



**Association between Active Pulmonary Tuberculosis and History of
Cannabis Use**

Kemmapon Chumchuen

**A Thesis Submitted in Fulfillment of the Requirements for the Degree of Doctor
of Philosophy in Epidemiology (International Program)**

Prince of Songkla University

2025

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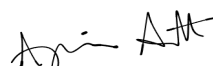
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ABSTRACT

Tuberculosis (TB) is a chronic lung disease caused by *Mycobacterium tuberculosis*. Tobacco smoking and sharing of instruments have been reported to increase TB risk. In 2022, cannabis was legalized in Thailand. Cannabis use can increase inflammatory responses in the respiratory tract. Sharing of cannabis waterpipes has also been anecdotally linked to increased tuberculosis risks. In this thesis, we conducted two studies to assess the increased TB risks at the population level in Thailand.

First, using a national in-patient databank, we aimed to 1) describe the spatiotemporal correlation between cannabis-related and tuberculosis hospital admissions, and 2) compare the rate of subsequent pulmonary tuberculosis admission between those with admissions for cannabis-related causes and those without. In the second part, a case-control study using pulmonary TB cases and neighborhood-age-sex matched healthy controls was conducted in the Songkhla province of Southern Thailand in 2023 to compare their history of cannabis consumption.

The national databank study indicated a decline in TB admissions alongside a rise in cannabis-related admissions. Detailed temporal analysis showed no significant lag association between the two. However, the two types of admissions correlated had a hotspot zone in Northeastern Thailand.

On the matched cohort of the in-patients, the incidence density rate of subsequent TB admissions was not significantly different between that in the cannabis-related admission cohort and that in the control non-cannabis cohort (hazard ratio: 1.48, $P = 0.268$).

Similarly, in the case-control study, there was no significant difference in the history of oral (odds ratio of 0.65; 95% CI: 0.28–1.52), and general smoking cannabis consumptions (odds ratio of 0.72; 95% CI: 0.04–12.38) between the TB cases

and their matched control. However, the TB cases had a higher prevalence of sharing bong in smoking cannabis than the control did with an odds ratio of 4.22 (95% CI: 1.47–12.07). The population-attributable fraction of this type of exposure was 12.16, close to that of tobacco smoking (PAF = 12.62).

In conclusion, education should be provided to the population to reduce bong sharing among the cannabis users.

Keyword : Tuberculosis, cannabis, bong sharing, case-control, national databank

ชื่อวิทยานิพนธ์ ความสัมพันธ์ระหว่างวัณโรคปอดและประวัติการใช้กัญชา

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บทคัดย่อ

วัณโรค (TB) เป็นโรคปอดเรื้อรังที่เกิดจากการติดเชื้อ *Mycobacterium tuberculosis* นอกจากนี้ยังพบว่าการสูบบุหรี่และการแชร์เครื่องมือการสูบรวมกันนั้นสามารถเพิ่มความเสี่ยงในการเกิดวัณโรคได้ ในปี 2565 กัญชาได้ถูกถอนจากบัญชียาเสพติดควบคุมในประเทศไทย การใช้กัญชาถูกรายงานว่าสามารถเพิ่มการอักเสบในระบบทางเดินหายใจ นอกจากนี้การใช้บ้องกัญชาร่วมกันยังได้ถูกเชื่อมโยงถึงการเพิ่มความเสี่ยงในการเป็นวัณโรคจากบทความวิจัยบทความหนึ่ง ในวิทยานิพนธ์นี้ผู้เขียนได้ดำเนินการสองการศึกษาย่อยเพื่อประเมินความเสี่ยงที่เพิ่มขึ้นของวัณโรคในระดับประชากรในประเทศไทย

ในการศึกษาแรกผู้เขียนได้ใช้ฐานข้อมูลผู้ป่วยในระดับประเทศ โดยมีจุดประสงค์ของการศึกษาที่จะ 1) อธิบายความสัมพันธ์เชิงพื้นที่และเวลา (spatiotemporal correlation) ระหว่างการเข้ารับการรักษาในโรงพยาบาลที่เกี่ยวข้องกับกัญชากับการเข้ารับการรักษาจากวัณโรค และ 2) เปรียบเทียบอุบัติการณ์การเข้ารับการรักษาวัณโรคทางปอดระหว่างกลุ่มที่เข้ารับการรักษาที่เกี่ยวข้องกับกัญชากับกลุ่มที่ไม่เคยเข้ารับการรักษาจากสาเหตุที่เกี่ยวข้องกับกัญชา การศึกษาที่สองคือการศึกษามีกลุ่มควบคุม โดยใช้กลุ่มผู้ป่วยวัณโรคทางปอดและกลุ่มควบคุมที่ตรงกับอายุ เพศ และที่อยู่อาศัยของกลุ่มผู้ป่วยในจังหวัดสงขลา โดยการศึกษานี้ถูกจัดทำเพื่อเปรียบเทียบประวัติการใช้กัญชาระหว่างทั้งสองกลุ่ม

ผลการศึกษาจากการศึกษาแรกพบว่าการเข้ารับการรักษาของวัณโรคมีจำนวนลดลงขณะที่การเข้ารับการรักษาในโรงพยาบาลที่เกี่ยวข้องกับกัญชานั้นสูงขึ้น นอกจากนี้จากการวิเคราะห์ในเชิงเวลาแสดงให้เห็นว่า ไม่มีความสัมพันธ์ในเชิงความล่าช้าระหว่างทั้งสองการเข้ารับการรักษาในโรงพยาบาล อย่างไรก็ตามพบว่ามีฮอตสปอตของทั้งสองการเข้ารับการรักษาในโรงพยาบาลทั้งสองประเภทในภาคตะวันออกเฉียงเหนือของประเทศไทย

ในเชิงการเปรียบเทียบอุบัติการณ์การเข้ารับการรักษาวัณโรคทางปอด พบว่าอุบัติการณ์การเข้ารับการรักษาวัณโรคทางปอดในครั้งถัดไปไม่แตกต่างกันอย่างมีนัยสำคัญระหว่างกลุ่มที่เข้ารับการรักษาที่เกี่ยวข้องกับกัญชากับกลุ่มที่ไม่เคยเข้ารับการรักษาจากสาเหตุที่เกี่ยวข้องกับกัญชา (อัตราเสี่ยง: 1.48, $P = 0.268$)

จากการศึกษาที่มีควบคุมพบว่าไม่มีความแตกต่างที่มีนัยสำคัญทางสถิติในประวัติการใช้กัญชาในรูปแบบรับประทาน (อัตราส่วนออดส์ 0.65; 95% CI: 0.28–1.52) และการใช้กัญชาแบบทั่วไป (อัตราส่วนออดส์ 0.72; 95% CI: 0.04–12.38) ระหว่างกลุ่มวัณโรคและกลุ่มควบคุมที่ อย่างไรก็ตามพบผู้ป่วย

วัดโรคมีอัตราการใช้บ่งกัณชา่วมกันในการสูบกัณชาสูงกว่ากลุ่มควบคุม โดยมีอัตราส่วนอัตรา 4.22 (95% CI: 1.47–12.07) โดยสัดส่วนของการเกิดโรคในประชากรจากตัวแปรนี้ (population-attributable fraction) อยู่ที่ 12.16 ซึ่งใกล้เคียงกับสัดส่วนที่ได้มาจากการสูบบุหรี่ (PAF = 12.62)

จากข้อมูลเหล่านี้มีผลสรุปว่าการให้ความรู้แก่ประชากรเพื่อลดการใช้บ่งกัณชา่วมกันในกลุ่มผู้สูบกัณชาเป็นเรื่องที่สำคัญ

คำสำคัญ : วัดโรค, กัณชา, การใช้บ่งกัณชา่วมกัน, การศึกษากรณีควบคุม, ฐานข้อมูลระดับประเทศ

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Part of this study was conducted using the Thailand Health Information Portal (THIP). I would like to thank all the individuals behind the THIP team for their assistance with data curation.

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Kemmapon Chumchuen

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LISTS OF ABBREVIATIONS AND SYMBOLS

TB	Tuberculosis
MTB	<i>Mycobacterium tuberculosis</i>
THIP	Thai Health Information Portal
COVID-19	Coronavirus disease 2019
WHO	World Health Organization
MDR	Multidrug-resistance
HIV	Human immunodeficiency virus
AFB	Acid Fast Bacilli
CXR	Chest X-ray
OR	Odds ratio
CSV	Comma-separated vales
SD	Standard deviation
IQR	Interquartile range
AIC	Akaike information criterion
CI	Confidence interval
NHSO	National Health Office
NSTDA	National Science and Technology Development Agency
ICD	International Classification of Diseases
HR	Hazard ratio
IDR	Incidence density rate
PAF	Population-attributable fraction
ACF	Autocorrelation function
CCF	Cross-correlation function
ARDL	Autoregressive Distributed Lag

LISTS OF PUBLICATIONS

1. Chumchuen K, Wichaidit W, Chongsuvivatwong V. Relationship between hospitalization from cannabis usage and pulmonary tuberculosis in Thailand from 2017 to 2022. PLOS ONE. 2024; 10.1371/journal.pone.0312139.
2. Chumchuen K, Chongsuvivatwong V. Increased active pulmonary tuberculosis risk from sharing bong of cannabis: a case–control study from Thailand. Front Public Health. 12:1474761.

SUMMARY OF CONTENTS

1. Introduction

1.1 Background

1.1.1 Tuberculosis and its situation in Thailand

Tuberculosis (TB) is an infectious lung disease caused by *Mycobacterium tuberculosis*. The infection begins when a person inhales the pathogen suspended in the air, which is excreted from an infected host via coughing or sneezing. Once exposed to the pathogen, the host either clears the infection through their own immune response or becomes infected. TB infection can present with signs and symptoms or remain asymptomatic until further reactivation of the pathogen. *M. tuberculosis* is an obligate aerobic bacterium, meaning it requires air. The pathogen migrates to the host's lungs and infects the alveolar spaces, resulting in lung damage. Without effective treatment, the infected host can develop extensive lung damage or even die¹.

Tuberculosis causes a significant burden in both morbidity and mortality worldwide. Prior to the COVID-19 pandemic, tuberculosis was responsible for the highest number of deaths from a single pathogen. The elimination of tuberculosis, in line with the End TB Strategy, had been progressing steadily over the years. However, since the COVID-19 pandemic, progress in eliminating tuberculosis has been hindered or even reversed to some extent^{2,3}.

Since tuberculosis was first reported in Thailand in the 19th century, it has become an endemic disease in the country, similar to other nations in Asia. Thailand has been classified as a country with a high burden of tuberculosis for over 10 years⁴⁻⁶. According to a national TB survey conducted in 2012-2013, the prevalence of TB was highest among the elderly. TB was found to be more common in males compared to females, with the majority of cases occurring in the Northeastern region. The incidence rate from the national prevalence survey was 242 cases per 100,000 population⁷.

Before the COVID-19 pandemic, the incidence of TB in Thailand had been steadily declining over the years. In 2019, the incidence rate was estimated to be 150 per 100,000 population (uncertainty interval: 114-191)⁸. A decrease in newly diagnosed TB cases was observed during 2020-2021, although this reduction was suggested to be due to a decline in case detection and reporting affected by the pandemic, rather than an actual decrease in TB transmission. In 2021, Thailand transitioned out of the list of countries with a high burden of multidrug-resistant (MDR) TB. However, the burden of TB in general and the coinfection between TB and HIV (human immunodeficiency virus) remained high, as shown in Figure 1².

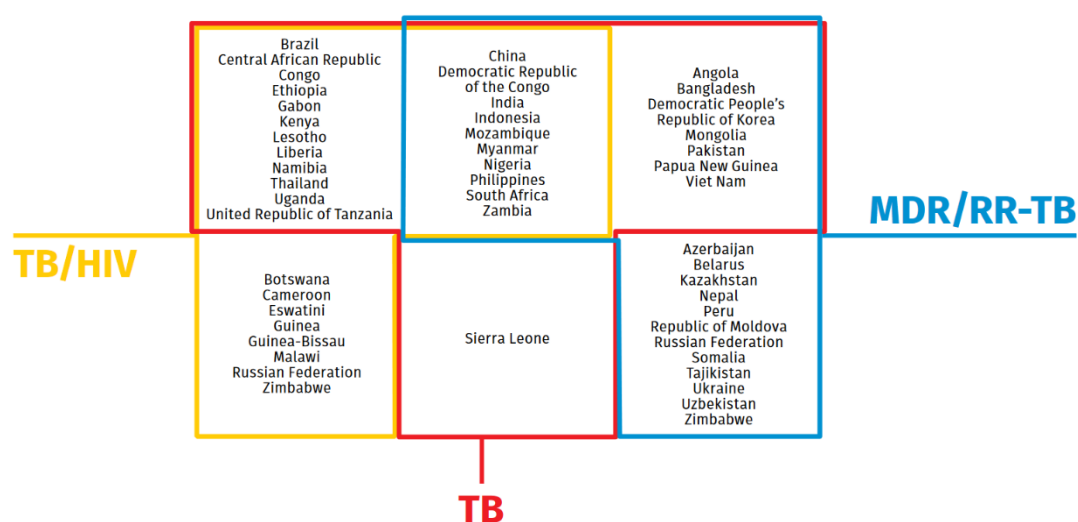


Figure 1 Lists of countries stratified by type of TB burden

Source: WHO, 2021²

1.1.2 Cannabis in Thailand

Cannabis, also known by many names such as marijuana or ganja, is a flowering plant belonging to the Cannabaceae family, originating from Central Asia or Western China. It is currently the most widely used psychoactive substance in the world, with its popularity as a recreational drug only behind caffeine, alcohol, and tobacco^{9,10}. Cannabis has existed for a long time, with its use dating back 5,000 years. In ancient times, cannabis was used in various ways, such as therapeutically in the form of medicinal tea, as a spice in cooking, and as part of religious ceremonies^{11,12}.

Regarding cannabis in Thailand, it is believed to have been introduced through trade with India in the past, supported by the similarity of the plant name, ganja, used in both countries. During that time, Thai locals used cannabis as an analgesic, sedative, and muscle relaxer, especially among labor workers^{12,13}. The use of cannabis in Thailand was not deemed illegal until the enactment of the first Thailand Narcotic Act in 1922, which was established in response to the formation of the League of Nations International Opium Convention of 1912. After the first Narcotic Act, the Thailand Marijuana Act was subsequently enacted in 1937, further enforcing cannabis control and penalties. The usage and consumption of cannabis were tightened again after another edition of the Thailand Narcotic Act in 1979. Following this, the remaining production of cannabis in Thailand was forced to move to neighboring countries such as Laos and Cambodia¹⁴.

Following a surge of interest in cannabis as a therapeutic substance in other countries, the movement for cannabis legalization in Thailand started in 2016 and gradually gained momentum as it became one of the promised policies from the elected political party during 2018 and 2019¹⁵. In February 2019, medical cannabis was legalized as announced in the Thailand Narcotic Act of 2019. However, regular cannabis was still considered a controlled narcotic substance, and recreational use remained illegal¹⁶. In June 2022, the law entitled "Unlocking Cannabis" announced that cannabis was removed from the controlled narcotic substance group. This law was established to enhance the value of cannabis in three aspects: 1) medicinal value, 2) economic value, contributed by several industries such as cosmetics, traditional herbs, food, and innovation, and 3) its value as an alternative choice for self-care. Furthermore, this law enables Thai people to grow and own cannabis in their households. Similar to Kratom, the legality of the plant could increase the prevalence of cannabis consumers, leading to the necessity of investigating its effects.

1.1.3 Overlap between high TB risk population and cannabis consumers

Evidence from past studies has shown that men are at a higher risk of TB due to their disadvantages in seeking or accessing healthcare^{17,18}. Moreover, cannabis use is also more likely to be found in males than females^{19,20}. A study by Leung et al. reported that the highest prevalence of cannabis users was among young adults aged 26 to 35²¹; however, increased trends of cannabis consumption have also been reported in older male adults over the years²². Additionally, the prevalence of cannabis use has been found to be associated with socioeconomic adversities²³. As reported in several past studies^{24–27}, the risk of contracting tuberculosis is higher in low socioeconomic groups or those living in poverty. This association is suggested to be mediated mainly through the fact that those living in poverty are likely to reside in crowded spaces, hence having higher chances of being exposed to tuberculosis^{24,28,29}. As there are several possible overlaps in the population between those likely to use substances and those prone to getting tuberculosis, investigating the association between these populations is needed.

