary disorders	*0*	*0.00*	*1*	*0.49*
Liver abscess	0		1	
Immune system disorders	*0*	*0.00*	*1*	*0.49*
Hypersensitivity	0		1	
Total	40	22.61	56	27.45

1. Ordered by the rate of serious adverse events in the cannabis group
2. Incidence rate=events/ 100 person-years

Table 4-6: Non-serious adverse events, categorized by system organ class

System Organ Class (MedDRA)[1]	Cannabis			Control		
	Number of persons reporting symptoms	Number of events reported	Rate [2]	Number of persons reporting symptoms	Number of events reported	Rate[2]
Nervous system disorders	101	163	0.92	71	93	0.46
Gastrointestinal disorders	66	109	0.62	68	99	0.49
Respiratory, thoracic and mediastinal disorders	77	103	0.58	48	66	0.32
Infections and infestations	63	89	0.50	48	67	0.33
Musculoskeletal and connective tissue disorders	49	77	0.44	49	65	0.32
Psychiatric disorders	47	57	0.32	21	24	0.12
General disorders and administration site conditions	29	35	0.20	20	23	0.11
Injury, poisoning and procedural complications	23	31	0.18	21	23	0.11
Renal and urinary disorders	23	29	0.16	18	22	0.11
Skin and subcutaneous tissue disorders	18	22	0.12	17	18	0.09
Investigations	21	21	0.12	8	8	0.04
Eye disorders	16	20	0.11	13	14	0.07

1. Ordered by rate of non-serious adverse events in the cannabis group
2. Incidence rate=events/ person-year

System Organ Class (MedDRA)[1]	Cannabis			Control		
	Number of persons reporting symptoms	Number of events reported	Rate[2]	Number of persons reporting symptoms	Number of events reported	Rate[2]
Reproductive system and breast disorders	11	15	0.08	5	6	0.03
Metabolism and nutrition disorders	14	14	0.08	7	7	0.03
Vascular disorders	8	8	0.05	9	9	0.04
Surgical and medical procedures	5	6	0.03	10	12	0.06
Cardiac disorders	4	4	0.02	7	7	0.03
Blood and lymphatic system disorders	4	4	0.02	0	0	0.00
Ear and labyrinth disorders	3	3	0.02	5	5	0.02
Immune system disorders	1	2	0.01	3	3	0.01
Hepatobiliary disorders	2	2	0.01	1	1	0.00
Endocrine disorders	1	1	0.01	0	0	0.00
Neoplasms benign, malignant and unspecified	0	0	0.00	2	2	0.01
Total	190	816	4.61	184	574	2.81
Unadjusted odds ratio (95% CI)	1.32 (0.75-2.32)			1		
Unadjusted incidence rate ratio (95% CI)	1.64 (1.35-1.99)			1		

1. Ordered by rate of non-serious adverse events in the cannabis group
2. Incidence rate=events/ person-year

Figure 4-1: Unadjusted incidence rate ratios for each System Organ Class (MedDRA) of non-serious adverse events

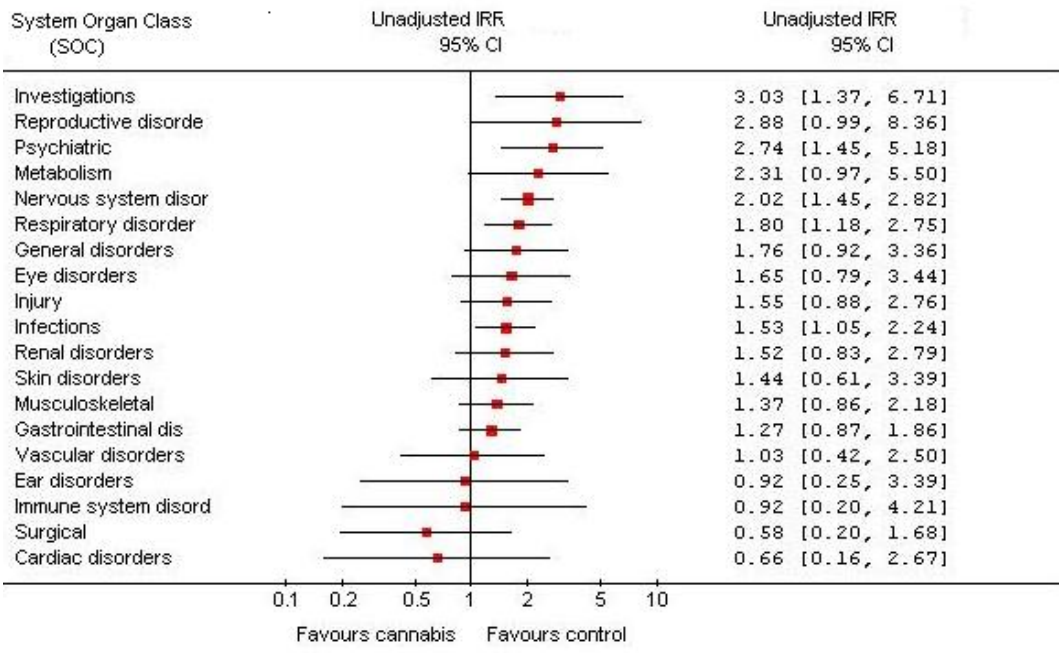

Table 4-7: Most frequently reported non-serious adverse events (more than 10 events in the cannabis group) [1]

Adverse Event (Preferred term)	Cannabis	Control
Headache	40 (4.9%)	24 (4.2%)
Nasopharyngitis	37 (4.5%)	22 (3.8%)
Nausea	36 (4.4%)	21 (3.7%)
Somnolence	29 (3.6%)	10 (1.7%)
Dizziness	27 (3.3%)	21 (3.7%)
Upper respiratory tract infection	21 (2.6%)	21 (3.7%)
Influenza	19 (2.3%)	24 (4.2%)
Pharyngolaryngeal pain	19 (2.3%)	8 (1.4%)
Vomiting	17 (2.1%)	14 (2.4%)
Cough	16 (2.0%)	3 (0.5%)
Rash	14 (1.7%)	9 (1.6%)
Diarrhoea	13 (1.6%)	10 (1.9%)
Urinary tract infection	13 (1.6%)	11 (1.9%)
Back pain	12 (1.5%)	9 (1.6%)
Muscle spasms	11 (1.3%)	4 (0.7%)
Depression	10 (1.2%)	10 (1.7%)
Anxiety	10 (1.2%)	2 (0.3%)

1. Data are presented as occurrences of events (percentage).

Table 4-8: In the cannabis group, summary of causality for non-serious adverse events [1]

System Organ Class (MedDRA)	Certain	Probable/ likely	Possible	Unlikely
Nervous system disorders	16 (40%)	51 (44%)	35 (23%)	60 (12%)
Gastrointestinal disorders	6 (15%)	13 (11%)	25 (17%)	61 (12%)
Respiratory, thoracic and mediastinal disorders	4 (10%)	16 (14%)	32 (21%)	51 (10%)
Infections and infestations	0	0	1 (1%)	86 (17%)
Musculoskeletal and connective tissue disorders	0	2 (2%)	3 (2%)	72 (14%)
Psychiatric disorders	8 (20%)	16 (14%)	18 (12%)	15 (3%)
General disorders and administration site conditions	2 (5%)	3 (3%)	6 (4%)	24 (5%)
Injury, poisoning and procedural complications	0	0	2 (1%)	29 (6%)
Renal and urinary disorders	0	0	2 (1%)	27 (5%)
Skin and subcutaneous tissue disorders	1 (3%)	0	2 (1%)	17 (3%)
Investigations	0	3 (3%)	7 (5%)	11 (2%)
Eye disorders	1 (3%)	4 (3%)	4 (3%)	11 (2%)
Reproductive system and breast disorders	0	1 (<1%)	4 (3%)	10 (2%)
Metabolism and nutrition disorders	2 (5%)	3 (3%)	4 (3%)	5 (1%)
Vascular disorders	0	1 (<1%)	1 (<1%)	6 (1%)
Surgical and medical procedures	0	0	0	6 (1%)
Cardiac disorders	0	1 (<1%)	3 (2%)	0
Blood and lymphatic system disorders	0	0	0	4 (<1%)
Ear and labyrinth disorders	0	2 (2%)	0	2 (<1%)
Immune system disorders	0	0	1 (<1%)	3 (<1%)
Hepatobiliary disorders	0	0	0	2 (<1%)
Endocrine disorders	0	0	0	1 (<1%)
Total [2]	40	116	150	503

1. Data are presented as occurrences of events (percentage).
2. Causality of 7 adverse events was “unclassifiable”.

Table 4-9: Unadjusted and adjusted rate ratios of adverse events for medical cannabis

	Cannabis	Control	Unadjusted IRR (95% CI)	Adjusted IRR[1] (95% CI)
All patients				
Number of patients	215	216	--	--
Cumulative person-years	176.9	204.1	--	--
Number of SAEs	40	56	0.82 (0.46-1.46)	1.08 (0.57-2.04)
Number of AEs	816	574	1.64 (1.35-1.99)	1.74 (1.42-2.14)
Patients excluding "current cannabis users"[2] at baseline				
Number of patients	74	216	--	--
Cumulative person-years	52.2	204.1	--	--
Number of SAEs	20	56	1.40 (0.66-2.93)	1.77 (0.72-4.32)
Number of AEs	316	574	2.15 (1.69-2.74)	2.07 (1.59-2.70)

IRR=Incidence rate ratio; 95% CI=95% confidence interval;
SAE=serious adverse event; AE=non-serious adverse event

1. Adjusted for age at enrollment, gender, baseline pain intensity, baseline concomitant pain medication (yes/no), disability status (yes/no), tobacco use (current vs. former or never smokers), alcohol use (current vs. former or never users), past cannabis use (ever/never), and study sites.
2. "Current cannabis users" were those who reported using cannabis and were still using at baseline interview.