1.2 Rationale

Since the legalization of cannabis in Thailand, its popularity has surged, resulting in an increasing number of consumers for both medicinal and recreational purposes. The population of cannabis consumers overlaps with populations prone to TB infection, such as males and those residing in low socioeconomic or low hygienic areas. While evidence of immunosuppression from cannabis is inconclusive based on past studies, the increased risk of TB infection can be attributed to several factors, such as inflammation and cell damage in the respiratory tract due to cannabis smoking, and exposure to pathogens via sharing smoking utensils like water pipes or the cannabis itself. Therefore, investigating the health effects of cannabis use is necessary.

To assess the increased pulmonary TB risks from cannabis use, epidemiological evidence is required. We started by using an available national databank of in-patient data to conduct a national-scale secondary data analysis to: 1) investigate the spatiotemporal correlation between pulmonary TB admission incidence and cannabis-related admission incidence, and 2) determine the subsequent TB admission rate in those admitted with cannabis-related causes and compare it with that of general in-

patients. To follow up on the national-scale findings, we then conducted a matched case-control study to compare the history of cannabis consumption between TB cases and age-sex-neighborhood matched controls in a more individualized aspect.

1.3 Objectives

We hypothesized that cannabis use could increase the risk of contracting active pulmonary TB. Therefore, to assess the increased risk of infection, we aimed to:

1. Investigate the spatiotemporal correlation between pulmonary TB admission incidence and cannabis-related admission incidence.
2. Determine the subsequent TB admission rate for those admitted with cannabis-related causes and compare it with that of general in-patients.
3. Determine the odds ratio of past cannabis use on pulmonary TB using a case-control study with active pulmonary tuberculosis cases and age-sex-community matched tuberculosis-free controls.

1.4 Conceptual frameworks

1.4.1 Conceptual framework of the secondary data analysis study

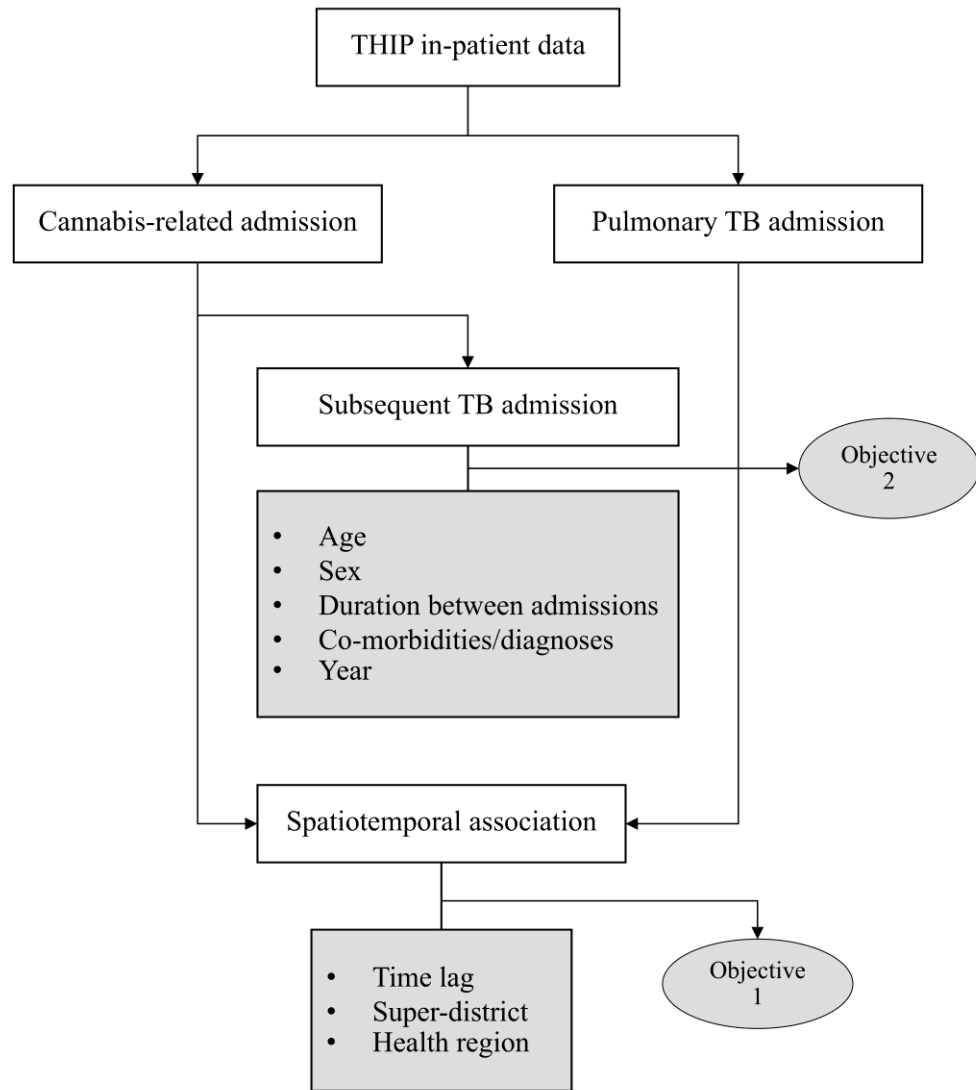


Figure 2 Conceptual framework of the secondary data analysis study

1.4.2 Conceptual framework of the case-control study

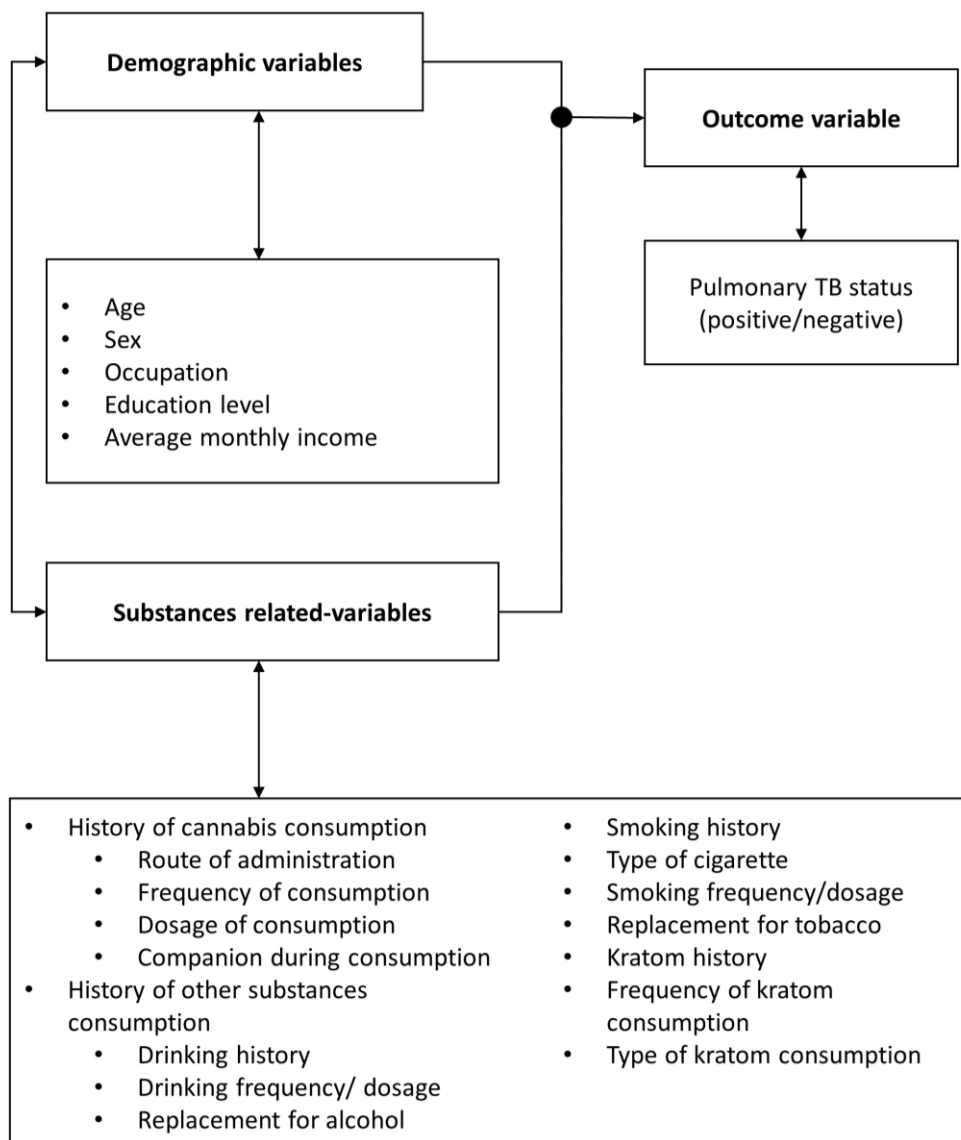


Figure 3 Conceptual framework of the case-control study

2. Methodology

2.1 Methodology of the secondary data analysis study

2.1.1 Study design

A secondary data analysis study using the national in-patient databank was conducted.

2.1.2 Data source

This study was conducted using Thai Health Information Portal (THIP) databank. THIP is a collaborative project, jointly managed by the National Health Security Office (NHSO), the National Science and Technology Development Agency (NSTDA) and the Institute of Research and Development for Health of Southern Thailand. THIP contains data from admitted patients from the whole nation who filed for reimbursement from NHSO for the medical fees. Since the start of the collaboration, in-patient data from between 2017 and 2022 were made available for analysis.

2.1.3 Data curation

THIP data can be queried using the International Classification of Diseases (ICD-10) codes. Admission records of in-patients that had conditions presented in either their primary or secondary diagnosis that matched with the queried ICD-10 codes will be selected for data extraction. As a proxy for cannabis user population, those admitted with conditions including mental and behavioral disorders due to use of cannabinoids, cannabis poisoning, and Cannabinosis were queried from THIP. To obtain the pulmonary TB history of these in-patients along with the aim to estimate and compare subsequent pulmonary TB admission rate with the general in-patients, ICD-10 codes related to TB were also used for the query processes. All ICD-10 codes used in the query process along with their description are shown in Appendix 6.

2.1.4 Sample populations and definitions

National Thai in-patients were used for secondary data analysis study. Those diagnosed with cannabis related causes as show in the appendix were defined as

cannabis-related in-patients, a similar process was also conducted to define TB in-patients. For the second objective, the general in-patients in the databank who were never diagnosed with cannabis-related causes and did not admit with TB in their first visit were used as control population for matching analysis.

2.1.5 Variables

Both the exposure (cannabis-related admission) and the outcome (TB admission) variables were derived from the full diagnoses of the in-patient. In THIP, each admission records contain one primary diagnosis column and 21 available columns for the secondary diagnoses. For the exposure variable of interest, we defined in-patients that had the diagnosis of cannabis-related conditions (Appendix Table) in any diagnosis column as those with history of cannabis-related admission. A similar process was employed for pulmonary TB admission, the outcome variables. Both the exposure and outcome variables were treated as binary variables in this study.

Other variables available in the databank that were present in this study included age, sex, province of residence, and date of admission. The latter was used to determine causal relationship between the exposure and outcome variables. We categorized age group for analysis process, separating those under and older or equal to 40 years of age. For the second objective, co-diagnoses were pre-selected for estimating increased risk in the form of hazard ratio (HR). We selected common (>10%) co-diagnoses presented in the first admission in any diagnosis column of those who later admitted with pulmonary TB.

2.1.6 Statistical analysis and data management

Concerning the spatiotemporal relationship (the first objective), we aggregated admission count into monthly unit and plotted a line graph with Hans Rosling's principal to display their temporal pattern over the years. Monthly aggregated admission frequencies were also used for temporal analyses including Pearson's correlation test between admission frequency, trend and stationarity assessments, autocorrelation function, cross correlation function, lag analysis such distributed lag model and autocorrelated distributed lag model.

For the spatial investigation, we aggregated the admission counts into province-level of each year. The counts were then divided by the population of each province and presented as admission incidence density rate (IDR) per 100,000 population. We plotted choropleth maps from 2017 to 2022 while using the calculated rate for color gradients to visualize spatial patterns. Pearson's correlation test was also performed in the spatial aggregated unit of superdistrict and provincial level.

Regarding the second objective, we matched in-patients who admitted with cannabis-related causes with those the general in-patient from THIP data using specific age, sex, year of admission and superdistrict as matching variables. We calculated incidence density rate (IDR) by dividing the number of subsequent TB admission in each group by their cumulative person-year. The person-year was defined as the time between their first admission entry in THIP data and their endpoint, which was the last admission entry if pronounce dead or 30th September 2022, the last entry of THIP data for alive in-patients.

We then statistically compared the matched populations using univariate analysis to assess matching balance and differences in demographic variables and outcome-related variables. The pre-selected common co-diagnoses from those who later developed subsequent TB admission were also included in this univariate process. We performed Mann-Whitney U test, chi-squared test, and Poisson Exact test for non-normally distributed continuous variables, categorical variables, and comparison between IDR, respectively.

To assess the increased risk of subsequent pulmonary TB admissions while adjusting for covariates, we performed Cox regression between the matched population for the outcome of the first subsequent TB admission. The result of Cox regression was displayed as adjusted hazard ratio (HR) table.

All data including for THIP were managed and analyzed using R program version 4.2.3. Packages such as tidyverse, stringr, and plyr were used to manage the national data.

2.2 Methodology of the case-control study

2.2.1 Study design

A case-control study was conducted to determine association between cannabis consumption and pulmonary TB status using pulmonary TB outpatients and their age-sex-community matched TB free healthy controls.

2.2.2 Study setting

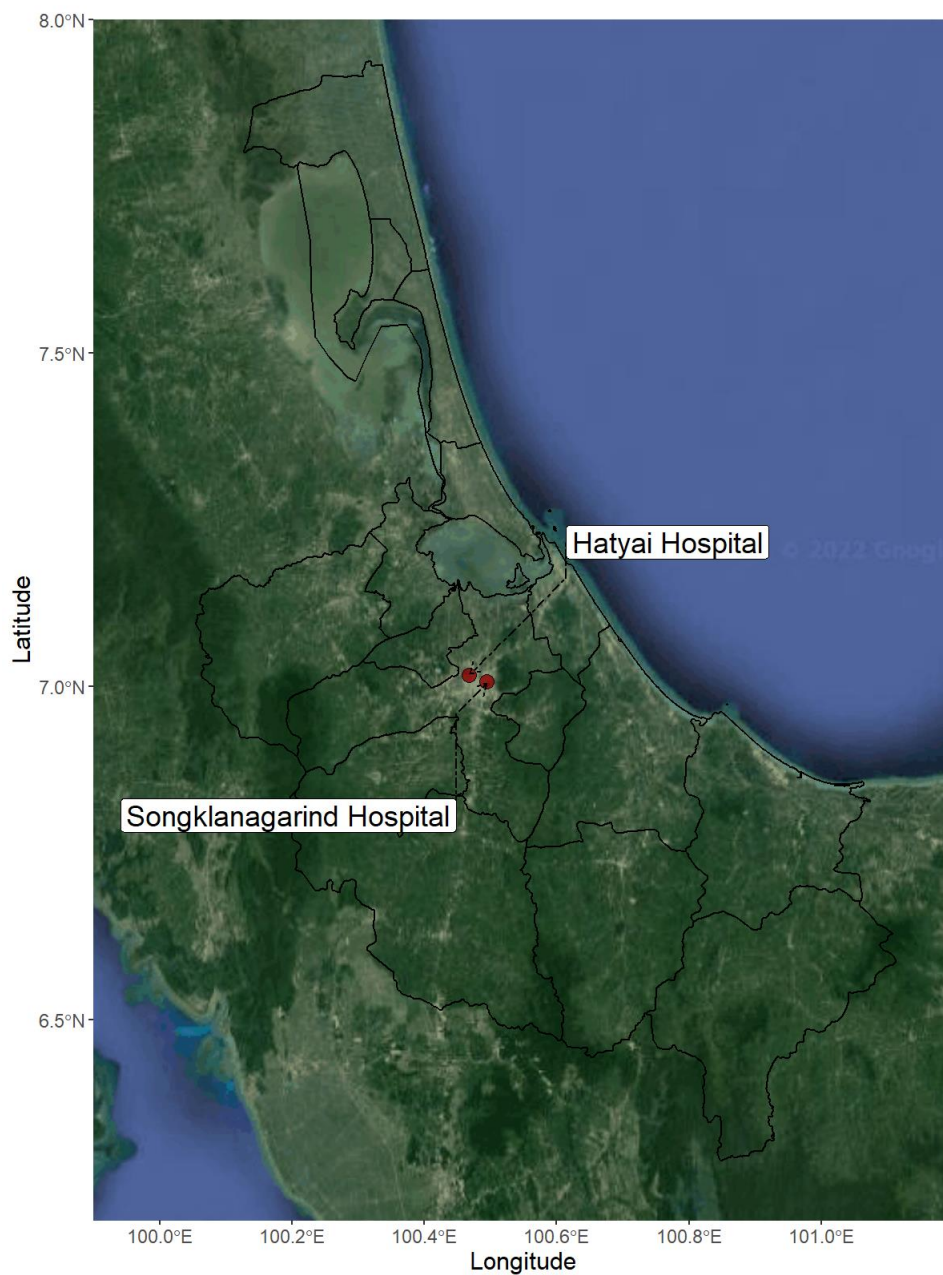


Figure 4 Map of Songkhla stratified by districts. Two red dots represent the two local hospitals.