Table 4-10: Unadjusted and adjusted rate ratios of (serious) adverse events for medical cannabis, by daily dose category

Average daily dose	Number of patients[1]	Cumulative person-years	Number of Events	Incidence rate [2]	Unadjusted IRR (95% CI)	Adjusted IRR [3] (95%CI)
Serious adverse event (SAE)						
0	216	204.1	56	0.27	1.00	1.00
<1 grams/day	29	20.6	1	0.05	0.18 (0.01-2.81)	0.34 (0.03-4.16)
1-1.99 grams/day	53	40.6	7	0.17	0.63 (0.21-1.89)	1.31 (0.41-4.15)
2-2.99 grams/day	73	61.1	18	0.29	1.07 (0.51-2.26)	1.51 (0.62-3.73)
>= 3 grams/day	59	54.7	14	0.26	0.93 (0.41-2.11)	1.34 (0.50-3.63)
Non-serious adverse event (AE)						
0	216	204.1	574	2.81	1.00	1.00
<1 grams/day	29	20.6	157	7.62	2.71 (1.99-3.70)	2.34 (1.69-3.25)
1-1.99 grams/day	53	40.6	182	4.48	1.59 (1.19-2.14)	1.72 (1.25-2.38)
2-2.99 grams/day	73	61.1	294	4.81	1.71 (1.34-2.19)	1.63 (1.21-2.19)
>= 3 grams/day	59	54.7	183	3.35	1.19 (0.89-1.59)	1.40 (0.67-1.95)

IRR=Incidence rate ratio; 95% CI=95% confidence interval

1. One patient in the cannabis group did no have information on daily dosage.
2. Incidence rate=events/person-year
3. Adjusted for age at enrollment, gender, baseline pain intensity, baseline concomitant pain medication (yes/no), disability status (yes/no), tobacco use (current vs. former or never smokers), alcohol use (current vs. former or never users), past cannabis use (ever vs. never), and study sites.

Table 4-11: Occurrences (incidence rate) of adverse events, by past cannabis use [1]

Adverse events	Group	Current cannabis users		Ex cannabis users		Naïve users	
		N [2]	Incidence rate (95% CI) [3]	N [2]	Incidence rate (95% CI) [3]	N [2]	Incidence rate (95% CI) [3]
All SAE	Cannabis	20	0.16 (0.09-0.23)	13	0.31 (0.14-0.48)	7	0.65 (0.17-1.13)
	Control	--	----	12	0.19 (0.08-0.30)	44	0.31 (0.22-0.41)
All Non-serious adverse events	Cannabis	500	4.01 (3.66-4.36)	255	6.16 (5.40-6.92)	61	5.65 (4.25-7.09)
	Control	--	----	184	2.89 (2.48-3.31)	390	2.78 (2.50-3.05)
	System Organ Class (MedDRA)						
Nervous system disorders	Cannabis	83	0.67 (0.52-0.81)	66	1.59 (1.21-1.98)	14	1.30 (0.62-1.98)
	Control	--	----	23	0.36 (0.21-0.51)	70	0.50 (0.38-0.62)
Gastro-intestinal disorders	Cannabis	62	0.50 (0.37-0.62)	33	0.80 (0.52-1.07)	14	1.30 (0.62-1.98)
	Control	--	----	25	0.39 (0.24-0.55)	74	0.53 (0.41-0.65)
Respiratory, thoracic and mediastinal disorders	Cannabis	67	0.54 (0.41-0.66)	31	0.75 (0.49-1.01)	5	0.46 (0.06-0.87)
	Control	--	----	24	0.38 (0.23-0.53)	42	0.30 (0.21-0.39)
Infections and infestations	Cannabis	55	0.44 (0.32-0.56)	28	0.68 (0.43-0.93)	6	0.56 (0.11-1.00)
	Control	--	----	26	0.41 (0.25-0.57)	41	0.29 (0.20-0.38)

Adverse events	Group	Current cannabis users		Ex cannabis users		Naïve users	
		N [2]	Incidence rate (95% CI) [3]	N [2]	Incidence rate (95% CI) [3]	N [2]	Incidence rate (95% CI) [3]
Musculo-skeletal and connective tissue disorders	Cannabis	57	0.46 (0.34-0.58)	15	0.36 (0.18-0.55)	5	0.46 (0.06-0.87)
	Control	--	----	22	0.35 (0.20-0.49)	43	0.31 (0.21-0.40)
Psychiatric disorders	Cannabis	32	0.26 (0.14-0.35)	21	0.51 (0.29-0.72)	4	0.37 (0.01-0.74)
	Control	--	----	8	0.13 (0.04-0.21)	16	0.11 (0.06-0.17)
General disorders and adminis-tration site conditions	Cannabis	16	0.13 (0.07-0.19)	15	0.36 (0.18-0.55)	4	0.37 (0.01-0.74)
	Control	--	----	9	0.14 (0.05-0.23)	14	0.10 (0.05-0.15)

1. "Current cannabis users" were those who reported using cannabis and were still using at baseline interview; "Ex cannabis users" were those who reported having used cannabis but were not using at baseline interview; "naïve users" were those who reported never using cannabis prior to baseline interview.
2. N=Number of events reported.
3. Incidence rate=events/person-year; 95%CI=95% confidence interval

Table 4-12: Mean values[1] of the neurocognitive measures in cannabis-exposed subjects before the use of study cannabis and in control patients before the study, by month of follow-up

	Group	Number of patients	Before cannabis (baseline)	6 months after cannabis	12 months after cannabis
WMS®-III [2]					
Verbal paired associates I					
Recall	Cannabis	77	16.92 (7.69)	20.97 (8.01)	22.97 (7.56)
(Max: 32 points)	Control	53	17.42 (7.85)	19.25 (8.70)	22.72 (8.53)
Verbal paired associates II					
Recall	Cannabis	76	5.67 (2.35)	6.29 (2.05)	6.54 (1.81)
(Max: 8 points)	Control	53	5.45 (2.55)	6.02 (2.45)	6.64 (1.95)
Recognition	Cannabis	76	23.80 (0.80)	23.92 (0.32)	23.78 (1.41)
(Max: 24 points)	Control	53	23.94 (0.23)	23.98 (0.14)	23.98 (0.14)
WAIS®-III [3]					
Digit symbol-coding	Cannabis	72	50.21 (21.60)	53.31 (23.64)	55.90 (23.11)
(Max: 133 points)	Control	53	49.94 (18.82)	54.64 (20.26)	55.00 (17.65)
Picture arrangement	Cannabis	76	11.64 (3.91)	13.67 (5.03)	14.18 (4.36)
(Max: 22 points)	Control	53	11.42 (4.65)	13.32 (5.14)	14.24 (5.53)

1. Data are presented as mean (SD).
2. WMS®-III: Wechsler Memory Scale – Third Edition
3. WAIS®-III: Wechsler Adult Intelligence Scale – Third Edition

Table 4-13: Fitted random effects model[1] using the neurocognitive function tests as the dependent variable

Neurocognitive function tests	Independent variables	ß[2]	SE[3]	P
Verbal paired associates I - Recall	Cannabis vs. controls	-1.458	1.515	0.337
	6 month vs. baseline	*1.791*	*0.853*	*0.037*
	12 months vs. baseline	*5.367*	*0.848*	*<0.001*
Verbal paired associates II- Recall	Cannabis vs. controls	0.043	0.423	0.919
	6 month vs. baseline	*0.600*	*0.241*	*0.013*
	12 months vs. baseline	*1.231*	*0.239*	*<0.001*
Digit-symbol coding	Cannabis vs. controls	-2.479	3.786	0.513
	6 month vs. baseline	*4.468*	*2.198*	*0.043*
	12 months vs. baseline	*4.597*	*2.187*	*0.037*
Picture arrangement	Cannabis vs. controls	-1.120	0.928	0.228
	6 month vs. baseline	*1.976*	*0.476*	*<0.001*
	12 months vs. baseline	*3.103*	*0.473*	*<0.001*

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, education (college/university vs. high school/elementary), disability status (yes/no), alcohol use (current vs. former or never users), past cannabis use (ever/never), average pain intensity and quality of life (evaluated by Physical Component Summary and Mental Component Summary) at each time point, and study sites
2. ß=fixed regression coefficient for cannabis use
3. SE=standard error

Table 4-14: Mean values and standard deviations (SD) of pulmonary function measures in cannabis-exposed subjects with smoking as one of routes of administration, by tobacco smoking status

Pulmonary function tests	Current tobacco users			Former or never tobacco users		
	Number of patients	Before cannabis (baseline)	1-year after Cannabis	Number of patients	Before cannabis (baseline)	1-year after Cannabis
SVC, L	63	4.24 (1.05)	4.21 (1.06)	72	4.24 (1.01)	4.23 (1.01)
FRC, L	54	3.33 (1.09)	3.55 (1.28)	64	3.08 (0.77)	3.00 (0.72)
RV, L	62	2.19 (0.77)	1.99 (0.89)	72	1.82 (0.65)	1.73 (0.61)
TLC, L	60	6.38 (1.63)	6.34 (1.63)	68	6.11 (1.15)	6.05 (1.11)
DL_{CO}	59	21.23 (5.21)	19.37 (6.53)	69	23.30 (7.82)	22.90 (7.61)
FEV_1,L	63	3.15 (0.76)	3.08 (0.75)	72	3.28 (0.79)	3.24 (0.84)
FVC, L	63	4.25 (1.03)	4.21 (1.04)	72	4.25 (0.99)	4.19 (1.03)
FEV_1/FVC (%)	63	74.51 (8.15)	73.40 (8.69)	71	77.51 (7.46)	77.01 (7.50)
$FEF_{25-75\%}$	63	2.70 (1.17)	2.37 (1.08)	72	2.93 (1.52)	2.84 (1.32)

Table 4-15**:** Fitted random effects model[1] using pulmonary function tests as the dependent variable

Pulmonary function tests	**ß[2]**	**SE[3]**	**P**
SVC, L	-0.021	0.031	0.507
FRC, L	0.054	0.066	0.414
RV, L	*-0.142*	*0.061*	*0.021*
TLC, L	-0.040	0.071	0.575
DL_{CO}	*-1.086*	*0.446*	*0.016*
FEV_1,L	*-0.054*	*0.021*	*0.010*
FVC, L	-0.053	0.028	0.061
FEV_1/FVC (%)	*-0.780*	*0.386*	*0.045*
$FEF_{25-75\%}$	*-0.200*	*0.078*	*0.011*

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, tobacco (current vs. former or never users), past cannabis use (current cannabis users vs. ex or naïve users), and study sites.
2. ß=fixed regression coefficient for cannabis use.
3. SE=standard error

Table 4-16: Comparison of the average pain intensity scores at five time points

Average pain intensity	**Cannabis (N=145)**	**Control (N=157)**
Clinic visits	**Mean (SD)**	**Mean (SD)**
Baseline	6.78 (1.65)	5.89 (1.98)
3 months	5.79 (2.13)	5.99 (2.14)
6 months	5.45 (2.20)	5.88 (2.17)
9 months	5.94 (2.10)	6.02 (2.21)
12 months	5.54 (2.11)	6.10 (2.13)

Comparison [1]	**ß (SE)**[2]	**P**
Cannabis vs. control	0.527 (0.286)	0.065
Time difference	0.015 (0.013)	0.246
Cannabis by time interaction	*-0.092 (0.018)*	*<0.001*

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, disability status (yes/no), baseline concomitant pain medication (yes/no), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), past cannabis use (ever/never) and study sites
2. ß=fixed regression coefficient for cannabis use; SE=standard error

Table 4-17: Comparison of the two SF-36v2® summaries at three clinic visits

	Physical Component Summary		Mental Component Summary	
	Cannabis (N=142)	**Control (N=146)**	**Cannabis (N=142)**	**Control (N=146)**
Clinic visits	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline	27.15 (7.00)	30.89 (8.50)	41.94 (11.72)	42.34 (13.30)
6 months	30.05 (8.03)	31.43 (8.70)	42.55 (11.77)	43.16 (13.60)
12 months	30.25 (8.96)	32.38 (8.76)	42.88 (12.14)	41.70 (13.32)
Comparisons [1]	**ß (SE)[2]**	**P**	**ß (SE) [2]**	**P**
Cannabis vs. control	-3.937 (1.187)	0.001	0.441 (1.853)	0.812
Time difference				
6 months vs. baseline	0.536 (0.546)	0.326	0.821 (0.916)	0.370
12 months vs. baseline	1.484 (0.546)	0.007	-0.640 (0.916)	0.485
Group by time interaction				
Group× (6 months)	2.360 (0.777)	0.003	-0.206 (1.304)	0.875
Group× (12 months)	1.619 (0.777)	0.038	1.584 (1.304)	0.225

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, disability status (yes/no), baseline concomitant pain medication (yes/no), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), past cannabis use (ever/never) and study sites
2. ß=fixed regression coefficient for cannabis use; SE=standard error

CHAPTER 5: CONSIDERATIONS OF STATISTICAL EFFICIENTY IN THE CHOICE OF MATCHED AND UNMATCHED COHORT STUDY DESIGNS

This chapter addresses methodological issues related to designing a prospective cohort study, such as one to study the safety of medical cannabis. Specifically, we compare the statistical efficiency of a matched cohort study to a multiple model with adjustment for confounders in an unmatched cohort study. Presented in Chapter 5 are the results obtained from an algebraic examination, computations, and a real example.

5.1 Introduction

As previously discussed, observational epidemiologic studies with an appropriate control group are an important consideration in evaluating the adverse events of medical cannabis. There is a particular advantage to choosing cohort studies when there is a need to estimate the incidence rate of adverse events or to investigate multiple adverse events in one study. On the other hand, observational studies are vulnerable to confounding and other biases.

Matching on a potential confounder is a common method used to control for confounding in observational studies. The statistical efficiency of matching in a case-control study has been extensively studied.[63-69] However, little attention has been paid to the impact of matching on efficiency in a cohort study. While the validity of the result can be assured by either the use of matching in the design stage or the use of adjustment in the analysis stage,[64,68] most discussions about

choosing an unmatched over a matched cohort design are primarily focused on the potential difficulty and increased cost of identifying matched subjects.[70-72]

The statistical efficiency (also referred as precision for a fixed sample size) of an estimator of a parameter is given by the inverse of the variance of the estimator. In a cohort study with a dichotomous outcome, the logarithm of the risk ratio [Ln(RR)] is typically the parameter of interest.[262] After many years of confusion and debate on matching, Kupper first claimed in his study that matching in cohort studies and matching in case-control studies should be separately considered, and he also noted that matching on a confounder was always expected to lead to a gain in efficiency in cohort studies, relative to an unmatched design with stratified analyses.[64] However, matching in case-control studies was not as advantageous as in cohort studies, and could lead to a loss of efficiency in some situations.

Greenland et al expanded on the Kupper et al study and found that a matched cohort design did not always increase efficiency.[263] Instead, they found that matching can increase efficiency when the crude risk ratio is confounded away from the null, while unmatched designs may be preferable under conditions when the crude risk ratio is confounded toward the null.[263]

Although Greenland presented criteria to help decide when using a matched cohort design is preferable to an unmatched design, they did not examine situations in which the exposure or confounder is negatively associated with the outcome of interest in their imputations. Therefore, we decided to conduct a study by extending the Greenland study to all combinations of directions of the exposure-confounder-outcome relations. Specifically, we compare the statistical efficiency of the estimated Ln(RR) in matched and unmatched cohort designs, given a fixed number of subjects. We first address this issue by conducting an algebraic examination on statistical efficiency in a simple situation. Then, we further investigate the extent to which matching may improve efficiency in a cohort study. Finally, we provide examples to compare the statistical efficiency of

matched with unmatched cohort studies, and consider how revised guidelines may help decide when matching is likely to improve efficiency.

5.2 An algebraic examination

Following Kupper and Greenland, we restrict our study to the situation with exposure E (1=exposed and 0=unexposed), matching factor K (1=stratum 1 and 0=stratum 0) and outcome D (1=diseased and 0=non-diseased) all dichotomous. Either frequency matching based on the matching factor K or random sampling is used to select unexposed subjects for a matched or unmatched cohort design, respectively, and comparison of efficiency between those two cohort designs is made.

5.2.1 Definitions of parameters in the hypothesized study

We generate the study population based on the following parameters, whose notations and definition are listed in Table 5-1. Let N_1 and N_0 be the total number of exposed and unexposed subjects in the hypothesized cohort study, N_{1k} and N_{0k} be the number of exposed and unexposed subjects in stratum k, R_{1k} and R_{0k} be the risks in exposed and unexposed in stratum k, and $E_{1k}=N_{1k}\times R_{1k}$ and $E_{0k}=R_{0k}\times N_{0k}$ be the expected numbers of exposed and unexposed cases in stratum k. The probability of being in stratum K=1 among exposed subjects is defined by $P_{k|E,}$ and $P_{k|\bar{E}}$ among unexposed subjects. The probability of being in stratum K=0 among exposed subjects is defined by $(1-P_{k|E})$, and $(1-P_{k|\bar{E}})$ among unexposed subjects.

We derive the exposure-confounder-outcome relations from the above-mentioned parameters. The true risk ratio between the exposure and outcome of interest (labeled as RR) is R_{10}/R_{00}, the ratio of risk among the exposed group to that

among the unexposed group in stratum 0 of the matching factor. The confounder-outcome association in the unexposed group (labeled as RR_{kd}) is given by R_{01}/R_{00}. The confounder-exposure association (the association between K=1 and E=1, labeled as RR_{ke}) is generated by $P_{k|E} / P_{k|\bar{E}}$.

5.2.2 Assumptions about the study population

We assume no effect modification, which gives identical risk ratio (RR) in all strata. We also restrict the strength of the exposure-outcome relation (RR), the exposure-confounder relation (RR_{ke}) and the confounder-outcome (RR_{kd}) relation to the range 0.2 to 5. More extreme RRs are not tested, because the improvement of efficiency under these circumstances is very unlikely to affect the results.