Pulmonary TB cases were collected from two hospital located within Songkhla province, Thailand, of which are Songklanagarind Hospital and Hatyai Hospital. Both hospitals were selected based on the difference in patient population background, as we planned to collect from both urban and rural population, which are the population type of patients from Songklanagarind Hospital and Hatyai Hospital, respectively.

Songklanagarind Hospital is located in Prince of Songkla University, Hatyai district, the main business district of Songkhla province. Being a university teaching hospital affiliated with Faculty of Medicine of Songkla University, and a hospital with super tertiary care capacity, patients of Songklanagarind Hospital can be from local Songkhla residence, or people travel from all over Southern region to receive a treatment here. Regarding TB patients, there were 173 new TB cases diagnosed in 2020 in Songklanagarind Hospital. TB cases in Songklanagarind Hospital are generally distributed to 3 departments: infectious department, chest department, and screening center. For this study, TB cases were recruited from the screening center.

Hatyai Hospital is the main hospital of Hatyai district, the capital district of Songkhla province. It is classified as a general hospital, operated by the Ministry of Public Health, and affiliated with the Faculty of Medicine of Prince of Songkla University as a teaching hospital. In contrast to Songklanagarind Hospital, patients of Hatyai Hospital are usually the residents of Hatyai district, due to the restriction of hospital when using the universal health care of Thailand. In Hatyai Hospital, TB cases are registered and treated at the TB clinic of the hospital, which was the place where the cases were recruited in this study.

2.2.3 Case definition

We included individuals aged ≥ 20 years old, diagnosed with active pulmonary tuberculosis since 1st of January 2022. The diagnosis was either bacteriologically (B+) confirmed or clinically diagnosed (B-). In case of B+, the confirmation was based on MTB positive culture, Acid- Fast Bacilli (AFB) smear positive with CXR image suggesting TB infection, or MTB positive from Gene Xpert. Regarding clinically diagnosed TB patients, the decision was accompanied with abnormal CXR result with pulmonary TB symptoms, physician decision in starting TB

treatment (after 2 weeks of treatment with broad spectrum antibiotics without fluoroquinolones). Furthermore, only outpatients that were resided in Songkhla and treated at either the screening center of Songklanagarind Hospital or TB clinic of Hatyai Hospital were included in this study.

Regarding exclusion criteria, pulmonary TB patients who were diagnosed with diseases or had conditions that affected their immune response were excluded from this study. The disease and conditions included HIV positive, cancer, receiving chemotherapy, diabetes patients, and malnourished. Those who could not partake in face-to-face interview were also excluded from the study.

2.2.4 Control definition

Controls in this study was matched with the cases using age group, sex, and community as the matching variables. Control matching varied between urban and rural cases due to differences in TB transmission, influenced by factors such as high population density, crowded living conditions, and low hygiene^{30,31}. For rural areas, we defined a community as a village in which the patient resided. For the urban setting, we defined the study community as an alley of the patient's home. The responsible healthcare center for each study community was approached. The study protocol was explained to the patients. The health offices were requested to invite health volunteers in charge to participate in the control selection. Information on the age group (10-year range) and sex of the patients in that community was used to match with the cases and guide the health volunteers to select controls. The exclusion criteria for controls were the same as those for the case group. Potential controls were not included if they had been diagnosed with TB. However, we did not attempt to exclude patients with TB from the control group using any tests, including chest radiography.

2.2.5 Sample size calculation

$$n_1 = \left[\frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}(1+\frac{1}{r})} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2 \quad (1)$$

$$r = \frac{n_2}{n_1}, q_1 = 1 - p_1, q_2 = 1 - p_2 \quad (2)$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p} \quad (3)$$

This study sample size was calculated using two independent proportion formulas (formulas 1-3). For the exposure proportion in the control group, we used the previously reported prevalence of Thai people who had ever used cannabis for medicinal purposes, which was 0.32 for P_1 . We assumed the proportion of cannabis consumption among the cases (P_2) to be 0.49, which was sufficient to generate an OR of 2. With a significance level of 0.05, a power of 0.8, and a 1:1 case-to-control ratio, the required total sample size was 148 cases and 148 controls.

2.2.6 Recruitment and sampling processes

No sampling technique was performed for the case group. All available eligible TB cases were approached for recruitment by the nurse teams of both hospitals, while they waited for their scheduled examination or payment processes. After approached by the nurse team, the primary investigator explained the study to the eligible cases, while handing out the participant information sheet before asking for their verbal informed consent. Cases were approached from both hospitals until the number of cases met the sample size requirement.

Regarding the sampling of control, recruitment of the control group was assigned to the health volunteers or research staffs who responsible or resided at the sub-district/community where the cases were resided in. For each case, the health volunteers or research staffs were told to randomly select one eligible control (matched in age group, sex, and community) from the community. When more than one eligible control was available for each TB case, volunteers were advised to randomly select one.

2.2.7 Data collection

The primary investigator was stationed at the screening center of Songklanagarind Hospital on every Tuesday and Thursday during the data collection period, while the cases from Hatyai Hospital were approached and recruited on every Monday, Wednesday, and Friday when the TB clinic was operational.

Data collection was done using face-to-face interview with a structured questionnaire (Appendix). The structured questionnaire contained 3 sections of items included 1) demographic information, 2) alcohol-tobacco-kratom-related information, and 3) cannabis-related information. The interview duration was limited to at most 10 minutes to avoid discomfort of the case group. The interview of the case group was conducted at the hospital where they were recruited, while eligible controls were contacted to come for an interview at their nearby local health center. Data collection was performed only once the verbal informed consent was obtained from the participant.

2.2.8 Variables

In this study, dependent variable or outcome variable was the status of active pulmonary TB, of which either was pulmonary TB positive or pulmonary TB negative. Pulmonary TB status of the case population was obtained from the hospital that the cases are registered and receiving treatment at. Pulmonary TB status depended on TB diagnosis, of which based on either TB culture result, or AFB staining result combined with CXR image. As there are 2 outcomes for pulmonary TB status, positive or negative, this variable was treated as a binary variable. Independent variables consisted of 3 domains, as described in Table 1 shown below.

Table 1 Independent variable table with description and type of variables

Domain 1: demographic variables		
Variable name	Description	Type of variable
Sub-district location	Sub-district where that participant located	Categorical variable
Village/block	Sub-district where that participant located	Categorical variable

Age	Age of participant at the day of interview	Continuous variable
Sex	Sex of the participant	Categorical variable
Occupation	Occupation of the participant	Categorical variable
Education level	Education level of the participant.	Categorical variable
Average monthly income	Monthly income of the participant. In case of variation between months, the average will be asked.	Continuous variable
Registration type (case group)	Registration type from the hospital, in case of being a TB case	Categorical variable
TB household contact status	Currently living with TB case, in the same house 3 months before onset of symptom or diagnosis of pulmonary TB	Categorical variable
Domain 2: tobacco, alcohol and kratom-related variables		
History of smoking	Participant history of smoking: Yes or No	Categorical variable
Currently a smoker	Currently a smoker: Yes (≥ 1 cigarette in past month), No (hasn't smoked in the past 6 months), or just quit (hasn't smoked in the < 6 months)	Categorical variable
Start smoking	In case of being a smoker/ex-smoker. Age when the participant started smoking will be asked	Continuous variable
Time of quitting	In case of being an ex-smoker. Time of quitting will be measured in year since stop smoking	Continuous variable
Type of smoking	Type of smoking substance the participant smokes	Categorical variable
Smoking frequency	How often does the participant smoke: daily, weekly, or monthly	Categorical variable
Smoking dosage	Number of cigarettes consume per frequency answered in the prior item. In case that the participant smokes daily or weekly, the dosage will be calculated into monthly equivalent	Continuous variable

Replacement for tobacco	In case of quitting, is there a product used as a replacement for tobacco (stop craving or reduce withdrawal effects)	Categorical variable
Reason behind the replacement of tobacco	Reason behind choosing the replacement substance for tobacco	Categorical variable
History of alcohol consumption	Participant history of alcohol consumption: Yes or No	Categorical variable
Currently an alcohol drinker	Currently an alcohol drinker: Yes (≥ 1 drink in the past 12 months) or No (hasn't drunk in the past 12 months)	Categorical variable
Start drinking	In case of being a drinker/ex-drinker. Age when the participant started drinking will be asked	Continuous variable
Time of quitting	In case of being an ex-drinker. Time of quitting will be measured in year since stop drinking alcohol	Continuous variable
Drinking frequency	How often does the participant drink alcohol: daily, weekly, or monthly	Categorical variable
Dosage of alcohol consumption (per month)	Number of drinks consume per frequency answered in the prior item. In case that the participant drink alcohol daily or weekly, the dosage will be calculated into monthly equivalent	Continuous variable
Replacement for alcohol	In case of quitting, is there a product used as a replacement for alcohol (stop craving or reduce withdrawal effects)	Categorical variable
Reason behind the replacement of alcohol	Reason behind choosing the replacement substance for alcohol	Categorical variable
History of kratom use	Participant history of kratom use: Yes or No	Categorical variable
Currently use kratom	Currently use/consume kratom	Categorical variable
Start using kratom	In case of being a user/ex- user. Age when the participant started using kratom will be asked	Continuous variable
Time of quitting	In case of having history of kratom use but not a current user. Time of quitting will be measured in year since stop using kratom	Continuous variable

Main reason behind using kratom	Reason (recreational vs therapeutic) will be asked in kratom user	Categorical variable
Desired therapeutic effect from kratom	In case the user used kratom for therapeutic effect, specific ailment that kratom is used for will be asked	Categorical variable
Types of kratom consumption	How kratom is consumed	Categorical variable
Additive used with kratom	In case the user consumes kratom as cocktail mixture, additive for the cocktail will be asked	Categorical variable
Frequency of kratom consumption	How often does the participant consume kratom	Categorical variable
Dosage of kratom consumption (per month)	Average number of kratom leaves consumed per frequency answered in the prior item. In case that the participant consumes kratom daily or weekly, the dosage will be calculated into monthly equivalent	Continuous variable
Companions presented during kratom consumption	The number of companions during kratom consumption	Continuous variable
Domain 3: cannabis-related variables		
History of cannabis use	Participant history of cannabis use: Yes or No	Categorical variable
Currently use cannabis	Currently use/consume cannabis	Categorical variable
Start using cannabis	In case of being a user/ex- user. Age when the participant started using cannabis will be asked	Continuous variable
Time of quitting	In case of having history of cannabis use but not a current user. Time of	Continuous variable

	quitting will be measured in year since stop using cannabis	
Main reason behind using cannabis	Reason (recreational vs therapeutic) will be asked in cannabis user	Categorical variable
Desired therapeutic effect from cannabis	In case the user used cannabis for therapeutic effect, specific ailment that cannabis is used for will be asked	Categorical variable
Types of cannabis consumption	How cannabis is consumed	Categorical variable
Location where cannabis is consumed	Where cannabis is generally consumed	Categorical variable
Ventilation at place of consumption	Ventilation status of place of consumption: Well ventilated (open door/window, outdoor) Poorly ventilated (close door/window, hotboxing)	Categorical variable
Sharing of cannabis	In case that cannabis is consumed via smoking, sharing of cannabis will be asked	Categorical variable
Companions presented during consumption	The number of companions during cannabis consumption	Continuous variable
Pipe hygiene	In case that cannabis is smoked via water pipe, frequency of pipe cleaning will be asked	Categorical variable
Frequency of cannabis consumption	How often does the participant consume cannabis	Categorical variable
Dosage of cannabis consumption (per month)	Average cost of cannabis consumed per frequency answered in the prior item. In case that the participant consumes cannabis daily or weekly,	Continuous variable

	the dosage will be calculated into monthly equivalent	
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2.2.9 Data management

This study used the REDCap server hosted by the Research Development Office of Prince of Songkla University to enter and store data. To avoid potential human error and recall bias, all data collected during face-to-face interviews was directly entered into the REDCap mobile application (Figure 5). To access the mobile application, the primary investigator and all field staff were required to install the mobile application before data collection, along with setting up login IDs and passwords to increase data security. The interview data stored in the mobile application was then synced with the REDCap server at the end of each day of the data collection period.

Only the primary investigator was allowed to access the database of this study. The database was restricted via two-factor authentication using an ID and password, and an email one-time password (OTP). This was conducted to safeguard participant information and confidentiality. Furthermore, data collected in both mobile structured questionnaires and collection instruments on the database did not contain the names of the participants. Data from the REDCap database was separately exported into comma-separated values (CSV) data files and R files. The R files will be used to read and label REDCap data via the R Hmisc package.

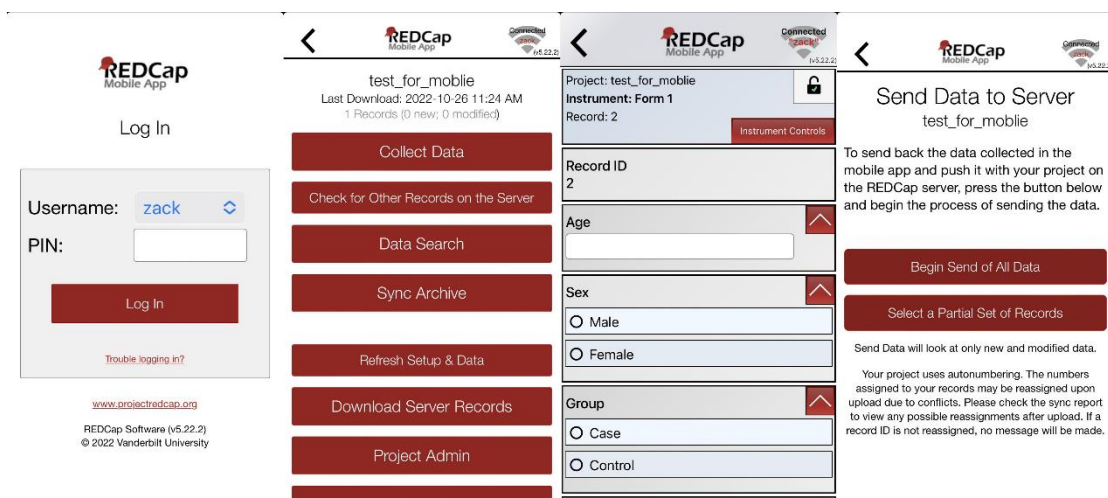


Figure 5 Data entry processes on REDCap mobile application

2.2.10 Statistical analysis

Descriptive statistics were used to summarize all independent variables and were stratified by the outcome variable. Frequency and percentage were used for categorical variables, whereas continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR) based on their distribution. Univariate association analysis was conducted using either the chi-square test or Fisher's exact test for small, expected cell counts, while the Student's t-test or Mann–Whitney U test was performed for continuous variables depending on the variable's distribution. A logistic regression analysis was performed to adjust for the remaining confounding factors. The key independent variables maintained in the model were cannabis use and smoking. Other covariates included in the model as potential confounders were those that showed a significant association with the outcome in the univariate analysis ($P < 0.2$).

Because smoking tobacco is a strong confounder, a multivariate model was initially performed without it. This model was then compared with the model in which it was included. The coefficient/OR of cannabis in the model, including smoking tobacco, reflected its direct effect on TB risk. This stepwise modeling approach was used separately to analyze the effects of cannabis use and cannabis smoking. To compare the different models, we used the Akaike information criterion (AIC) values. The model with the lowest AIC was considered the best-fit model, given that the set of records was the same. In the case of collinearity between two exposure variables, the variable with the lowest AIC was selected. This model was then summarized to display the OR with a 95% confidence interval (CI) for each independent variable. In addition, the population-attributable fraction (PAF) based on Levin's formula was computed for modifiable risk factors³², particularly cannabis use. The significance level (α) for multivariate analysis was set at 0.05.