5.2.3 An algebraic examination results

Formally, the statistical efficiency in this problem is equal to $\underline{\Sigma(1/E_{1k}+1/E_{0k}-1/N_{1k}-1/N_{0k})^{-1}}$, the inverse of the variance of Ln(RR).[64,72,263] Following Greenland, we assume that N_{ik} is large and use the approximation $\underline{\Sigma\,(1/E_{1k}+1/E_{0k})^{-1}}$. When the matching factor K is dichotomous, the efficiency is equal to

$$1/(1/E_{11}+1/E_{01})+ 1/(1/E_{10}+1/E_{00}). \qquad (1)$$

Since the harmonic mean of $(a_1, a_2, \ldots a_N)$ is defined as the reciprocal of the arithmetic mean of the reciprocals of the positive real numbers, $N/(1/a_1+1/a_2+1/a_3+1/a_4+.....+1/a_N)$, with only two expected case numbers in stratum K=i, the harmonic mean is $2/(1/A_{1i}+1/A_{0i})$.

We can express (1) as one-half of the sums of two stratum-specific harmonic means of the expected case numbers in this hypothetical study population, expressing on (2).

$$2/(1/E_{11}+1/E_{01})+2/(1/E_{10}+1/E_{00}). \quad (2)$$

The harmonic mean is affected by two components: the relative magnitude and the absolute magnitude of the averaged case numbers (E_{11}, E_{01}, E_{10} and E_{00}).[263] In a 1:1 cohort study, matching results in a constant ratio of exposed to unexposed expected case numbers across strata (E_{11}/E_{01m} in stratum K=1, and E_{10}/E_{00m} in stratum K=0); each is equal to the RR (see Appendix 4). Therefore, we would expect that the harmonic mean is more sensitive to absolute magnitude of expected case numbers ($E_{11,}$ E_{01}, E_{10} and E_{00}). Since the expected number of exposed cases in each stratum, E_{11} and $E_{10,}$ are the same in two designs, we would expect the design with the larger expected number of unexposed cases, ($E_{01}+E_{00}$), to have larger statistical efficiency.

We therefore focus on comparing ($E_{01m}+E_{00m}$) in a matched 1:1 cohort study to ($E_{01u}+E_{00u}$) in an unmatched 1:1 cohort study, to find out under which conditions we would expect to obtain more unexposed cases, ($E_{01}+E_{00}$).

In a matched 1:1 cohort study, $N_1 = N_0 = N$, and $P_{k|\bar{E}}=P_{k|E}$, so we have:

K=1 (i.e. stratum 1)

	D_1	D_0	Total
E_1	$E_{11}=N_{11}\times R_{11}$		$N_{11}=N\times P_{k\|E}$
E_0	$E_{01m}=N_{01m}\times R_{01}$		$N_{01m}=N\times P_{k\|E}$

K=0 (i.e. stratum 0)

	D_1	D_0	Total
E_1	$E_{10}=N_{10}\times R_{10}$		$N_{10}=N\times(1- P_{k\|E})$
E_0	$E_{00m}=N_{00m}\times R_{00}$		$N_{00m}=N\times(1- P_{k\|E})$

Therefore, the number of expected unexposed cases in a 1:1 matched cohort design is:

$E_{01m}+E_{00m} = N_{01m}\times R_{01} + N_{00m}\times R_{00}$

$= N\times P_{k|E}\times R_{01} + N\times (1- P_{k|E}) \times R_{00}$

$= N\times P_{k|E}\times R_{00}\times RR_{kd} + N\times (1- P_{k|E})\times R_{00}$

With the same logic applied to an unmatched 1:1 cohort study:

K=1 (i.e. stratum 1)

	D_1	D_0	Total
E_1	$E_{11}=N_{11}\times R_{11}$		$N_{11}=N\times P_{k\|E}$
E_0	$E_{01u}=N_{01u}\times R_{01}$		$N_{01u} =N\times P_{k\|\bar{E}}$

K=0 (i.e. stratum 0)

	D_1	D_0	Total
E_1	$E_{10}=N_{10}\times R_{10}$		$N_{10}=N\times (1- P_{k\|E})$
E_0	$E_{00u} =N_{00u}\times R_{00}$		$N_{00u} =N\times (1- P_{k\|\bar{E}})$

Therefore, the total number of expected unexposed cases in a 1:1 unmatched cohort design is:

$E_{01u}+E_{00u} = N_{01u}\times R_{01} + N_{00u}\times R_{00}$

$= N\times P_{k|\bar{E}}\times R_{01} + N\times (1- P_{k|\bar{E}}) \times R_{00}$

$= N\times P_{k|\bar{E}} \times R_{00}\times RR_{kd} + N\times (1- P_{k|\bar{E}}) \times R_{00}$

Now, $(E_{01m}+E_{00m})/(E_{01u} +E_{00u})$

$= [N\times P_{k|E}\times R_{00}\times RR_{kd} + N\times(1- P_{k|E})\times R_{00}] \ / \ [N\times P_{k|\bar{E}}\times R_{00}\times RR_{kd} + N\times (1- P_{k|\bar{E}})\times R_{00}]$

$= [P_{k|E}\times RR_{kd} + (1- P_{k|E})] \ / \ [P_{k|\bar{E}}\times RR_{kd} + (1- P_{k|\bar{E}})]$

$= [P_{k|E} \times (RR_{kd} -1)+1] \ / \ [P_{k|\bar{E}} \times (RR_{kd} - 1) +1]$

We consider the expression in the following different scenarios:

Scenario 1) If $RR_{kd}>1$, and $1> P_{k|E} > P_{k|\bar{E}} >0$ (i.e.$RR_{ke}>1$), then

$$[P_{k|E} \times (RR_{kd} -1)+1] > [P_{k|\bar{E}} \times (RR_{kd} - 1) +1],$$

which means $(E_{01m}+E_{00m}) > (E_{01u}+E_{00u})$;

Scenario 2) If $RR_{kd} <1$, and $0< P_{k|E} < P_{k|\bar{E}} <1$ (i.e. $RR_{ke}<1$), then

$$[P_{k|E} \times (RR_{kd} -1)+1] > [P_{k|\bar{E}} \times (RR_{kd} - 1) +1],$$

which means $(E_{01m}+E_{00m}) > (E_{01u}+E_{00u})$;

Scenario 3) If $RR_{kd} >1$, and $0< P_{k|E} < P_{k|\bar{E}} <1$(i.e. $RR_{ke}<1$), then

$$[P_{k|E} \times (RR_{kd} -1)+1] < [P_{k|\bar{E}} \times (RR_{kd} - 1) +1],$$

which means $(E_{01m}+E_{00m}) < (E_{01u}+E_{00u})$;

Scenario 4) If $RR_{kd} <1$, and $1> P_{k|E} > P_{k|\bar{E}} >0$(i.e. $RR_{ke}>1$), then

$$[P_{k|E} \times (RR_{kd} -1)+1] < [P_{k|\bar{E}} \times (RR_{kd} - 1) +1],$$

which means $(E_{01m}+E_{00m}) < (E_{01u}+E_{00u})$;

When both the exposure and the outcome are positively associated with the matching factor (scenario 1) or are both negatively associated with the matching factor (scenario 2), we get larger expected number of unexposed cases in a matched cohort study compared to an unmatched cohort study. Therefore, we derive the following general guideline for the estimator of Ln(RR): regardless of the direction of the exposure-outcome association, a matched cohort design is expected to increase the efficiency when confounder-outcome association

(estimated as RR_{kd}) and confounder-exposure association (estimated as RR_{ke}) are both greater than 1 or both less than 1.

We divide our results into 12 scenarios by combining different directions of the exposure-confounder-outcome relations (summarized in Table 5-2). Table 5-2 shows that matching is preferable if criterion I holds. Note that "criterion I" contains 6 possible combinations (numbered as 1-6 in column 2 of Table 5-2) of exposure-confounder-outcome relations when the direction of the confounder-exposure relation and the confounder-outcome relation are the same. It is easy to find that these conditions in "criterion I" produce confounding away from the null in the crude unmatched estimator when true RR>1, and produce confounding toward the null in the crude unmatched estimator when true RR<1.

On the other hand, the unmatched cohort design is preferable if "criterion II" holds, consisting of another 6 combinations (numbered as 7-12 in Table 5-2) of exposure-confounder-outcome relations when the directions of the confounder-exposure relation and the confounder-outcome relation are opposite. Note that these conditions in "criterion II" produce confounding toward the null in the crude unmatched estimator when true RR>1, and produce confounding away from the null in the crude unmatched estimator when true RR<1.

These general rules do not address the extent to which matching improves the efficiency in a cohort study. To further investigate whether the gain from such matching is likely to be of practical importance, we compute the efficiency of Ln(RR) in matched and unmatched cohort designs for a complete range of scenarios regarding the association of a dichotomous exposure and a dichotomous matching factor in the population and the associations of each of these factors with the outcome of interest.

5.3 Computations

5.3.1 Scenarios

Using the notation and definitions specified in Table 5-1, we consider: RR=0.25, 0.5, 1, 2, 4; R_{01}=0.01, 0.03, 0.10; $R_{11}/R_{10}=R_{01}/R_{00}$=0.20, 0.40, 0.67, 1.5, 2.5, 5.0. $P_{k|E}$ and $P_{k|\bar{E}}$ are varied over all combinations of 0.1, 0.3, 0.5, 0.7, 0.9 that give ratios of these probabilities between 0.2 and 5. The information on parameters is summarized in Table 5-1. We consider all possible combinations of these varied parameter values and divide them to each pre-defined situation presented in Table 5-2 (situations 1-6 in criterion I and situations 7-12 in criterion II).