3. Results and Discussion

3.1 Results of secondary data analysis

3.1.1 Temporal analyses

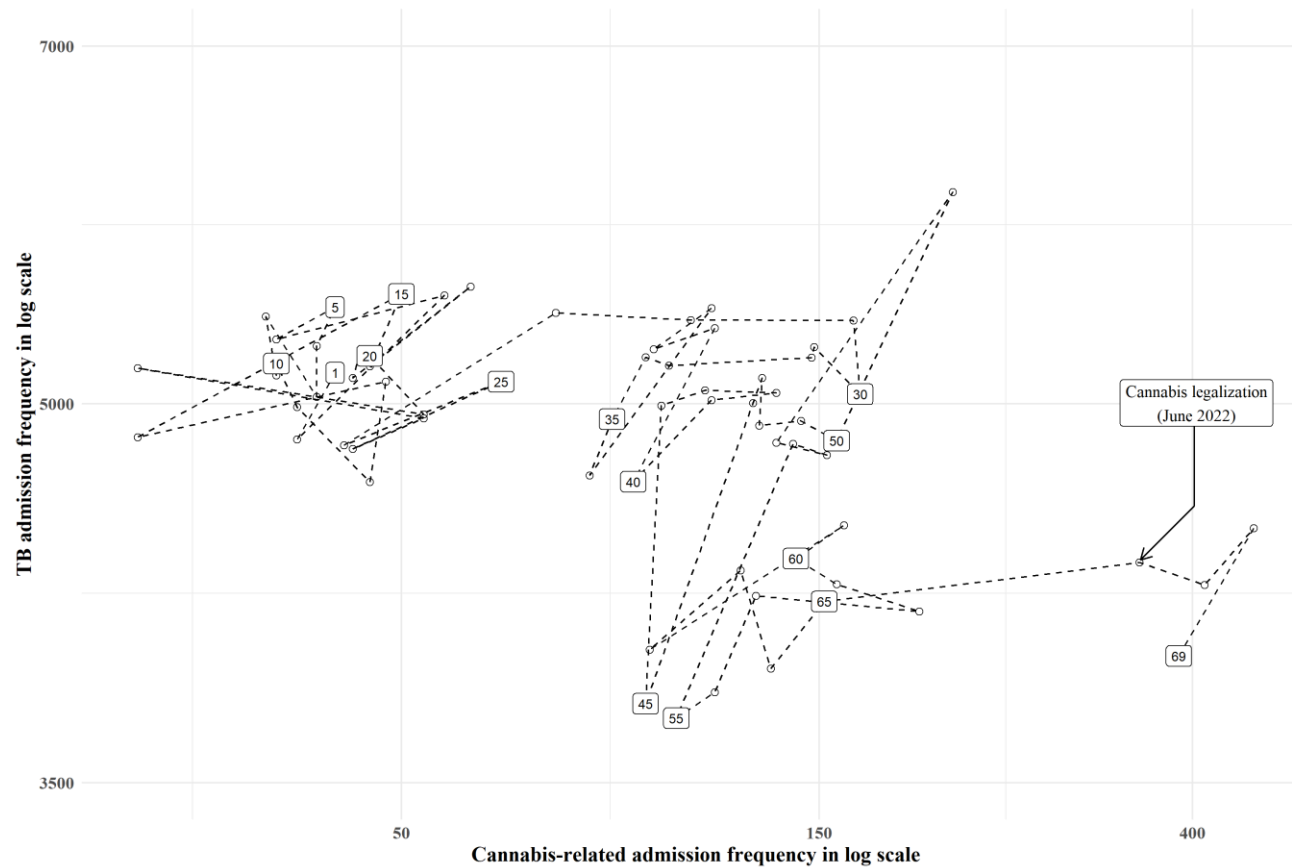


Figure 6 Chronological line plot of admission frequencies of cannabis-related and pulmonary TB diagnoses

Figure 6 illustrated dynamics of monthly admission frequency from cannabis related causes in the X axis and those from pulmonary TB admission of the same month in the Y axis. The number in the points denote the number of months of follow up: 1 denotes January 2017, 5 denotes May 2017, stepping up at 5-month interval until month 69 on September 2022. From month 1 to month 27, the frequencies of cannabis-related admissions were relatively low (below 55 admission per month), whereas those of TB admission were relatively high (above 4500 admission per month). During the COVID-19 pandemic, from month 28 to month 65, the number of monthly cannabis-related admission distributed in the middle of the X axis (from 82 to 213 admission per month), while pulmonary TB admission widely distributed on the Y axis. Finally, in month 66 to 69, the number of cannabis-related admission were on its peak contrasted to those of pulmonary TB. The trends of both admission types in log scale are separately displayed in Figure 7 and Figure 8.

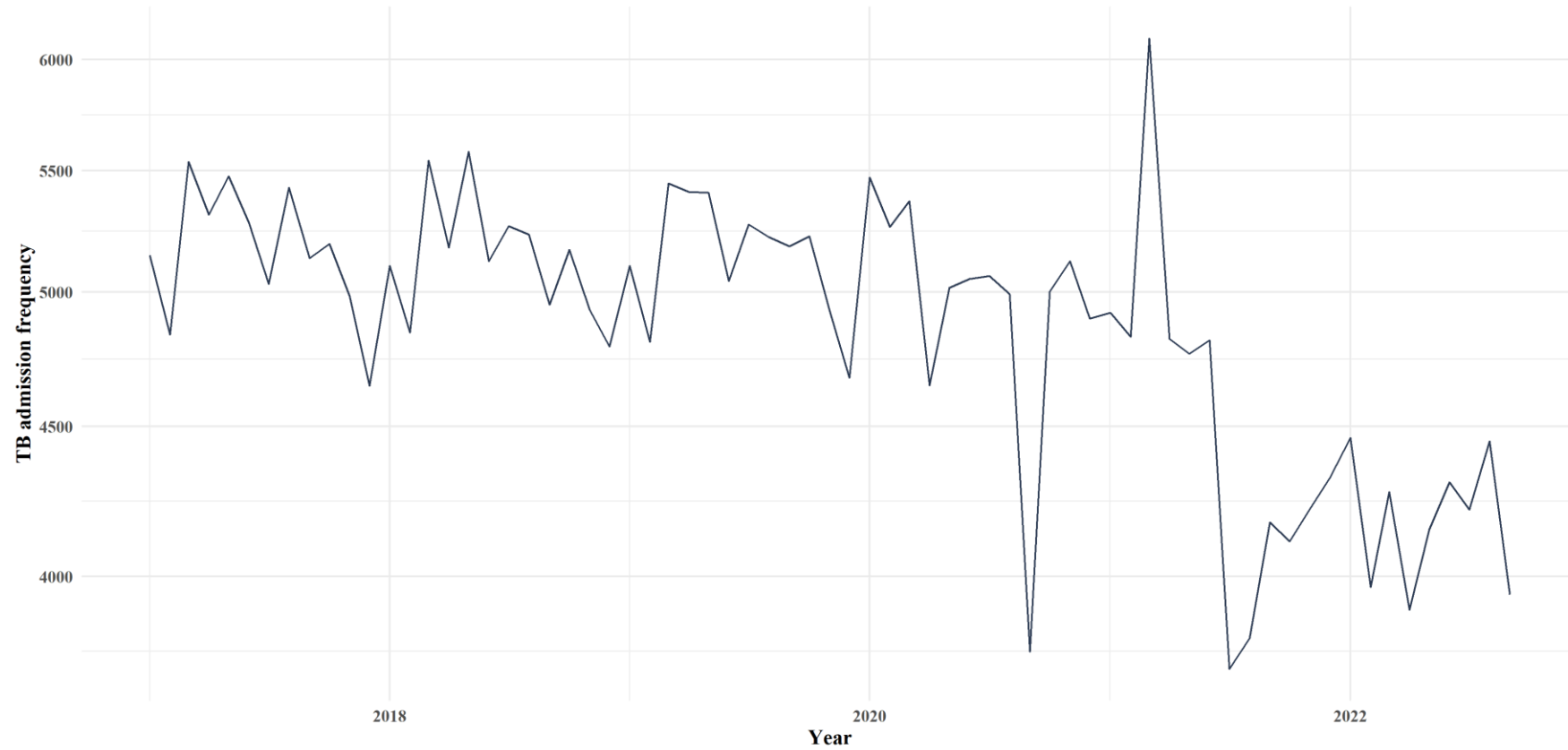


Figure 7 Trend of TB admission frequency in log scale



Figure 8 Trend of cannabis-related admission frequency in log scale

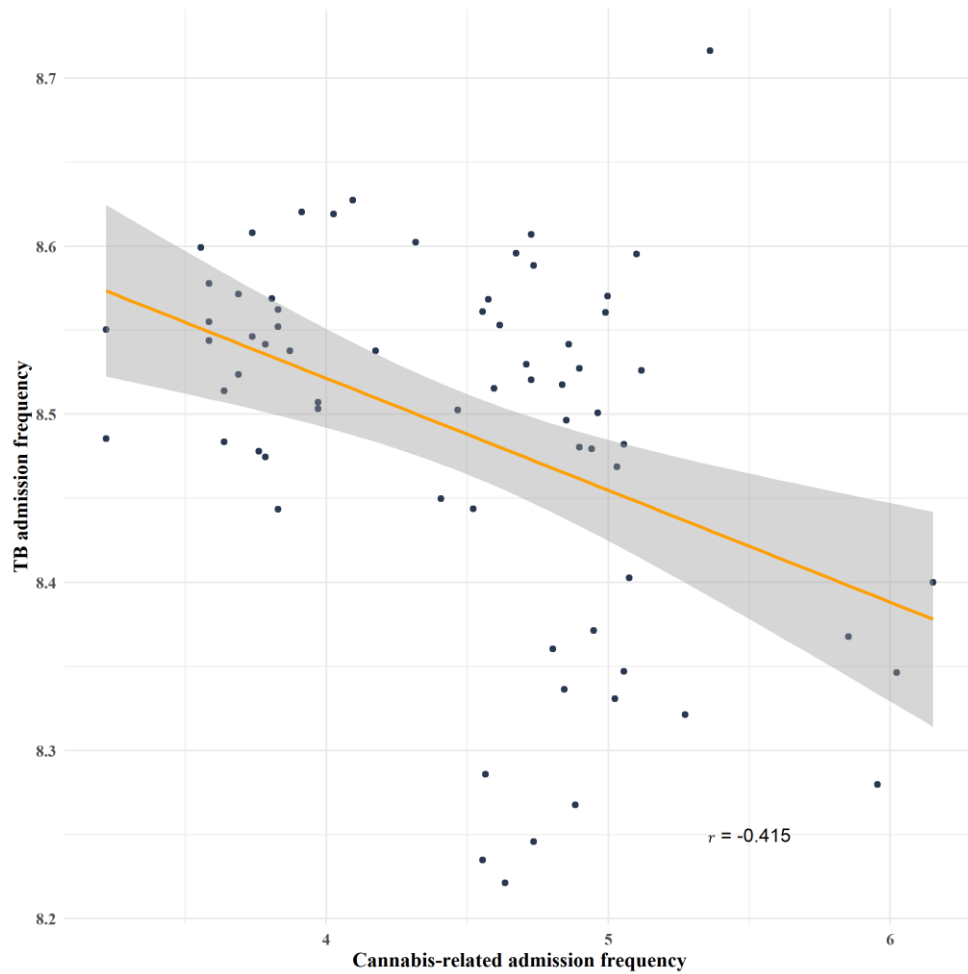


Figure 9 Scatter plot between two admission frequencies in log scale

Concerning the relationship between cannabis related admission and those of TB diagnoses, without accounting for lag aspect, negative correlation was detected between the two admission frequency; Pearson's correlation value of -0.415 with $P < 0.001$ was found as shown in Figure 9.

However, when investigating the relationship in each year of THIP data (Figure 10), we found weak to medium positive correlations were found between the two admission frequencies. A statistically significant correlation of 0.662 was detected in 2021 with $P = 0.019$.

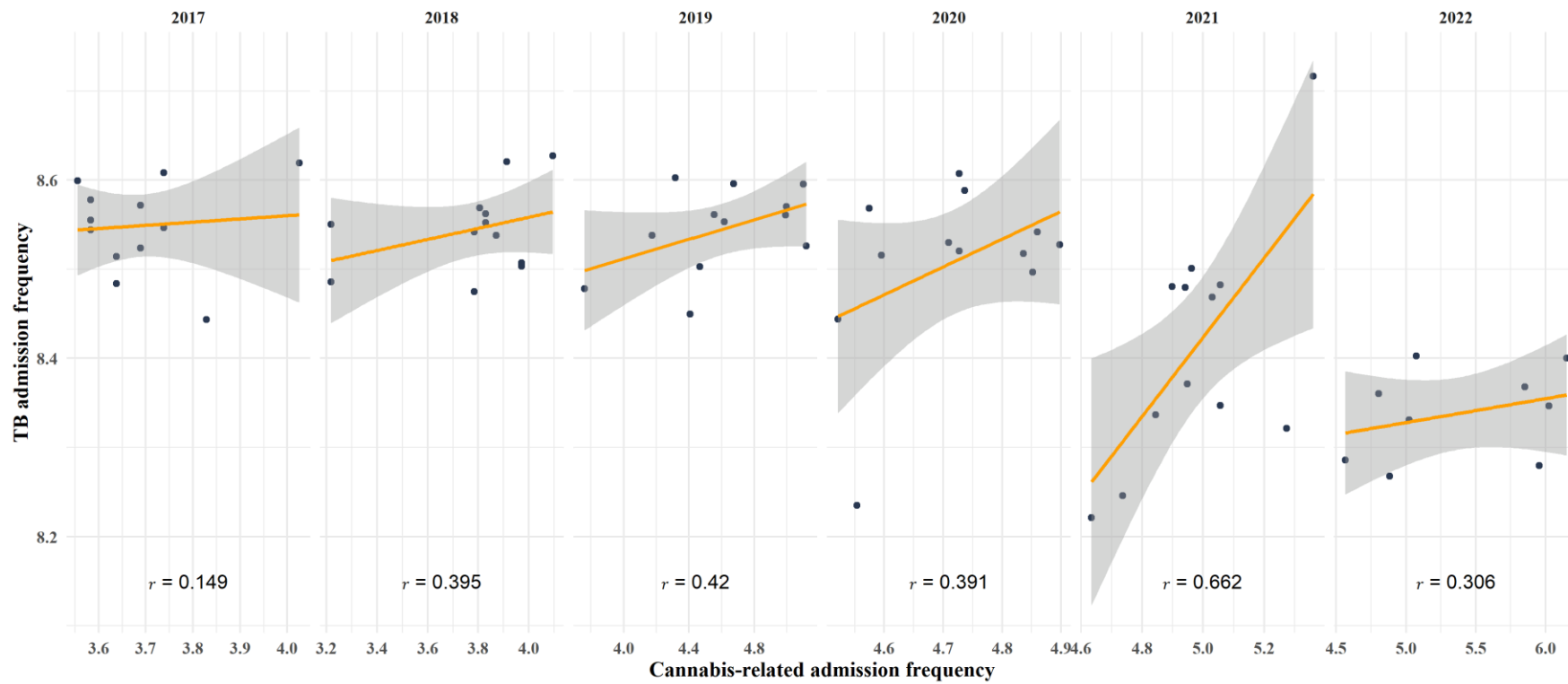


Figure 10 Scatter plot between two admission frequencies in log scale in each year of THIP data

Regarding, the lag aspect, the autocorrelation of TB and cannabis-related admission frequency are shown in Figure 11 and Figure 12. Significant positive autocorrelations were found in both admission types between lag 0 (current lag) and lag 12 (in TB admission) and lag 17 (in cannabis-related admission).