5.3.2 Statistical analysis

The efficiency of Ln(RR) is first calculated for each matched and unmatched cohort design. The specific percentage of scenarios in which the matched cohort design is superior to the unmatched design in terms of having larger efficiency is then calculated in each pre-defined situation.

The relative increase in efficiency is obtained as: $\frac{Eff_m - Eff_u}{Eff_u}$

when Eff_m = Efficiency in a matched cohort design and Eff_u=Efficiency in an unmatched cohort design. The median relative increase of efficiency and range are also provided in each situation.

5.3.3 Computational results

We first examine 1440 possible combinations, covering all 12 situations, when the number of unexposed subjects is the same in the matched as in the unmatched

cohort design. Each combination is referred to as a scenario. Table 5-3 gives the percentages of scenarios in which a matched cohort design improved efficiency compared with a stratified analysis of an unmatched cohort design in each pre-defined situation. We can verify that matching always increases efficiency when criterion I is satisfied, i.e. when the direction of the confounder-exposure relation and the confounder-outcome relation are the same. However, the median of relative increase in efficiency varies across scenarios, ranging from 15.54% (situations 2 and 5) to 31.31% (situations 1 and 4). Compared to the unmatched cohort design, the efficiency is increased by more than 10% after introducing matched cohort design in more than 90% of scenarios under situation 1 and 4. In both situations, the exposure is positively associated with the outcome, and the relation of exposure-confounder and relation of outcome-confounder are in the same direction. On the other hand, when criterion II holds, i.e. when the directions of the confounder-exposure relation and the confounder-outcome relation are opposite, compared with the unmatched cohort studies, matching reduces efficiency of Ln(RR) in more than half of scenarios.

We then continue to examine all above-mentioned 1440 possible combinations under situations when the unexposed group is two times as large in the unmatched cohort design as in the matched cohort design (see Table 5-4). We find that the median increase in efficiency by using matching became negative in all situations. The results indicate that unmatched cohort designs provide a meaningful gain in efficiency over matched cohort designs by increasing the number of unexposed subjects.

5.4 Example

We provide an example, derived from a published matched cohort study by Lynskey comparing the risk of cocaine use at a later age among early cannabis user with that among subjects who were not early cannabis users.[264] Gender is

considered as a potential confounder here. Studying pairs of same sex twins allows them to use matching to eliminate the potential confounding effects of gender.

Is matching on gender worthwhile in this study? Can this decision be made before the study is conducted? These questions can be answered from the statistical efficiency perspective, by using the direction of associations of exposure-confounder and outcome-confounder, defined by our guideline.

The prevalence of cannabis use has been reported to be twice as high in men as in women.[265] National household surveys on drug abuse also show that there are more men than women exposed to cocaine.[266,267] The confounder-outcome association (gender-cocaine use in this example) and confounder-exposure (gender-cannabis use) association are in the same direction. As a result, matching on gender is expected to increase efficiency, as suggested by our guideline.

To validate this prediction, we first derive values for each parameter used in our theoretical model from this published matched cohort study (see Table 5-5).[264] We then create a new hypothetical unmatched cohort study by introducing the new unexposed group, whose gender distribution is different from the exposed group. The statistical efficiency of the already-published matched cohort study is calculated and compared with the hypothesized unmatched cohort design with a stratified analysis.

5.4.1 The published matched cohort study

In this matched cohort study, a total of 311 same-sex twin pairs were included. In each twin pair, one had used cannabis by age 17 years, while the other one had not. Data on subsequent cocaine use for the 311 pairs are extracted to the following tables, stratified by gender.

K=Male

	D_1	D_0	Total
E_1	E_{11}=85		N_{11}=153
E_0	E_{01m}=47		N_{01m}=153

K=Female

	D_1	D_0	Total
E_1	E_{10}=65		N_{10}=158
E_0	E_{00m}=36		N_{00m}=158

In this matched cohort study, the risk of cocaine use is 0.55 (85/153) among exposed males, 0.31(47/153) among unexposed males, 0.41 (65/158) among exposed females, and 0.23(36/158) among unexposed females. The risk ratio, the parameter of interest here, is 1.817, which has been provided in other papers.[268-270] The statistical efficiency, inverse of the gender-adjusted maximum-likelihood estimator of the Ln(RR),[72,262] is 82.86.

5.4.2 The hypothesized unmatched cohort study

If the unexposed cohort was not matched by gender to that of the exposed cohort, we create an unmatched cohort in which unexposed subjects are sampled from a population, to examine the association of early cannabis use with use of other drugs at a later age. We assume among sampled unexposed subjects, the percentage of female (i.e. 200 female unexposed subjects) is roughly twice that of male (i.e. 111 male unexposed subjects).

Suppose that the risk of cocaine use among exposed males, among unexposed males, among exposed females, and among unexposed females, are the same as those in the matched cohort study, 0.55, 0.31, 0.41, and 0.23, respectively. Suppose also that, the risk ratio (1.817) obtained from the matched cohort study is the true risk ratio. Table 5-5 presents values for each parameter in this unmatched cohort study.

The expected numbers of exposed and unexposed cases in each stratum are generated as follows:

K=Male

	D_1	D_0	Total
E_1	E_{11}=85		N_{11}=153
E_0	E_{01u}=34		N_{01u}=111

K=Female

	D_1	D_0	Total
E_1	E_{10}=65		N_{10}=158
E_0	E_{00u}=45		N_{00u}=200

The statistical efficiency of the gender-adjusted maximum-likelihood estimator of the Ln(RR) under this unmatched design is 77.07.[72,262] Comparing the matched to unmatched cohort study, the efficiency has increased 7.5% by introducing matching in the design.

5.4.3 Summary

In this example, the matching factor (being Male) is positively associated with exposure (early cannabis use), and positively associated with the outcome of interest (subsequent cocaine use). Our guideline recommends that matching be expected to increase the statistical efficiency in this situation (Situation 1 in Table 5-2). Comparison of efficiency in this example reassures that the use of a matched cohort design by the investigators was a good choice.[264]

5.5 Discussion

Our study shows that, given a fixed total number of subjects in the two designs, (i.e. the number of exposed and unexposed subjects are the same in the matched

as in the unmatched design), the impact of matching on the efficiency of Ln(RR) in cohort studies depends on the directions of both the confounder-outcome relation and the confounder-exposure relation. When these two associations are in the same direction, matching always increases the efficiency of risk ratio estimation. When these two associations are in opposite directions, the impact of matching on efficiency is not consistent. Under these circumstances, given the potential increase in cost and practical difficulties caused by employing the matching strategy, using unmatched cohort studies and removing confounding by using statistical techniques is preferred.

Our findings are generally consistent with Greenland's results. However, when either exposure or confounder is negatively associated with the outcome of interest, scenarios that are not investigated in previous studies, our results refine the conjectures of Greenland et al.[263] For example, when both the exposure and the matching factor are negatively associated with the outcome and negatively associated with each other, Greenland predicted that the unmatched cohort design was preferable because the crude RR was biased toward the null in this condition. However, our results demonstrate that matching improves efficiency in all scenarios under this condition, and relative improvement by more than 10% was found in 67% of scenarios, with the median increase of 16% (range: 4%-145%). Therefore, simple classification according to the direction of the confounding effect is not comprehensive enough to cover all conditions, and its use could lead to incomplete conclusions about impact of matching on the efficiency. This suggests directions of the exposure-confounder and outcome-confounder associations, available from the literature, should be considered when choosing an efficient cohort design.

In this study, we only addressed the situation in which the exposed/unexposed ratio was 1:1 in a matched cohort design. The efficiency of Ln(RR) in both designs would increase as a result of increasing the number of unexposed subjects. However, identifying two or more unexposed subjects to match one

index subject may become more complicated and costly; therefore, affecting the choice in favor of the matched cohort design.

Furthermore, we restricted our algebraic investigation to situations in which the number of unexposed subjects was same in a matched cohort design as in an unmatched cohort design. However, we computed the relative increase in efficiency for situations when the number of unexposed subjects was twice as large in an unmatched cohort design as in a matched cohort design. The results suggest that unmatched design would offer a meaningful gain in efficiency over frequency matching when the unexposed group was two times as large under unmatched as under matched cohort designs (Table 5-4). This finding has also been reported in two previous studies.[64,271]

Finally, we looked only at matching on a dichotomous variable. Many of our conclusions agree with previous numerical and theoretical results presented by Greenland,[263] Kupper,[64] Samuels[68] and Anderson,[272] which all came from a simple model including a dichotomous exposure, a dichotomous outcome and a dichotomous confounder. It has been suggested that the qualitative results evaluated from dichotomous confounders provide a rough guide to more complex situations, and appear to be similar to results from the situation when the confounder, which is also the matching variable, has more than two categories or is continuous.[65,66,263]

Our comparison has revealed that when the exposure is expected to have moderate effects on the outcome of interest, matching on a factor that has the same effect on exposure as on outcome in terms of direction of associations can lead to an obvious gain in efficiency. In particular, when the relation of exposure-confounder and relation of outcome-confounder is in the same direction, and the true RR is expected to be greater than 1, a matched cohort design increases the efficiency of Ln(RR) by more than 30% compared to an unmatched cohort design

in more than one-half of scenarios. Therefore, we suggest that choosing matching in the design phase should be given serious consideration under this circumstance.

Our study refines suggestions regarding the choice of a matched cohort design, and reinforces the fact that the impact of matching on efficiency in a cohort study should not be neglected when making a decision concerning the study design. However, the decision to employ a matched cohort design would be affected by the difficulty and relative cost of finding matching subjects.

In the next chapter we review the results of this thesis and consider the clinical and methodological implications.

5.6 Tables

Table 5-1: Notation and definition of parameters

K=1 (i.e. stratum 1)

	D_1	D_0	Total
E_1	E_{11}		N_{11}
E_0	E_{01}		N_{01}

K=0 (i.e. stratum 0)

	D_1	D_0	Total
E_1	E_{10}		N_{10}
E_0	E_{00}		N_{00}

Parameters	**Definition**	**Parameter values/formula**
$P_{k\|E}$	The probability of K=1 among exposed subjects	0.1,0.3,0.5,0.7, 0.9
$P_{k\|\bar{E}}$	The probability of K=1 among unexposed subjects	0.1,0.3,0.5,0.7, 0.9
$1\text{-}P_{k\|E}$	The probability of K=0 among exposed subjects	
$1\text{-}P_{k\|\bar{E}}$	The probability of K=0 among unexposed subjects	
N_{11}	The number of exposed subjects in stratum K=1	$N_{11}=N_1 \times P_{k\|E}$
N_{01}	The number of unexposed subjects in stratum K=1	$N_{01}=N_0 \times P_{k\|\bar{E}}$
N_{10}	The number of exposed subjects in stratum K=0	$N_{10}=N_1 \times (1\text{-}P_{k\|E})$
N_{00}	The number of unexposed subjects in stratum K=0	$N_{00}=N_0 \times (1\text{-}P_{k\|\bar{E}})$
N_1	The total number of exposed subjects	$N_1 =N_{11} + N_{10}$
N_0	The total number of unexposed subjects	$N_0 =N_{01} + N_{00}$
R_{1k}	The risk in exposed in stratum K	
R_{0k}	The risk in unexposed in stratum K	0.01,0.03,0.10
E_{1k}	The expected number of exposed cases in stratum K	$E_{1k} =N_{1k}\times R_{1k}$
E_{0k}	The expected number of unexposed cases in stratum K	$E_{0k} =N_{0k}\times R_{0k}$
RR	True risk ratio between exposure and outcome	$R_{11}/R_{01}= R_{10}/R_{00}$ 0.25, 0.5,1,2,4
RR_{kd}	The confounder-outcome association in the unexposed group	$RR_{kd}= R_{01} / R_{00}$ 0.20,0.40,0.67,1.5, 2.5,5.0
RR_{ke}	The confounder-exposure association	$RR_{ke}= P_{k\|E} / P_{k\|\bar{E}}$

Table 5-2: Summary of 12 conditions with efficiency comparisons

Criterion	Situation	Association between exposure and outcome (RR)	Association between confounder and outcome (RR_{kd})	Association between exposure and confounder (RR_{ke})
I	1	RR>1	RR_{kd} >1	RR_{ke} >1
	2	RR<1	RR_{kd} >1	RR_{ke} >1
	3	RR=1	RR_{kd} >1	RR_{ke} >1
	4	RR>1	RR_{kd} <1	RR_{ke} <1
	5	RR<1	RR_{kd} <1	RR_{ke} <1
	6	RR=1	RR_{kd} <1	RR_{ke} <1
II	7	RR>1	RR_{kd} <1	RR_{ke} >1
	8	RR<1	RR_{kd} <1	RR_{ke} >1
	9	RR=1	RR_{kd} <1	RR_{ke} >1
	10	RR>1	RR_{kd} >1	RR_{ke} <1
	11	RR<1	RR_{kd} >1	RR_{ke} <1
	12	RR=1	RR_{kd} >1	RR_{ke} <1

Table 5-3: Summary of 1440 scenarios with efficiency comparisons of a 1:1 matched cohort design and a 1:1 unmatched cohort design [1]

Criterion	Situation	# of scenarios	# (Percentage) of scenarios in which matching improved efficiency by more than 10%	Relative increase in efficiency (%)[2]	
				Median	Range
I	1	144	132 (91.7%)	31.31	9.04, 124.51
	2	144	96 (66.7%)	15.54	3.98, 80.90
	3	72	63 (87.5%)	28.39	8.00, 103.23
	4	144	132 (91.7%)	31.31	9.04, 320.64
	5	144	96 (66.7%)	15.54	3.98, 144.79
	6	72	63 (87.5%)	28.39	8.00, 243.13
II	7	144	12 (8.3%)	-8.15	-29.07, 42.72
	8	144	33 (22.9%)	1.14	-6.32, 40.00
	9	72	12 (16.7%)	-1.21	-12.70, 47.37
	10	144	6 (4.2%)	-8.43	-34.03, 21.05
	11	144	27(18.8%)	1.14	-6.32, 41.64
	12	72	12 (16.7)	-1.35	-12.70, 35.29

1. a. The number of the exposed group in the matched cohort design is same as that in the unmatched cohort design; b. The number of the unexposed group in the matched cohort design is same as that in the unmatched cohort design; c. Ratio of exposed to unexposed subjects is 1:1 in both designs.
2. The relative increase in efficiency is then obtained as: $\frac{Eff_m - Eff_u}{Eff_u}$

   when Eff_m = Efficiency in a matched cohort design and Eff_u=Efficiency in an unmatched cohort design.

Table 5-4: Summary of 1440 scenarios with efficiency comparisons of a 1:1 matched cohort design and a 1:2 unmatched cohort design [1]

Criterion	Situation	# of scenarios	# (Percentage) of scenarios in which matching improved efficiency by more than 10%	Relative increase in efficiency (%)[2]	
				Median	Range
I	1	144	24 (16.7%)	-17.44	-34.57, 35.48
	2	144	21 (14.6%)	-3.89	-13.35, 29.02
	3	72	15 (20.8%)	-8.69	-20.44, 35.67
	4	144	18 (12.5%)	-16.85	-34.57, 137.12
	5	144	30 (20.8%)	-3.89	-13.35, 63.48
	6	72	15 (20.8%)	-8.64	-20.44, 105.53
II	7	144	0 (0%)	-38.28	-52.75, -1.75
	8	144	0 (0%)	-10.32	-19.54, 6.20
	9	72	0 (0%)	-24.20	-29.74, 5.00
	10	144	0 (0%)	-38.92	-53.52, -9.80
	11	144	6(4.2%)	-10.40	-19.54, 14.44
	12	72	0 (0%)	-24.20	-29.74, 6.23

1. a. The number of the exposed group in the matched cohort design is same as that in the unmatched cohort design; b. The number of the unexposed group in the matched cohort design is half of that in the unmatched cohort design; c. Ratio of exposed to unexposed subjects is 1:1 in the matched cohort design, but 1:2 in the unmatched cohort design.
2. The relative increase in efficiency is then obtained as: $\frac{Eff_m - Eff_u}{Eff_u}$

   when Eff_m = Efficiency in a matched cohort design and Eff_u=Efficiency in an unmatched cohort design.

Table 5-5: Parameters and their values in examples of matched or unmatched cohort studies

Parameters	Definition	Matched cohort study	Unmatched cohort study
$P_{k\|E}$	The probability of MALE among exposed subjects	153/311=0.49	
$1-P_{k\|E}$	The probability of FEMALE among exposed subjects	158/311=0.51	
$P_{k\|\bar{E}}$	The probability of MALE among unexposed subjects	153/311=0.49	111/311=0.36
$1-P_{k\|\bar{E}}$	The probability of FEMALE among unexposed subjects	158/311=0.51	200/311=0.64
RR_{ke}	***The confounder-exposure association***	***1***	***1.38***
N_{11}	The number of exposed subjects in stratum k=MALE	153	
N_{01}	The number of unexposed subjects in stratum k=MALE	153	111
N_{10}	The number of exposed subjects in stratum k=FEMALE	158	
N_{00}	The number of unexposed subjects in stratum k=FEMALE	158	200
N_1	The total number of exposed subjects	311	
N_0	The total number of unexposed subjects	311	
RR	True risk ratio between exposure and outcome	1.82	
R_{11}	The risk in exposed in stratum k=MALE	0.55	
R_{01}	The risk in unexposed in stratum k=MALE	0.31	

Parameters	Definition	Matched cohort study	Unmatched cohort study
R_{10}	The risk in exposed in stratum k=FEMALE	0.41	
R_{00}	The risk in unexposed in stratum k=FEMALE	0.23	
RR_{kd}	***The confounder-outcome association in the unexposed group***	***1.35***	
E_{11}	The expected number of exposed cases in k=MALE	85	
E_{01}	The expected number of unexposed cases in k=MALE	47	34
E_{10}	The expected number of exposed cases in k=FEMALE	65	
E_{00}	The expected number of unexposed cases in k=FEMALE	36	45

CHAPTER 6: SUMMARY AND CONCLUSIONS

6.1 Assessing the safety of medical cannabis

A safe therapeutic agent is not risk-free, but "has reasonable risks given the magnitude of the benefits expected and the alternatives available."[273] The risks and benefits of medical cannabis use need to be evaluated in patients who suffer from chronic illnesses such as chronic pain, multiple sclerosis, and HIV/AIDS because these populations are already using cannabis to treat the symptoms of these illnesses, and the numbers continue to grow.