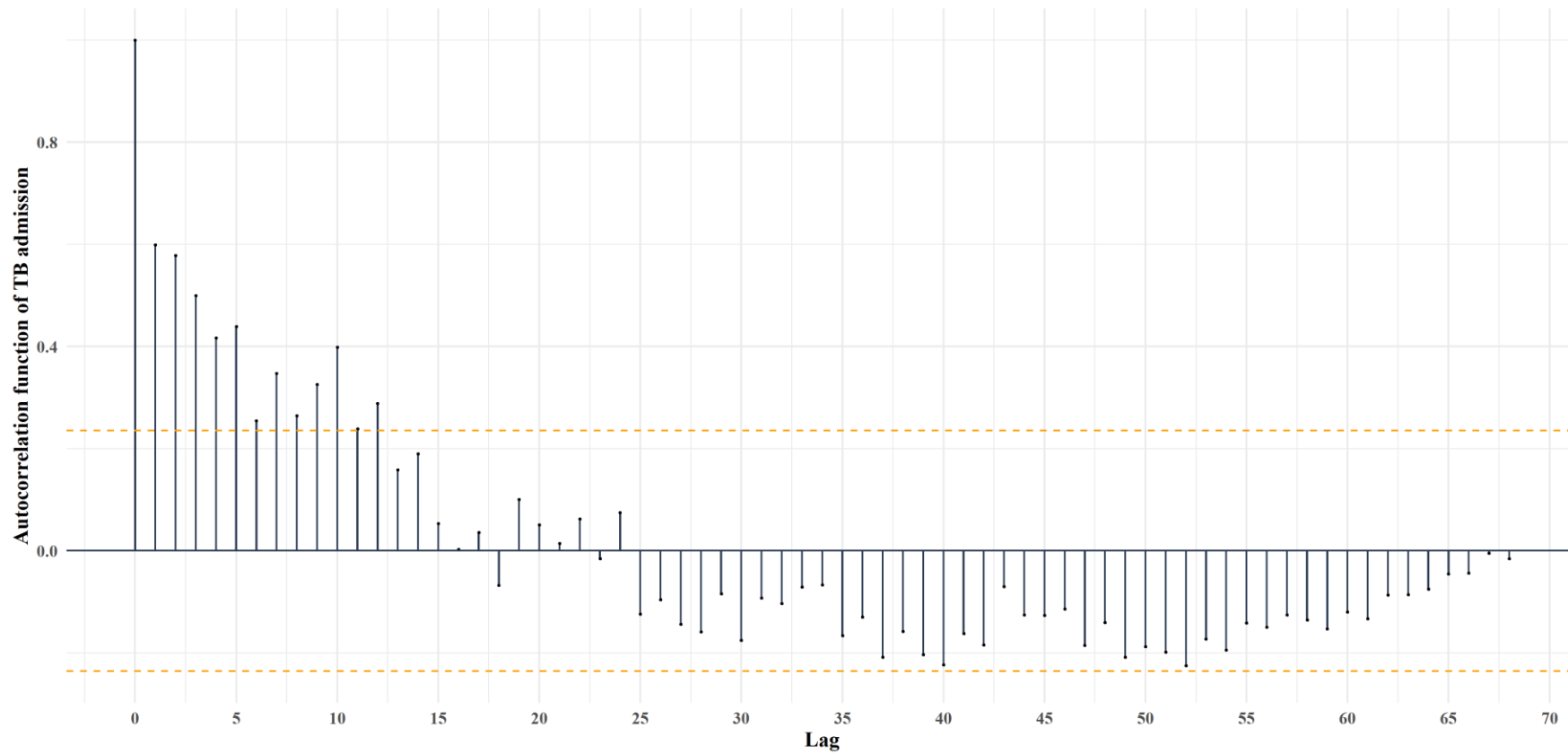


Figure 11 Autocorrelation function of monthly frequency of TB admission.

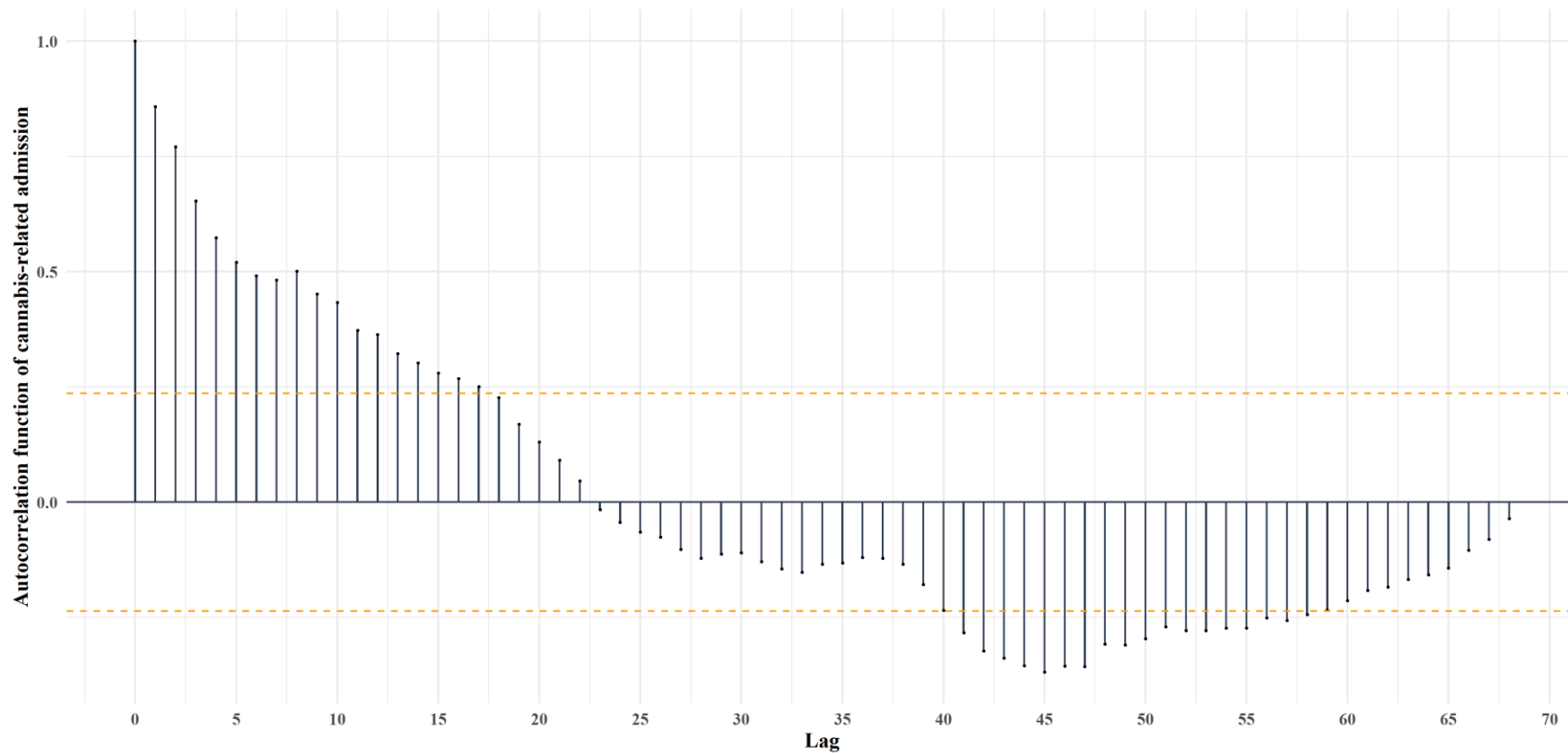


Figure 12 Autocorrelation function of monthly frequency of cannabis-related admission.

In addition, negative autocorrelations were found in monthly frequency of cannabis-related admission between lag of 41 to 58. All mentioned autocorrelations were outside the 95% confidence interval range.

Concerning the cross correlation between the two monthly admission frequencies, the cross correlation plot with the cannabis-related admission treated as an independent variable and TB admission treated an outcome variable is shown in Figure 13.

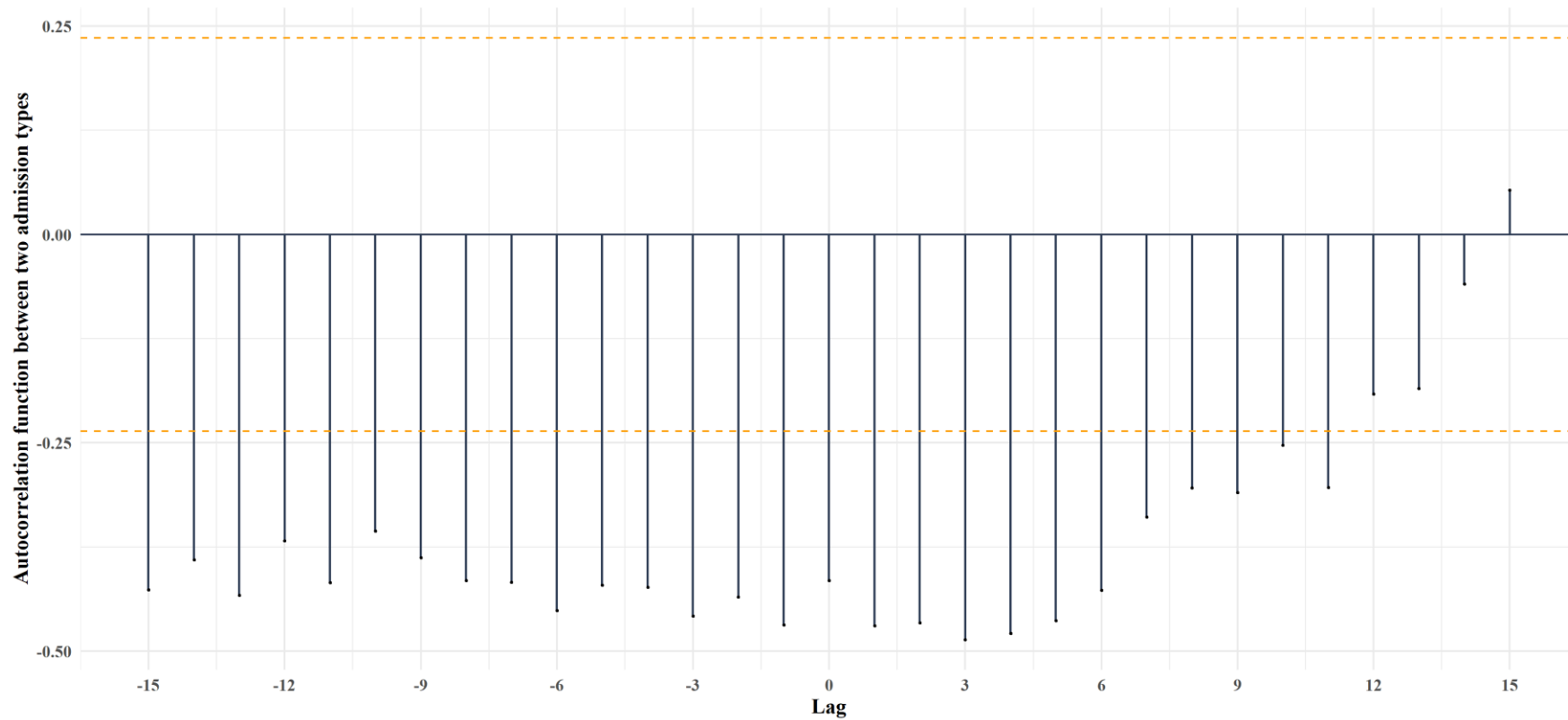


Figure 13 Cross correlation function between cannabis-related and TB admission monthly frequencies.

Statistically significant negative cross correlations were found in lag -15 to lag 11, indicating that both preceding and proceeding admission of frequencies of cannabis-related admissions had a negative correlation with those of TB admission. However, after adjusting for TB autocorrelation up to 12 lags (one year of past frequencies), the negative correlation turned out to non-statistical significance, while only the autocorrelation of TB in lag 10 possessed a statistically significant positive correlation of TB monthly admission frequency (Table 2).

Table 2 Autocorrelated distributed lag model table for TB monthly admission frequency.

Lags of variable	β	Std. Error	t value	P value
Monthly cannabis-related admission frequency				
Lag 3	-1.311	1.409	-0.930	0.358
Lag 6	-1.448	2.047	-0.707	0.484
Lag 9	1.984	2.237	0.887	0.381
Lag 12	-1.555	2.589	-0.601	0.552
Lag 15	0.248	1.892	0.131	0.896
Monthly TB admission frequency				
tb.count.1	0.272	0.170	1.598	0.119
tb.count.2	0.137	0.170	0.805	0.426
tb.count.3	0.160	0.167	0.956	0.345
tb.count.4	0.101	0.159	0.634	0.530
tb.count.5	0.062	0.158	0.392	0.697
tb.count.6	-0.159	0.174	-0.911	0.368
tb.count.7	0.057	0.160	0.358	0.722
tb.count.8	-0.051	0.156	-0.325	0.747
tb.count.9	0.082	0.176	0.467	0.643
tb.count.10	0.337	0.161	2.100	0.043
tb.count.11	-0.132	0.165	-0.797	0.430
tb.count.12	0.158	0.186	0.851	0.400

3.1.2 Spatial investigation

Without accounting for the temporal aspect, areas with high cannabis-related admission frequency were also found with high TB admission frequency. This correlation was found in both sub-region and superdistrict level as shown in Figure 14 and Figure 15.