During the past decade, a number of randomized controlled trials (RCTs) investigating the efficacy of pharmaceutical cannabinoid products in the management of chronic pain have been reported.[51,52,54,56,58-60,90,94-98] More recently, randomized controlled trials have also been conducted to assess the analgesic efficacy of herbal cannabis for neuropathic pain.[33-36] In contrast, most safety information comes from either observational studies that focus on recreational cannabis use or from adverse events reported in short-term RCTs.[42-45,47-50,274] Even though Netherlands and Canada have legalized medical cannabis-production programs,[5,37,38] the safety of medical cannabis has not yet been evaluated in a prospective epidemiological study. In light of the paucity of knowledge about safety of medical cannabis use, this thesis research was conducted.

Three key questions were addressed in order to comprehensively understand the safety of medical cannabis use. First, the safety profile of pharmaceutical cannabinoid products was examined in a meta-analysis of 23 RCTs. Second, this

thesis also explored the safety concerns of use of cannabis outside the RCT trials, such as the impact of cannabis exposure on driving, or adverse events associated with the prenatal cannabis use in a separate systematic review. Third, Health Canada has provided Canadian patients access to herbal cannabis under the Marihuana Medical Access Regulations (MMAR) since 2001, the safety of the Health Canada herbal cannabis products was assessed in a prospective cohort study.

6.1.1 Main findings

6.1.1.1 Safety of pharmaceutical cannabinoid products

This thesis first assessed existing safety information of pharmaceutical cannabinoid products in the meta-analysis. In the cannabinoid group of 1932 subjects from 23 RCTs, we identified a total of 4779 adverse events, of which most were non-serious (n=4615, 96.6%). Nervous system disorders (n=1695, 36.7%) were the most frequently reported non-serious adverse event (AE) category among cannabinoid-exposed subjects, specifically, dizziness (n=714, 15.5%) was the most commonly reported non-serious AE. As compared with placebo, pharmaceutical cannabinoid products increased the risk of non-serious adverse events (AEs) (RR=1.86; 95% CI = 1.57-2.21), in particular, non-serious nervous system disorders (RR=1.87; 95% CI=1.53-2.30) and psychiatric disorders (RR=2.73; 95% CI=1.69-4.41). However, the results of this study were inconclusive regarding the risk of serious adverse events (SAEs) associated with the cannabinoid products (RR =1.04; 95% CI = 0.78-1.39).

6.1.1.2 Safety of recreational cannabis use

In the meta-analysis described above, no RCTs of herbal cannabis were included because of a lack of quantifiable adverse event data. The impacts of cannabis on

driving or cancer were not available either. Therefore, a systematic review of 290 observational studies focusing on the safety of recreational cannabis use was conducted, in an effort to provide the complementary safety information on herbal cannabis. This review reports the consistently significant associations between recreational cannabis use and psychotic episodes and car accidents. Long-term developmental problems were also reported in the offspring of women who used cannabis during pregnancy. On the other hand, the associations between cannabis use and the risk of cancer or cognitive function decline were presented but less consistent.

6.1.1.3 Safety of Health Canada herbal cannabis

The systematic review improves our knowledge about the risks associated with recreational cannabis use. However, caution must be exercised when assuming that adverse effects of recreational cannabis use may be translated to medical cannabis use; the quality and amounts used and existence of co-morbidities are different in the two populations and should be evaluated separately. *The Cannabis for the Management of Pain, Assessment of Safety Study* (COMPASS) was therefore conducted to determine whether a significant association exists between use of Health Canada cannabis and the risk of adverse events in chronic pain patients.

After a median follow-up of one year, there were 40 SAEs and 816 non-serious AEs among 215 subjects who used the study cannabis. Nervous system disorders and gastrointestinal disorders were the most common non-serious AE categories. Headache, nasopharyngitis, nausea, somnolence, and dizziness were the five most common non-serious adverse events. Medical cannabis was associated with an increased risk of non-serious AEs compared to controls (adjusted IRR=1.74; 95% CI=1.42-2.14). In particular, medical cannabis users were at increased risk of non-serious AEs in the following MedDRA SOC category: nervous system disorders

(unadjusted IRR=2.02; 95% CI=1.45-2.82), psychiatric disorders (unadjusted IRR=2.74; 95% CI=1.45-5.18) and respiratory disorders (unadjusted IRR=1.80; 95% CI=1.18-2.75), compared with controls. On the other hand, the evidence concerning the risk of SAEs associated with the use of medical cannabis is inconclusive (adjusted IRR=1.08; 95% CI=0.57-2.04).

With respect to pulmonary function, clinically significant declines were observed in FEV_1 and FEV_1/FVC ratio after one year of exposure to cannabis, compared to baseline. Significant improvements in neurocognitive tests were seen in both the cannabis group and the control group, however, the extent of improvement did not differ significantly between the groups.

6.1.2 Contributions and implications

This thesis provides safety profiles of both pharmaceutical cannabinoid products and Health Canada herbal cannabis product to assist in clinical, regulatory and political decision-making. It significantly improves our knowledge about adverse events associated with medical cannabis. Findings of this thesis suggest the adverse effects of medical cannabis among experienced users are modest. The consistency of results from our meta-analysis and the COMPASS study allows us to more firmly conclude that medical cannabis was associated with an increased risk of non-serious AEs, in particular in relation to the nervous system and psychiatric disorders.

These findings have important implications in considering the use of herbal cannabis for chronic pain patients. Firstly, for experienced cannabis-using patients, from a safety perspective, our results only found an increased risk of non-serious adverse events associated with the use of Health Canada cannabis products. These findings should be considered in the context of risk and benefit of medical cannabis. In the situation of conventional treatments considered not

medically inappropriate or inadequate, cannabis can be used as part of pain management regimen for those patients who find it useful for their conditions. Secondly, naïve users seemed to be more likely to suffer adverse events than experienced users, especially in the following categories: nervous system disorders, gastrointestinal disorders, psychiatric disorders, and general disorders and administration site conditions, further vigilance is warranted in the prescribing of medical cannabis to naïve cannabis individuals. Thirdly, our study indicates that a modest decline in lung flow rates occur with cannabis. This finding warrants clinical attention in monitoring of pulmonary function on a longitudinal basis while prescribing of medical cannabis. Finally, our systematic review attests to a significant association between car accidents and the use of cannabis. This reinforces the need to caution patients about not driving while under the effects of cannabis.

6.2 Addressing the methodological challenge in a cohort study

In addition to assessing the safety of medical cannabis, this thesis also addressed the methodological challenge of finding the most efficient strategy to control for potential confounders in a cohort study between two common strategies: matching versus a multivariate model with adjustment for confounders. The statistical efficiency of matching in a case-control study has been extensively studied.[63-69] However, the use of a matching strategy in a cohort study has received less attention.

Kupper first claimed that matching in follow-up studies and matching in case-control studies should be separately considered, and noted that matching on a confounder was always expected to lead to a gain in efficiency in cohort studies, relative to an unmatched design with stratified analyses.[64] Greenland et al then found that a matched cohort design did not always increase efficiency. [263] It was a decade ago when Greenland presented criteria to help decide when using a

matched cohort design is preferable to an unmatched design.[263] This topic has gone unnoticed ever since. A matched cohort design continues to be implemented.[275-277] We decided to re-visit the issue regarding the matching and statistical efficiency in a cohort study. Meanwhile, we sought to propose a refined guideline since Greenland et al did not examine situations in which the exposure or confounder is negatively associated with the outcome of interest when proposing the guideline. Therefore, the respective statistical efficiency of matching and a multiple model with an adjustment for confounders were compared in a separate project involving all combinations of directions of the exposure-confounder-outcome relations.

Following Kupper and Greenland, a simple situation with exposure, matching factor and outcome all dichotomous was implemented. The impact of matching on the efficiency of risk ratios in cohort studies depends on the positive or negative directions of the confounder-outcome relation and the confounder-exposure relation. When these two associations are in the same direction, matching always increases the efficiency of risk ratio estimation. When these two associations are in the opposite direction, the impact of matching on efficiency is not consistently beneficial. However, the difficulty of recruiting controls plays a significant role in making the final decision as to whether to use a matched cohort design in many studies, like the conduct of COMPASS study.

In summary, the results reinforce the fact that, when matching is feasible, the impact of matching on efficiency in a cohort study should not be neglected. The refined guidelines should help researchers decide when matched cohort study is preferred over unmatched cohort study from the perspective of statistical efficiency.

6.3 Recommendations for future research

Adverse events of cannabis use, in particular, serious adverse events, should continue to be systematically collected. Future research should consider the following topics.

First, side effects are of particular concern in naïve cannabis users. However, due to the small number of cannabis-naïve patients (n=16, 7%) in COMPASS study and a significant dropout rate among them (n=9, 56%), the safety concerns in this group cannot be answered. Further studies with systematic long-term follow-up are required to characterize safety issues. Given that it may not be feasible to recruit a large group of naïve cannabis users in a clinical trial, creating a national research registry of patients who are prescribed cannabis would provide the capability for systematically following up the safety in this group. Moreover, current research is inconclusive regarding the relation between the cannabis use and the risk of serious adverse events. These inconclusive results also call for additional studies with larger sample sizes and longer-term follow-up to further assess the risk of serious adverse events.

A second topic for future research is to investigate the long-term effects of medicinal cannabis on pulmonary function. As cannabis smoke is very similar to tobacco smoke from many perspectives, much knowledge of the effects of smoked cannabis on lung function is predicted by the hazards of tobacco. Relatively little research has been done, and the results remain controversial.[42] Our study noted that a clinically significant decline in both FEV_1 and FEV_1/FVC ratio occur after one year of exposure to cannabis. This finding necessitates careful monitoring of pulmonary function on a longitudinal basis. Moreover, the synergistic effect of smoking both tobacco and cannabis on lung function has been reported.[43] Another interesting question would therefore be how heterogeneity in tobacco consumption affects the impact of smoked cannabis on lung function.