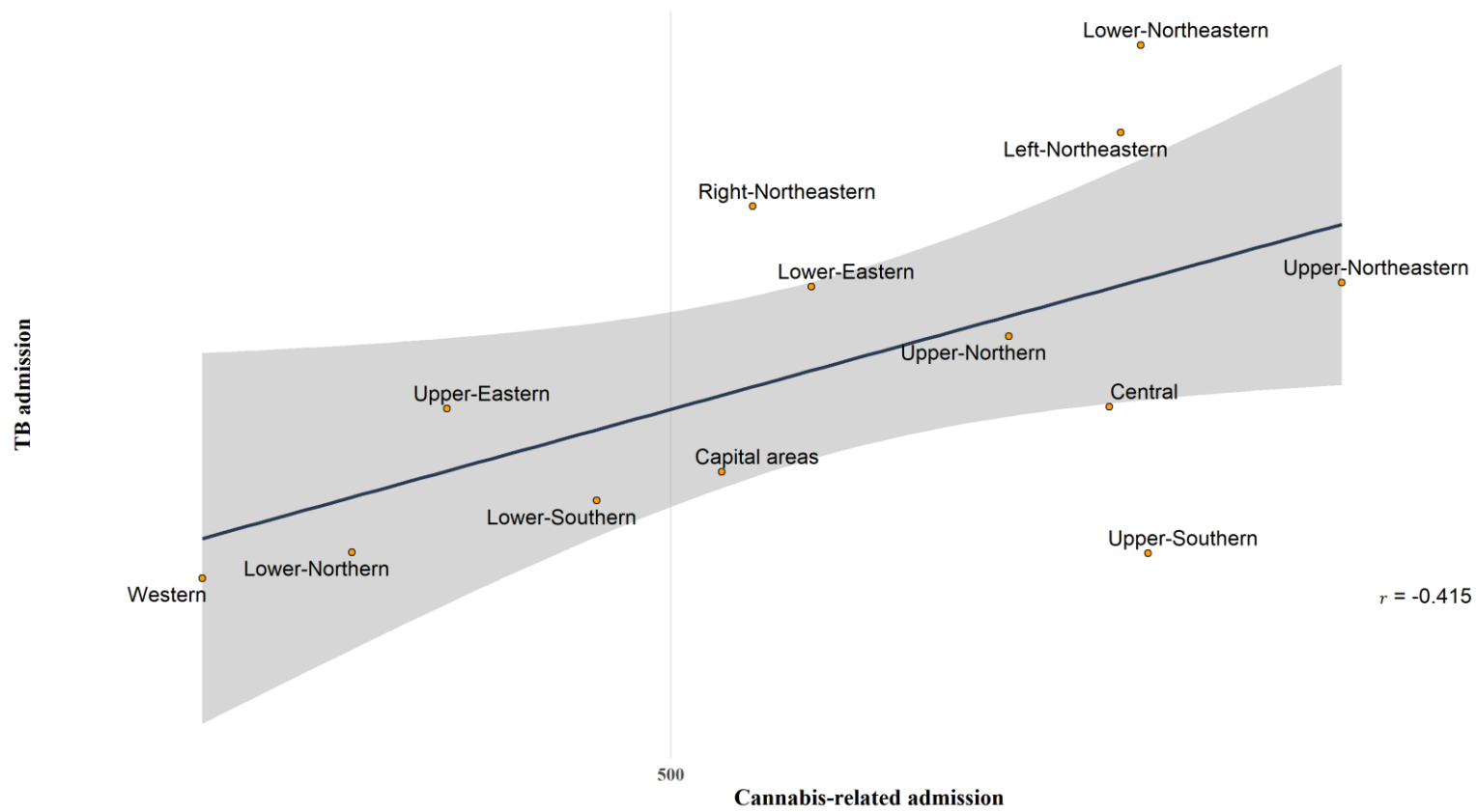


Figure 14 Scatter plot of admission frequencies aggregated into sub-region unit

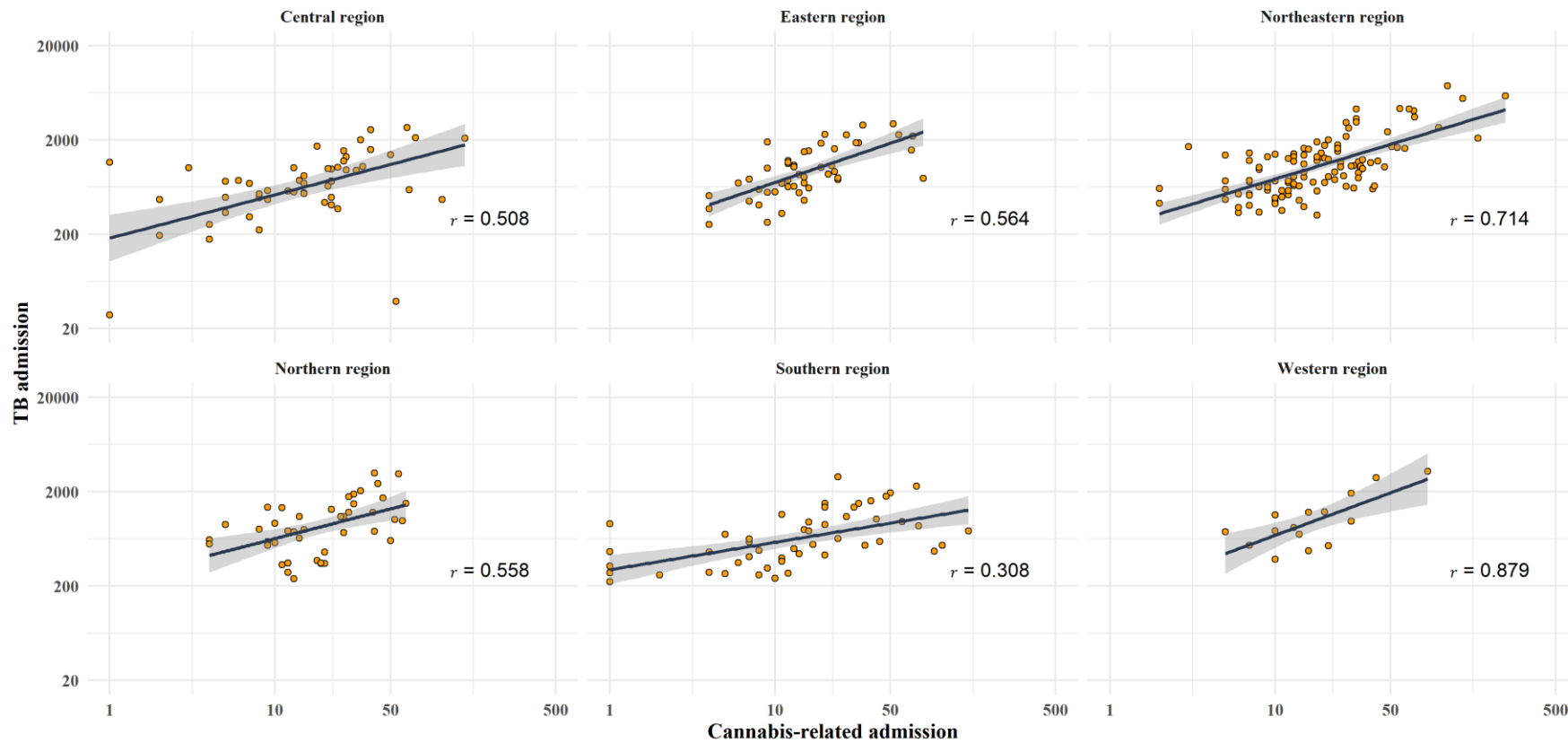


Figure 15 Scatter plot of admission frequencies aggregated into subdistrict unit of each stratified by region

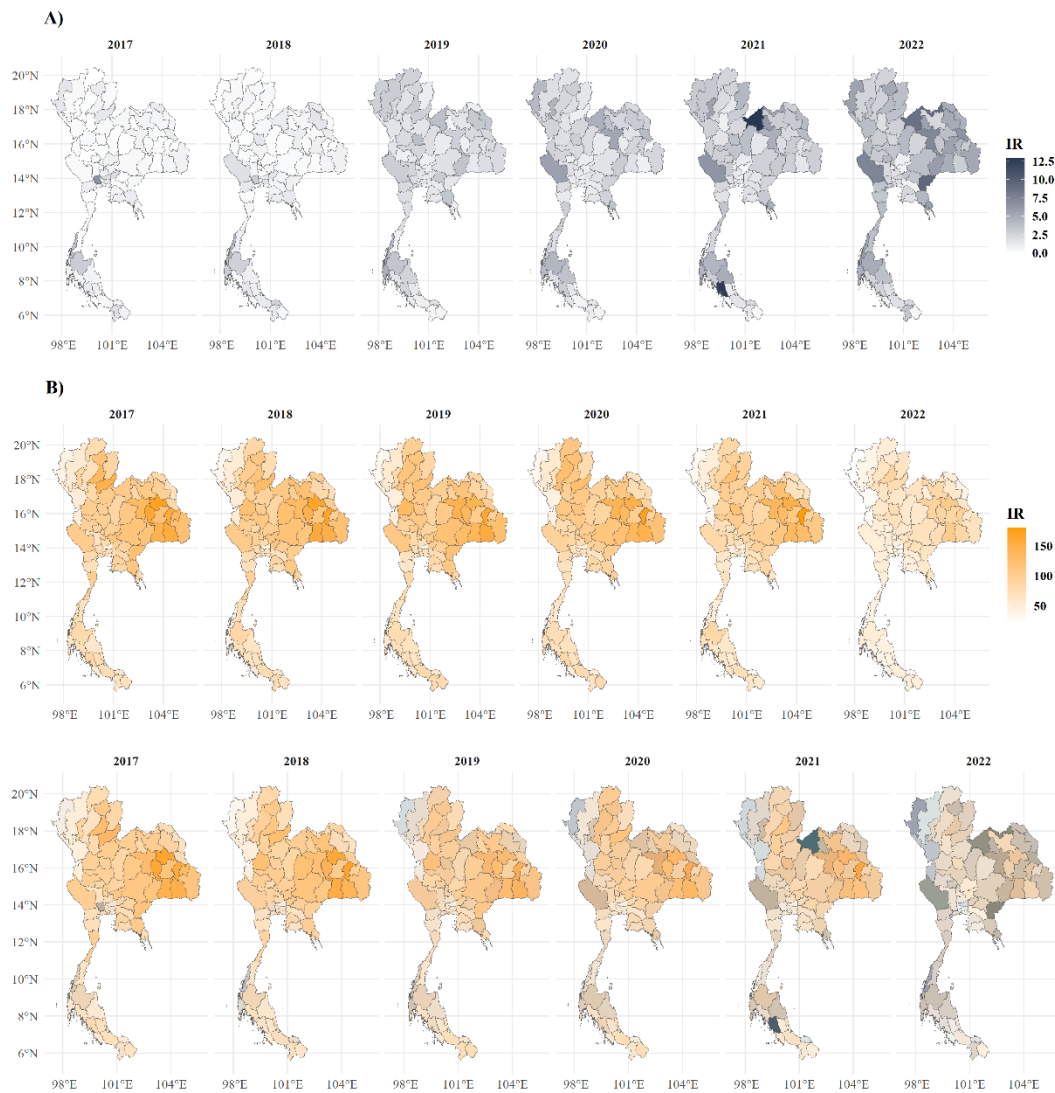


Figure 16 Thailand choropleth map based on the admission incidence rate per 100,000 population. A) cannabis-related causes, B) pulmonary TB, and C) the combination of both gradients.

Figure 16 illustrates the spatiotemporal changes of IDR of cannabis-related admission (16A), TB admission (16B), and the combination of in blue, red, and purple tones (16C). Distinct increases of cannabis admission were observed in the upper parts of Thailand, which eventually overtook the initial relatively high IDR in Surat Thani province in the middle of Southern Thailand. On the contrary, TB admission incidence remained highest in the Northeastern region throughout the years although the incidence tended to decline over time in all regions.

3.1.3 Demographic of in-patients

The flow diagram of data curation and cohort matching processes is shown in Figure 17. Throughout the 6-year period, 7,313 in-patients were admitted with cannabis-related causes recorded in their first data entry. The most common cannabis-related causes were “Mental and behavioral disorders due to use of cannabinoids” (83.5%) and “Poisoning, cannabis (derivatives)” (23%), with the diagnoses not being mutually exclusive. After excluding those co-diagnosed with pulmonary TB, 7,272 in-patients remained. Of these, 80 (1.1%) in-patients were deceased at the time of their first admission records.

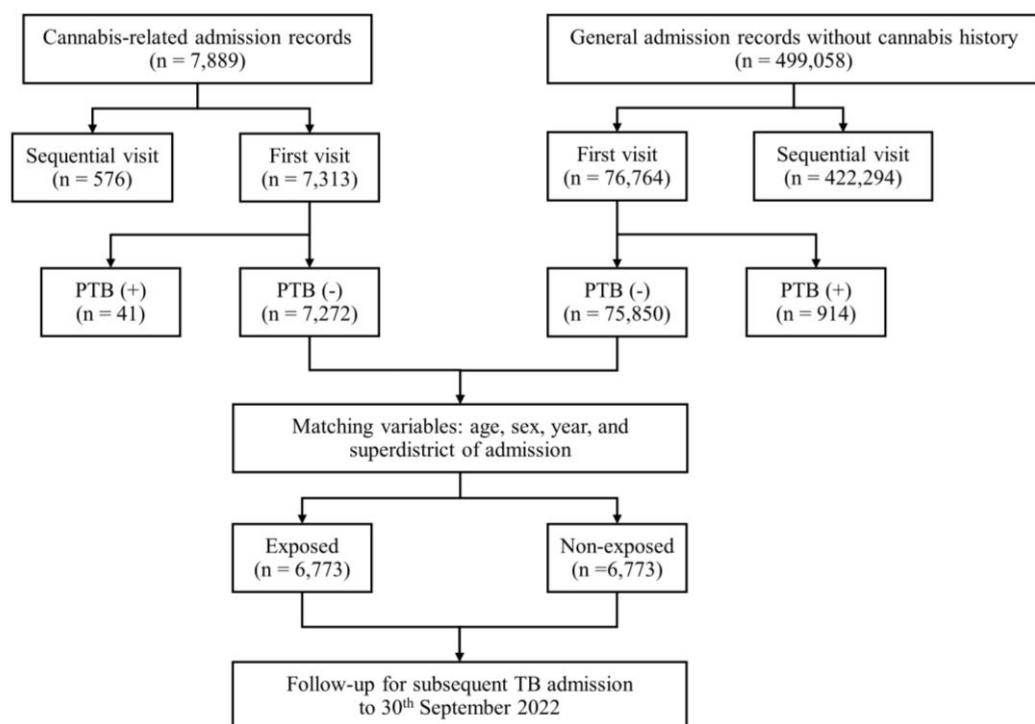


Figure 17 Flow diagram of data curation and matching processes.

We identified 37 subsequent pulmonary TB admissions among 23 in-patients, with 6 of these in-patients having more than one sequential TB admission. More than half (52.1%) of the 23 in-patients were admitted for TB within 10 months of their initial cannabis-related admission. Among the 23 in-patients, 78.26% were diagnosed with “Mental and behavioral disorders due to use of cannabinoids” on first admission, while “Poisoning, cannabis (derivatives)” was found in 26.09% of the patients. Other co-diagnoses occurring in > 10% of these in-patients included “Mental

and behavioral disorders due to use of alcohol” (17.39%), “Intentional self-poisoning by and exposure to narcotics and psychodysleptics” (13.04%), “Mental and behavioral disorders due to use of other stimulants, including caffeine” (17.39%), “Hypo-osmolality and hyponatremia” (17.39%), “Hypokalemia” (17.39%), “Pneumonia, unspecified” (13.04%), “Poisoning by and exposure to narcotics and psychodysleptics” (13.04%), and “Type 2 diabetes mellitus without complications” (13.04%).

For the control group, we obtained admission records of 75,850 general in-patients with no history of cannabis-related admission or co-diagnoses indicating pulmonary TB. Among these, 560 (0.7%) were deceased at the time of their first admission record. Regarding the matching of the two cohorts, we successfully matched 6,773 (93.1%) of the 7,272 in-patients diagnosed with cannabis-related causes with the general in-patients without a cannabis-related admission history or pulmonary TB in their first admission.

Table 3 Descriptive table of two cohorts

Variable	No history of cannabis-related admission	Admitted with cannabis-related causes	<i>p</i> value
Total	6773	6773	
Age			0.893 ^a
Median (IQR)	30 (21,47)	30 (21,47)	
Sex			1 ^b
Male	5746 (84.8)	5746 (84.8)	
Female	1027 (15.2)	1027 (15.2)	
Diabetes mellitus			< 0.001 ^b
No	6542 (96.6)	6465 (95.5)	
Yes	231 (3.4)	308 (4.5)	
Hypo-osmolarity			< 0.001 ^b
No	6610 (97.6)	6543 (96.6)	
Yes	163 (2.4)	230 (3.4)	
Hypokalemia			< 0.001 ^b
No	6099 (90)	5650 (83.4)	
Yes	674 (10)	1123 (16.6)	
Pneumonia			< 0.001 ^b
No	6651 (98.2)	6698 (98.9)	
Yes	122 (1.8)	75 (1.1)	

^a Mann-Whitney U test, and ^b Chi-squared test

Table 3 summarizes the background information of the cannabis-related admission cohort with their matched pairs. The distributions of age and sex were well-

matched, with a pre-dominance of young adults and male sex. The control participants were less likely to have metabolic comorbidities, such as diabetes mellitus, hypo-osmolality and hypokalemia, but were more likely to have pneumonia.

3.1.2 Comparison of incidence density rates

Table 4 presents various follow-up outcome variables in the univariate analysis format. The univariate analyses revealed a shorter interval between the first admission and the subsequent TB admission and higher IDR in the case group. However, none of these differences reached statistical significance ($P < 0.05$) in any of the analysis methods used.

Table 4 Comparison of variables related to pulmonary TB admission between cohorts

Variable	No history of cannabis-related admission	Admitted with cannabis-related causes	<i>P</i> value
Total	6773	6773	
Individual level			
Frequency of subsequent TB admission			0.392 ^a
0	6760 (99.8)	6751 (99.7)	
1	8 (0.1)	16 (0.2)	
2	3 (0)	3 (0)	
3	1 (0)	0 (0)	
4	0 (0)	1 (0)	
5	1 (0)	2 (0)	
Time until first subsequent TB admission (in-month)			0.049 ^b
Median (IQR)	4.1 (0.4 - 13.5)	11.4 (4.0 – 32.7)	
Population level			
Frequency of subsequent TB admission			0.087 ^c
Frequency	22	36	
Follow-up person year			
Median (IQR)	1.6 (0.5,3.1)	1.7 (0.5,3.2)	

Incidence density rate per person year per 100,000 population			0.087 ^c
IDR	165.9	267.6	

^aFisher's exact test, ^bMann-Whitney U test, and ^cExact Poisson test

Table 5 summarizes the results from the Cox regression for subsequent TB admission, including the HR and its 95% CI. The HR of the cannabis cohort was not significant (1.48, 95% CI: 0.74,2.96). Young age (< 40 years old), having diabetes mellitus, hypo-osmolarity, and pneumonia in the first admission were statistically significant predictors for subsequent pulmonary TB admission.

Table 5 Hazard ratio table.

Variable	Hazard ratio	95% CI	P value
History of cannabis-related admission (ref = no)			0.268
Yes	1.48	(0.74,2.96)	
Age group (ref = < 40 years old)			0.002
≥ 40 years old	3.45	(1.6,7.43)	
Sex (ref = female)			0.055
Male	4.11	(0.97,17.51)	
Diabetes mellitus (ref = no)			0.001
Yes	4.22	(1.77,10.08)	
Hypo-osmolarity (ref = no)			0.003
Yes	4.39	(1.67,11.53)	
Hypokalemia (ref = no)			0.561
Yes	0.76	(0.29,1.94)	
Pneumonia (ref = no)			< 0.001
Yes	10.12	(3.92,26.12)	

3.2 Result of case-control study

3.2.1 Demographic of case and control groups

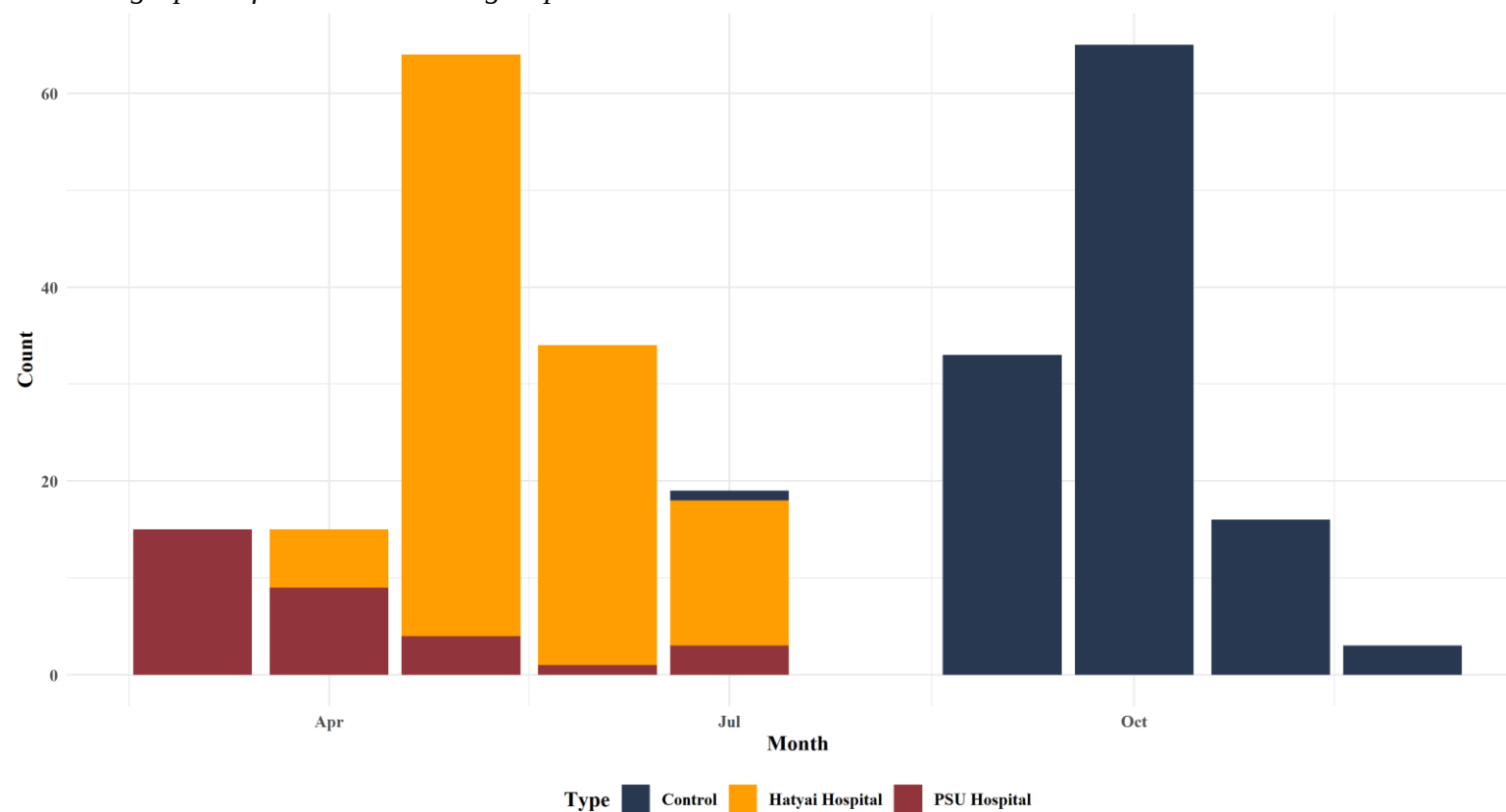


Figure 18 Collection timeline of case-control study

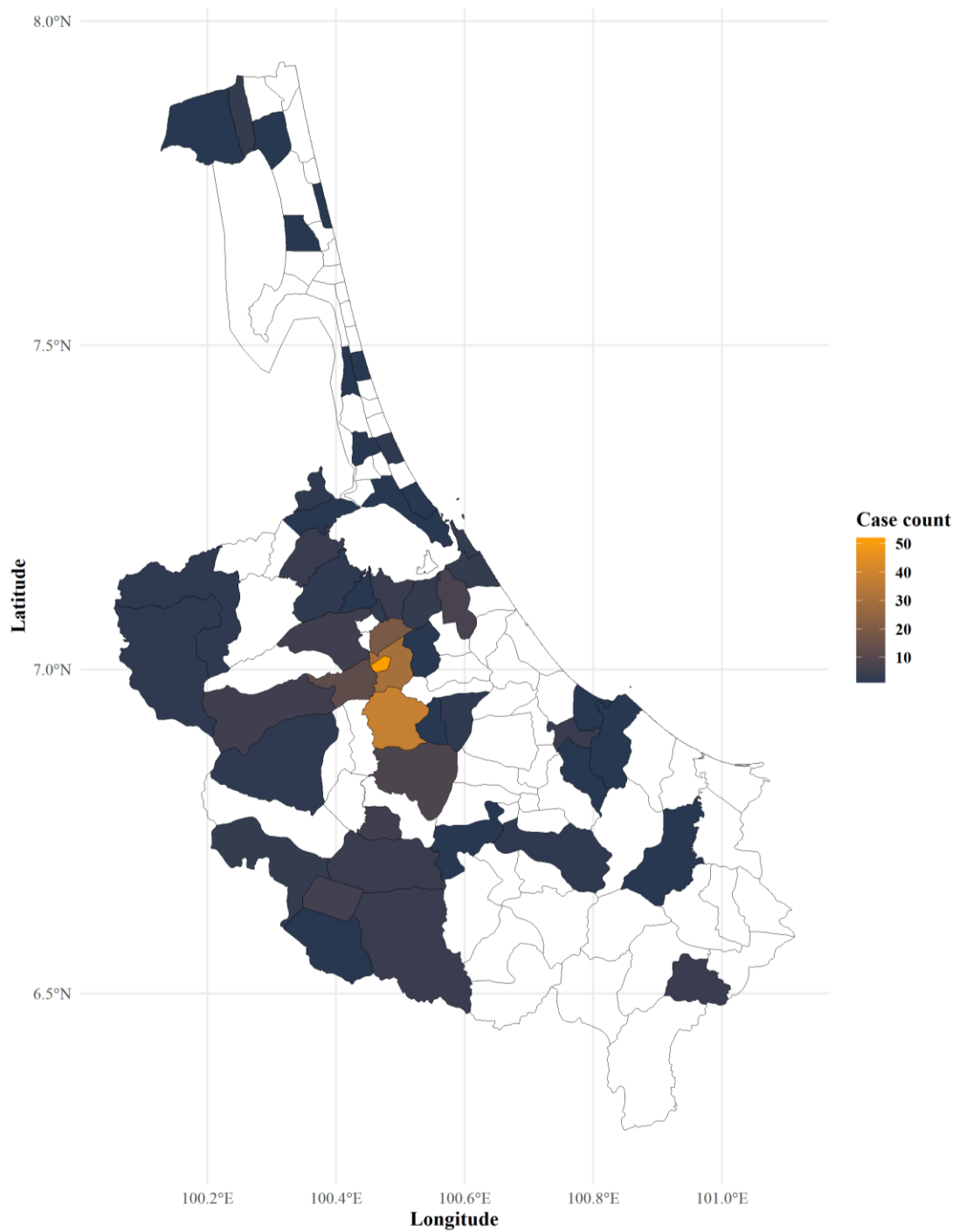


Figure 19 Distribution of TB cases in Songkhla province.

The collection period for the case-control study spanned from March to December of 2023 as shown in Figure 18. Cases were collected during March to July of 2023. The majority of the cases came from Hatyai Hospital (78%). The peak of case

collection period was in May of 2023. While the cases were distributed throughout the province, hotspot of TB cases were found in the urban sub-districts including Hat Yai, Ban Phru, Kho Hong, Khlong Hae, and Khuan Lang as shown in Figure 19.

Concerning the control group, we initially tested the control data collection processes in late July and fully conducted control collection between September and December of 2023.

Of 152 eligible TB patients, 148 patients gave their consent, a response rate of 97.4%. We obtained 117 age-sex-community matched controls from the health volunteer recruitment. As these controls were readily recruited by the health workers, we did not have the information on the number of eligible subjects and the response rate. Table 2 shows the results of the univariate analysis. The patients in the case group were generally younger than the controls, had a lower education level, and had a higher proportion of unemployed individuals and office workers. Substance use was more common in the case group, with a significantly higher proportion of individuals reporting ever-drunk alcohol and tobacco, along with a higher prevalence of current smoker. Additionally, the monthly cigarette dosage was significantly higher in those who had smoked tobacco.

Table 6 Descriptive table stratified by case and control group status

Variables	Control	Case	P value
Total	117	148	
Age			0.097 ^a
Mean (SD)	55.1 (15.9)	51.8 (16.2)	
Age group			0.351 ^c
≤ 40 years old	22 (18.8)	38 (25.7)	
41 - 60 years old	59 (50.4)	64 (43.2)	
> 60 years old	36 (30.8)	46 (31.1)	
Sex			0.492 ^c
Male	71 (60.7)	97 (65.5)	
Female	46 (39.3)	51 (34.5)	
Education			0.042 ^c
< High school	54 (46.2)	88 (59.5)	
≥ High school	63 (53.8)	60 (40.5)	
Occupation			0.065 ^c
Business owner/freelance	31 (26.5)	22 (14.9)	

Laborer	32 (27.4)	40 (27)	
Office worker	12 (10.3)	26 (17.6)	
Retired/unemployed/student	42 (35.9)	60 (40.5)	
Monthly income (thousand baht) (n = 235)			0.388 ^b
Median (IQR)	6 (0,15)	8 (0,15)	
Ever drank alcohol			0.004 ^c
No	54 (46.2)	42 (28.4)	
Yes	63 (53.8)	106 (71.6)	
Current drinker			0.707 ^c
No	78 (66.7)	103 (69.6)	
Yes	39 (33.3)	45 (30.4)	
Monthly drink count (n = 123)			0.004 ^b
Median (IQR)	24 (10,60)	60 (16,120)	
Ever smoke			< 0.001 ^c
No	69 (59)	49 (33.1)	
Yes	48 (41)	99 (66.9)	
Current smoker			0.035 ^c
No	90 (76.9)	95 (64.2)	
Yes	27 (23.1)	53 (35.8)	
Monthly cigarette count (n = 137)			0.004 ^b
Median (IQR)	155 (55,480)	300 (150,600)	

^aStudent's t-test

^bMann-Whitney U test

^cChi-square test

3.2.2 Active pulmonary TB association with cannabis use

The details of cannabis consumption among cases and controls are summarized in Table 3. Eleven percent of the controls were current cannabis users, whereas nearly 19% had used cannabis at least once before, most commonly through oral consumption (12.8%). Cannabis consumption among cases and controls was not significantly different among current users, quitting age, usage frequency, oral consumption, and health reasons behind cannabis use. Cases were more likely to have a history of ever using cannabis and smoking cannabis via a bong or joint, especially when sharing cannabis during the session. We obtained the ventilation status from 37

out of 38 bong smokers and 30 out of 33 joint smokers. Smoking in well-ventilated areas was reported by 33 (89.2%) of bong smokers and 26 (86.7%) of joint smokers.

Table 7 Comparison of cannabis use detail among cases and controls.

Variables	Control	Case	P value
Total	117	148	
Current user (within 1 year)			0.303 ^b
No	104 (88.9)	138 (93.2)	
Yes	13 (11.1)	10 (6.8)	
Ever used cannabis			0.002 ^b
No	95 (81.2)	94 (63.5)	
Yes	22 (18.8)	54 (36.5)	
<i>History of cannabis use</i>			
Starting age (n = 76)			0.064 ^a
Median (IQR)	22.5 (18.5,49.2)	19 (18,21)	
Year since last use (n = 49)			0.736 ^a
Median (IQR)	15 (2,38)	10 (3,26.5)	
Frequency (n = 76)			0.366 ^b
Occasionally	12 (54.5)	20 (37)	
Regularly	4 (18.2)	15 (27.8)	
Once or twice	6 (27.3)	19 (35.2)	
Usage via bong smoking			< 0.001 ^c
No	111 (94.9)	116 (78.4)	
Smoke only	1 (0.9)	1 (0.7)	
Smoke and share	5 (4.3)	31 (20.9)	
Usage via joint smoking			0.005 ^b
No	111 (94.9)	121 (81.8)	
Smoke only	3 (2.6)	11 (7.4)	
Smoke and share	3 (2.6)	16 (10.8)	
Usage via oral consumption			0.390 ^b
No	102 (87.2)	135 (91.2)	
Yes	15 (12.8)	13 (8.8)	
<i>Extra information among users</i>			
Paid for cannabis (n = 51)			
No	15 (93.8)	20 (57.1)	
Yes	1 (6.2)	15 (42.9)	
Monthly spending in THB (n = 16)			

Median (IQR)	50	300 (100,450)	
Using cannabis for health reasons (n = 11)			
To increase appetite	0 (0)	4 (57.14)	
To treat insomnia	1 (25)	2 (28.57)	
To freshen up	0 (0)	1 (14.29)	
For unknown medicinal benefits	2 (50)	0 (0)	
Missing	1 (25)	0 (0)	

^aMann-Whitney U test

^bChi-square test

^cFisher's exact test

Table 8 compares the AICs of all prediction models for active pulmonary TB from various types of cannabis use with different combinations of covariates. Owing to the collinearity between smoking via the bong and joints, they were separately analyzed and displayed. Row A displays the results from ever-used cannabis, while rows B and C display those from smoking cannabis via bong and joint, respectively. Model 1, incorporating all exposure variables, showed a significant crude odds ratio that remained significant after age, sex, education and occupation were included (Model 2). Of all the models, model 3B yielded the lowest AIC value and was therefore used to calculate the ORs and population-attributed fractions.

Table 9 displays the ORs (95% CI) of variables in model 3B. The effects from smoking and sharing cannabis via a bong were independently significant, as were the effects from tobacco smoking. The levels of ORs between smoking and sharing cannabis via a bong and tobacco smoking were similar (4.22; 95% CI: 1.47–12.07 and 4.36; 95% CI: 1.97–9.65, respectively). The percentages of PAF were 12.16 and 12.62 for the respective categories. Based on the likelihood ratio tests, all other independent variables in the model, except age, were also statistically significant. Using the same covariates, the adjusted OR for oral consumption cannabis was (0.65; 95% CI: 0.28–1.52).

Table 8 Comparison of AIC values among predicting models for active pulmonary TB

Key independent variables	Odds ratio		
	Model 1	Model 2	Model 3
Included covariates	-	Age group, sex, education, and occupation	Model 2 & history of tobacco smoking
A) Ever used cannabis (ref = never) AIC	2.48 (1.40,4.39)* 357.46	2.71 (1.47,5.01)* 353.61	2.00 (1.05,3.81)* 339.13
B) Smoking cannabis via bong (ref = no) Smoke only Smoke and shared AIC	0.96(0.06,15.49) 5.93 (2.23,15.80)* 351.36	0.95 (0.06,16.23) 6.35 (2.28,17.67)* 349.76	0.72 (0.04,12.38) 4.22 (1.47,12.07)* 336.78
C) Smoking cannabis via joint (ref = no) Smoke only Smoke and shared AIC	3.36 (0.91,12.37) 4.89 (1.39,17.24)* 358.31	4.50 (1.15,17.59)* 5.45 (1.46,20.34)* 353.63	3.32 (0.84,13.22) 3.42 (0.89,13.05) 339.23

*Statistical significance at $P < 0.05$

Table 9 Odds ratios of active pulmonary TB

Variable	OR (95% CI)	<i>P</i>_{Wald's test}	<i>P</i>_{LR-test}	PAF (%)
Smoking cannabis via bong (ref = no)			0.011	
Smoke only	0.72 (0.04,12.38)	0.823		0
Smoke and shared	4.22 (1.47,12.07)	0.007		12.16
Age (ref = ≤ 40 years old)			0.169	
41 - 60 years old	0.51 (0.24,1.07)	0.077		
> 60 years old	0.5 (0.21,1.17)	0.109		
Sex (ref = male)			0.034	
Female	2.28 (1.04,5.04)	0.041		
Education (ref = $\geq$ High school)			0.023	
< High school	2.02 (1.1,3.72)	0.024		
Occupation (ref = business owner)			0.038	
Laborer	1.1 (0.47,2.55)	0.83		
Office worker	3.55 (1.36,9.27)	0.01		
Retired/unemployed/student	1.65 (0.75,3.61)	0.212		
Ever smoked tobacco (ref = no)	4.36 (1.97,9.65)	< 0.001	< 0.001	12.62

3.3 Discussion

While the monthly frequencies of pulmonary TB admissions declined, those that were cannabis-related increased from 2017 to 2022. The increase in cannabis-related admissions was classified into three time periods. From January 2017 to March 2019, the monthly admissions ranged from 25 to 75 nationally. From April 2019 to May 2022, the monthly admissions ranged from 82 to 213 nationally. In June 2022, recreational cannabis was legalized; the number of admissions then further increased to over 348 national monthly admissions until the last data point available in September of 2022. Both cannabis and TB admissions shared a geographical hotspot in the Northeastern region.