Lastly, many believe that the development and use of pure cannabinoid compounds would involve less risks than medical herbal cannabis;[36,278] no controlled studies have been published to validate this claim. We observed the incidence rate of adverse events for pharmaceutical cannabinoid products (8.42 events/person-year) was different from that for Health Canada cannabis (4.61 events/person-year). We caution against a direct comparison of these two incidence rates, since they were obtained from different trials involving different study populations and different follow-up strategies. An interesting question would therefore be the comparison of herbal cannabis with cannabinoid product(s) on the efficacy and safety in well-designed clinical trials.

6.4 Conclusions

6.4.1 Safety of medical cannabis

- The adverse effects of Health Canada cannabis among experienced users are modest.
- Medical cannabis was associated with an increased risk of non-serious adverse events, in particular in relation to the nervous system and psychiatric disorders, compared to controls.
- Safety of cannabis use in naïve users requires study.
- More studies with long-term exposure are required to further characterize safety issues of medical cannabis, in particular, the risk of serious adverse events.
- Further studies concerning the long-term effects of medicinal cannabis on pulmonary and neurocognitive functions are required.

- The systematic review of recreational cannabis use suggests cannabis may be associated with an increased risk of car accidents and congenital disorders.

6.4.2 Methodological considerations

- The impact of matching on the efficiency of risk ratios in cohort studies depends on the positive or negative directions of the confounder-outcome relation and the confounder-exposure relation.

- Although the cost and difficulty of conducting matched cohort studies will affect the final decision regarding whether or not such studies can be conducted, the impact of matching on efficiency in a cohort study should not be neglected.

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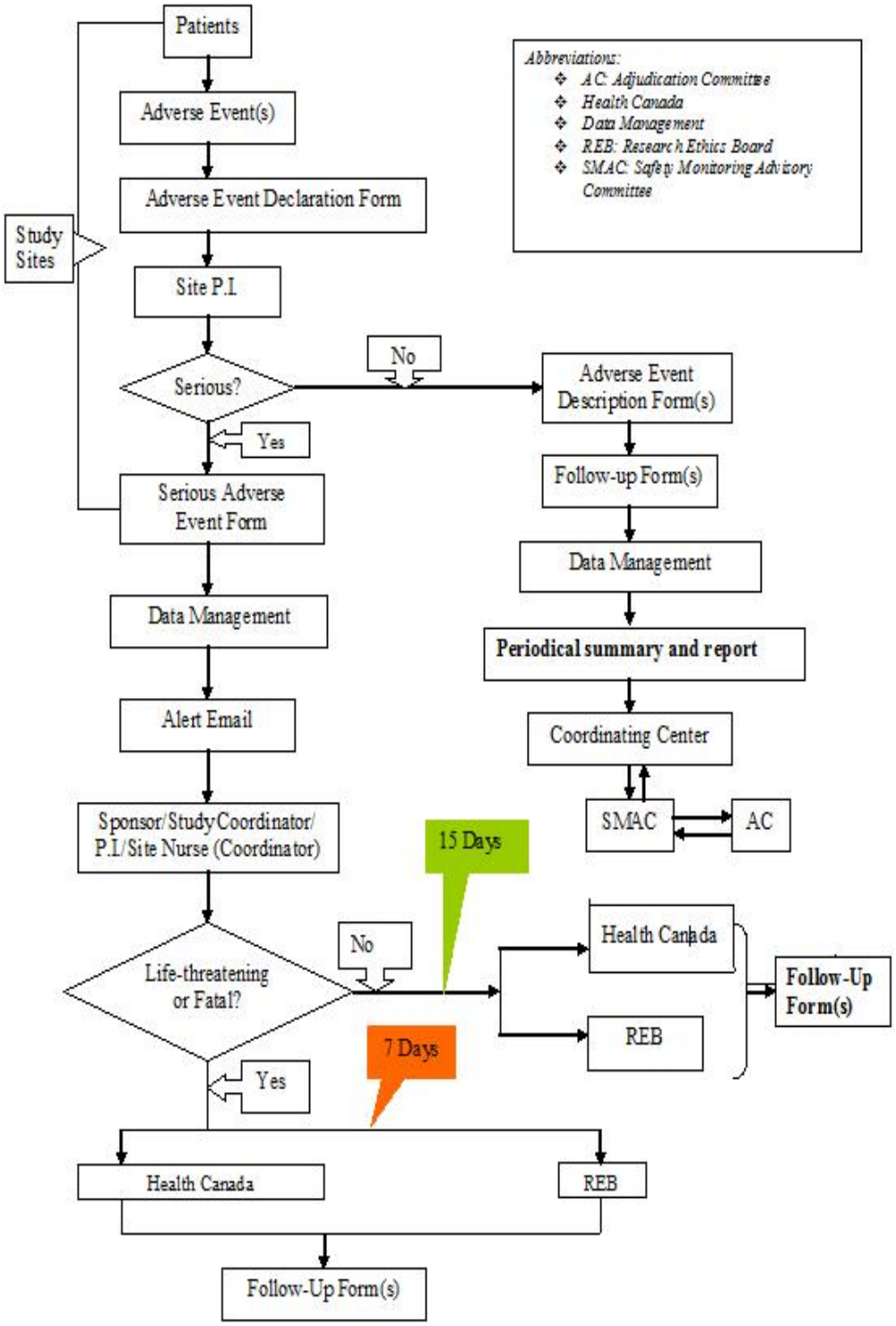
APPENDICES

Appendix 1: Adverse events reporting flowchart



Appendix 2: Schedules of visits and assessments

Measurement	Baseline	1, 2, 3 weeks	1, 2 months	3 months	6 months	9 months	1 year
Baseline assessments							
Demographics							
Age, gender, education, household income, marital status, occupational status, disability status	X/O						
Tobacco use history	X/O						
Alcohol use history	X/O						
Recreational drug use history	X/O						
Past cannabis use	X/O						
Reproductive history	X/O						
Pregnancy test	X/O						
Medical information							
Pain diagnosis	X/O						
Medication use	X/O						
Drug Abuse Screening Test (DAST)	X/O		X	X	X/O	X	X/O
Urine drug testing (UDT)	X/O		X	X	X/O	X	X/O
Study intervention							
Cannabis dose requirements	NR	X	X	X	X	X	X
Primary outcomes							
Serious and non-serious Adverse events	NR	X/O	X	X/O	X/O	X/O	X/O
Secondary outcomes							
Pulmonary function tests	X						X
Neurocognitive tests	X/O				X/O		X/O
Pain intensity	X/O	X/O	X	X/O	X/O	X/O	X/O
SF-36v2®	X/O				X/O		X/O

Note: X=Cannabis group; O=Control group; NR=not reported.

Appendix 3: Sample size calculation and statistical power

Expected incidence in the unexposed (control) group required for a specified power of 0.5, 0.6, 0.7, 0.8, 0.9 (two-tailed) α=0.05

Exposed:Unexposed	Power	RR (Rexp/Runexp)				
		1.2	1.5	2.0	3.0	4.0
1:3						
	0.5	403	69	19	6	3
	0.6	519	90	25	8	4
	0.7	660	115	33	10	5
	0.8	846	149	42	13	7
	0.9	1141	203	58	18	9
1:2						
	0.5	307	54	15	5	3
	0.6	394	69	20	6	3
	0.7	499	88	25	8	4
	0.8	638	113	33	10	5
	0.9	859	153	44	14	7
1:1						
	0.5	211	38	12	4	2
	0.6	269	49	15	5	3
	0.7	339	61	18	6	3
	0.8	431	78	23	7	4
	0.9	576	103	30	9	5

Appendix 4: Ratio of exposed to unexposed case numbers across strata in a matched 1:1 cohort study

In a matched 1:1 cohort study, $N_1 = N_0 = N$, and $P_{k|\bar{E}}=P_{k|E}$, so we have:

K=1 (i.e. stratum 1)

	D_1	D_0	Total
E_1	$E_{11}=N_{11}\times R_{11}$		$N_{11}=N\times P_{k\|E}$
E_0	$E_{01m}=N_{01}\times R_{01}$		$N_{01m}=N\times P_{k\|E}$

K=0 (i.e. stratum 0)

	D_1	D_0	Total
E_1	$E_{10}=N_{10}\times R_{10}$		$N_{10}=N\times(1- P_{k\|E})$
E_0	$E_{00m}=N_{00}\times R_{00}$		$N_{00m}=N\times(1- P_{k\|E})$

1) Ratio of exposed to expected unexposed cases in stratum K=1 is expressed as:

$$E_{11}/E_{01m}= (N_{11}\times R_{11}) / (N_{01m}\times R_{01})$$

$$= (N\times P_{k|E}\times R_{11}) / (N\times P_{k|E}\times R_{01})$$

$$= R_{11}/ R_{01}$$

$$= RR$$

2) Ratio of exposed to expected unexposed cases in stratum K=0 is written as:

$$E_{10}/E_{00m}= (N_{10}\times R_{10})/ (N_{00m}\times R_{00})$$

$$= (N\times (1-P_{k|E}) \times R_{10}) / (N\times (1-P_{k|E}) \times R_{00})$$

$$= R_{10}/ R_{00}$$

$$= RR$$