In the analysis of anonymized in-patients, the risk of subsequent TB admission among those previously admitted for cannabis-related issues was not significantly higher than that for those admitted due to other causes or diseases.

The steady decline in TB admissions during the pre-COVID-19 period may partially reflect the success of the National End TB Program³³. The sharp decline during the COVID-19 period, however, is likely attributable to the disruption of the health care system from the pandemic. Similar declines in notified cases were reported in China^{34,35}, the USA³⁶, and several lower-and middle income countries³⁷. However, rebounds in notified cases after the pandemic subsided was also detected in several regions, including the Americas and South-East Asia³⁷. In addition, several reports showed an increase in TB mortality while the notification rate declined during the pandemic^{34,38,39}.

Our data suggest that legalization of recreational cannabis may increase the incidence of hospitalization from cannabis use. Availability of cannabis outlets was shown to lead to a higher likelihood of cannabis consumption⁴⁰, thereby increasing the chance of hospital admission. Similar findings of increased cannabis consumption after legalization have previously been reported; Martins et al. detected an increase in past-year cannabis use of 1–3.7% in the US⁴¹. Following the legalization of cannabis in Canada, Sandhu et al. reported that 20% of Canadians evinced an increased interest in trying cannabis⁴², and the prevalence of cannabis use increased by 5.6%⁴³. Similarly,

increased hospitalization rates due to cannabis were also reported in Canada after cannabis commercialization during the pandemic⁴⁴.

After accounting for the yearly (Figure 10) or monthly (Table 2) decline in TB admissions, the transition from a significant negative correlation to a non-significant correlation between the two admission types provided no evidence of a link, either concurrently or with a lag.

In the spatial aspect, both TB and cannabis-related admissions were highest in the Northeastern region of Thailand, which is well-known for its poverty and general ill health^{45,46}. These factors may potentially explain the geographical association^{47,48}. However, the opposite trend suggests a non-causal association between cannabis use and TB admissions.

When analyzing individual-level associations, we did not detect an increased risk of subsequent TB admission in patients priorly admitted for cannabis-related causes. Therefore, this study does not provide evidence to support cannabis consumption as a risk factor for pulmonary TB hospitalization.

In a non-hospitalized context, a contact-tracing study in Queensland reported an association between sharing cannabis pipe with TB index case and transmission of TB⁴⁹. Thus, so far, only instrument sharing has been identified as a risk factor for TB transmission. Hypotheses related to respiratory tract damage causing depletion of local immunity remain unsupported by evidence. However, the lack of association found in this study does not provide sufficient grounds for policy implications regarding cannabis regulation, given the need to consider other adverse health effects of cannabis that are beyond the scope of this investigation.

The limitations of this secondary data analysis study stemmed from the usage of a national in-patient data registry. We could not rule out possible past TB status; thus, the outcomes in this study were either new TB (either from new infection or from reactivation of latent TB) or relapse TB cases, with symptoms severe enough to require hospitalization. Patients in cannabis-related admission cases may exhibit different settings and behaviors compared to the general cannabis consumer population. Thus, the results should be interpreted with caution. Moreover, the use of

hospitalization data based on ICD-10 codes limited us in acquiring information regarding route, type, duration, and frequency of cannabis consumption. This information is vital when assessing associations between infection and substance use, as the pathogenesis can vary depending on how the substance was consumed. Similar limitations were also highlighted in another study investigating the impact of cannabis consumption on primary spontaneous pneumothorax⁵⁰. Since increased inflammation of the respiratory tract and exposure to MTB are more likely to result from smoking cannabis rather than consuming it in edible form^{49,51}.

Regarding, the case-control study, our TB cases were more likely to have a lower SES than community-matched controls in terms of education. They were also more likely to consume alcohol and tobacco. Univariate analysis showed that both bong and joint sharing were associated with the disease. However, multivariate analysis suggested that bong sharing was a stronger risk factor, with an OR and PAF close to those of smoking tobacco.

Our study conformed with most previous research that found that low SES^{26,47,52} and tobacco smoking were risk factors for TB⁵³. These factors are associated with addiction, including cannabis use, particularly in Thailand. Therefore, it is important to adjust for these factors when assessing the effects of cannabis in increasing pulmonary TB risk.

In this study, we tested the effects of different forms of cannabis. Oral consumption was not a risk factor, although it was the most common form of consumption. Leaves are commonly added to food to enhance its flavor and appetite. No plausible mechanism linking this to the risk of pulmonary TB was evident.

Without instrument sharing, we do not have enough evidence to suggest that cannabis smoking has the same effect as tobacco smoking. Notably, non-shared cannabis smoking is uncommon. This lack of evidence is likely explained by the small sample size of the non-sharing groups. Thus, we could not test the hypothesis that cannabis causes respiratory inflammation, which leads to increased TB risk.

In our setting, bong sharing was a significant risk factor for TB, which corresponds well with that reported in a previous contact-tracing study⁴⁹.

In general, bong smoking involves a behavior known as puff smoking, which is referred to as the Beirut smoking protocol⁵⁴. Puff smoking is well-established to generate a high volume of aerosol along with harmful particles⁵⁵⁻⁵⁷. Two plausible mechanisms behind the increased TB risk from bong smoking, which may not be found in other smoking methods, are: 1) longer duration of smoking/sharing sessions, and 2) increased MTB droplet viability due to humidity.

The duration of bong smoking can last as long as an hour⁵⁸, which is drastically longer compared to the average 5-minute cigarette smoking session⁵⁹. Combined with reports that MTB can remain viable in aerosol droplets for up to 60 minutes⁶⁰, the longer exposure duration from bong smoking sessions could explain the increased TB exposure risk, especially if the smoker shares the bong with a TB index case present during the session.

Another mechanism that could facilitate the spread of MTB through bong smoking is the process of passing the smoke through water, which generates aerosol water along with the smoke⁶¹. These aerosol waters could increase both the viability and transmissibility of MTB droplet nuclei. A study by Barasona *et al.* reported significantly higher detection of *Mycobacterium tuberculosis* complex in areas with water points⁶². Furthermore, increased humidity from aerosol water could enhance the dispersal of respiratory droplets containing MTB bacteria⁶³.

However, this evidence only supports mechanisms related to the air suspension of TB droplet nuclei, as TB cannot be transmitted through kissing or sharing saliva or instruments like cups or toothbrushes⁶⁴. Therefore, reusing a bong for smoking sessions may not lead to increased TB transmission risk from remaining saliva on the instrument unless it is reusing unwashed bong of which the TB index case directly coughs and deposits TB droplets on the mouthpiece of the bong. This route of transmission is plausible, as TB droplets have been reported to remain viable for up to a year in soil⁶⁵, and for months on dry surfaces⁶⁶.

Unfortunately, bong sharing is a socializing activity among cannabis smokers. Aiding by the plausible mechanisms stated above, aerosol droplets produced by a smoker can enter the bong cavity from the coughing of a patient with active pulmonary TB and be inhaled by the sharer shortly thereafter. Conversely, although more than 85% of bong and joint cannabis smokers were reported to smoke in well-ventilated areas, the possibility of inhaling aerosol droplets without sharing remains if the smokers are seated in close proximity.

Joint sharing is also a common practice among cannabis smokers. Infectious MTB aerosol droplets can be transmitted to other smokers during a smoking session that is often conducted in a closed space ⁶⁷. A similar mechanism has been reported for SARS-CoV-2 transmission among tobacco smokers who share the same cigarette ⁶⁸. The collinearity between joint and bong sharing compelled us to opt supporting only one interest. Our choice to choose bong sharing as the main interest was due to its significant adjusted ORs (4.22; 95% CI: 1.47–12.07), compared to the non-significant adjusted OR of joint sharing (3.42; 95% CI: 0.89–13.05). Our study may lack sufficient power to demonstrate the effect of joint sharing because of the small sample size of joint sharing behavior.

Tobacco smoking had similar levels of adjusted OR and PAF as those calculated from the sharing of bongs of cannabis. Tobacco smoking causes ciliary dysfunction and reduces local immunity against MTB infection ⁶⁹. Although sharing instruments for tobacco smoking may be a risk factor for TB transmission ⁷⁰, this behavior is not as common as that observed in cannabis smokers. Therefore, at the population level, the mechanisms attributed to TB cases are different.

The strengths of this study lie in the time and place where the study was conceptualized. Thailand, a high TB burden country, and also the first country in Asia to legalize cannabis. It added evidence of this association in general population setting from those derived from a TB contact tracing study⁴⁹.

A limitation of the study might come from uncommon setting that number of cases was higher than number of controls, as not all cases could have an eligible control to match with. However, the post-hoc analysis confirmed sufficient

power for our hypothesis testing. In addition, sensitivity analyses using only cases with matched control (Appendix 3, 4 & 5) showed similar results in both univariate and multivariate analyses, with marginal differences in proportions in the former and a slightly lower odds ratio from sharing bong of cannabis in the latter. These results suggest that not having enough controls for a 1:1 case-control ratio could slightly overestimate the association, as the incomplete control group was not a perfect representation of the matched-population. However, including cases without matched control in the analysis provided slightly higher statistical power. The collinearity between joint and bong sharing among cannabis smokers disabled us to separate these two factors well enough. Our TB cases (and thus also the matched control) were generally older than cannabis consumers in the general population. The prevalence of tobacco smoking in the control group (23.1%) was much higher than in the general population (19%), as reported in a 2017 national survey⁷¹. This might be due to the fact that our study subjects resided in low socio-economic areas. In addition, we excluded TB patients with immunocompromised conditions. This may reduce the generalizability of our findings, as it may not reflect the general TB patient population, especially for PAF. Moreover, the time lag between policy change in 2022 and the study period in 2023 was just one year. The association found may not be due to the change in the policy. Therefore, the findings of this study must be interpreted with caution.

Most cannabis smokers have started smoking since they were young. Recent changes in the prevalence of cannabis smoking were not observed in the present study. However, the legalization of cannabis in other countries has been followed by an increase in the number of users⁴¹. Therefore, this policy may have an impact on TB risk in lower-middle-income countries where TB is already highly prevalent.

4. Concluding

This thesis fulfills the research objectives by employing multiple research methods and two different studies. By investigating at both macro and micro levels, we found that while the hospitalization trend for TB was gradually declining, the hospitalization trend for cannabis-related causes increased, especially after legalization. Temporally, no correlation or association was found after accounting for the self-decline of the TB trend. We found that sharing cannabis instruments such as bongs or joints was significantly more frequent among TB patients. This evidence should be distributed to raise awareness of the harm from bong sharing among the cannabis consumer population. If this practice could not be reduced by all means, strict policy to reduce cannabis consumption should be indicate.

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APPENDICES

Appendix 1. Documentary Proof of Ethical Clearance

AL-011_TH



คณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์
คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

หนังสือรับรองฉบับนี้ให้ไว้เพื่อแสดงว่า

รหัสโครงการ :	REC.65-508-19-1	
ชื่อโครงการ :	การศึกษาแบบมีกลุ่มควบคุมเพื่อหาความสัมพันธ์ระหว่างวัณโรคปอดและ การใช้กัญชา (Association between active pulmonary tuberculosis and history of cannabis usages: a case-control study)	
ผู้วิจัยหลัก :	เชมภณ ชุ่มชื่น	หน่วยระบาดวิทยา
ผู้ร่วมวิจัย :	วิระศักดิ์ จงสุวิวัฒน์วงศ์	สาขาวิชาระบาดวิทยา คณะแพทย ศาสตร์ มหาวิทยาลัยสงขล านครินทร์

เอกสารที่รับรอง :

1. แบบเสนอเพื่อขอรับการพิจารณาจริยธรรมการวิจัยในมนุษย์ เวอร์ชัน 1.1 ฉบับวันที่ 31 มกราคม 2566
2. โครงการวิจัยฉบับสมบูรณ์ เวอร์ชัน 1.1 ฉบับวันที่ 31 มกราคม 2566
3. เอกสารชี้แจงผู้เข้าร่วมการวิจัย เวอร์ชัน 2.0 ฉบับวันที่ 1 กุมภาพันธ์ 2566
4. เอกสารแสดงเจตนายินยอมเข้าร่วมการวิจัยด้วยวาจา เวอร์ชัน 1.0 ฉบับวันที่ 31 มกราคม 2566
5. แบบเสนอขอรับการพิจารณาขออนุญาตถอนการยินยอมจากอาสาสมัคร (Waiver of Consent) เวอร์ชัน 1.0 ฉบับวันที่ 31 มกราคม 2566
6. แบบบันทึกข้อมูล เวอร์ชัน 2.0 ฉบับวันที่ 31 มกราคม 2566
7. ประวัติผู้วิจัยและหลักฐานการยอมรับจริยธรรมการวิจัย

ได้ผ่านการพิจารณาและรับรองจากคณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์คณะแพทย
ศาสตร์ มหาวิทยาลัยสงขลานครินทร์ โดยยึดหลักจริยธรรมของประกาศเฮลซิงกิ (Declaration of
Helsinki) และแนวทางการปฏิบัติการจัดทำทางคลินิกที่ดี (The International Conference on
Harmonization in Good Clinical Practice) ข้อมูลการพิจารณา บรรจุในบันทึกการประชุมคณะ
กรรมการ ครั้งที่ 3/2566 ชุดที่ 3 วาระที่ 4.3 วันที่ 24 มกราคม พ.ศ. 2566

ขอให้ผู้วิจัยรายงานความก้าวหน้าโครงการวิจัย ทุก 12 เดือนและยื่นต่ออายุก่อนถึงวันหมดอายุ
อย่างน้อย 30 วัน (กรณีเป็นรายงานผู้ป่วย ไม่ต้องรายงานความก้าวหน้าต่อคณะกรรมการพิจารณา
จริยธรรมการวิจัยในมนุษย์ แต่ขอให้รายงานสรุปผลการวิจัยเมื่อสิ้นสุดโครงการ)

ลงชื่อ

(รศ.นพ.บุญสัน ตั้งตระกูลวนิช)

ประธานคณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์

วันที่รับรอง : 16 กุมภาพันธ์ พ.ศ. 2566

หมดอายุ : 15 กุมภาพันธ์ พ.ศ. 2567

หน่วยจริยธรรมการวิจัยในมนุษย์

คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

15 ถนนกาญจนาภิเษย์ อำเภอหาดใหญ่ จังหวัดสงขลา 90110

โทรศัพท์ 074451149, 074451157

โทรสาร 074212900

Ref no. RdPi-csAN-rVSn-Nimus

มอ 351.7.2/ec.2629



Human Research Ethics Committee
Faculty of Medicine, Prince of Songkla University

PSU 104.2435172/ec_system.578

15 November, 2023

REF: Research Exemption Determination
Dear: Kemmapon Chumchuen

The submitted protocol entitled "Prevalence and Temporal Trend of Pulmonary Tuberculosis in Cannabis-related In-patients (ความชุกและแนวโน้มของวัณโรคปอดในผู้ป่วยจากการใช้กัญชา)" including all related documents (REC.66-479-18-5) have been reviewed by Human Research Ethics Committee of Faculty of Medicine Prince of Songkla University.

The committee determined on 15 November, 2023 that the submitted protocol met the criteria of the **Exemption Determination** (according to SOP version 3, Chapter 5)

The decision was acknowledged by Human Research Ethics Committee in the HREC meeting 34/2023 Agenda 3.3 in which the meeting minutes was documented.

(Prof. Boonsin Tangtrakulwanich)

Chairman of Human Research Ethics Committee
Faculty of Medicine, Prince of Songkla University

Remarks

- No continuing reports are required by Ethics Committee. However, progress report to funding source (if any) is still necessary.
- Changes to the research protocol regarding research methodology and target population must be submitted for approval from EC.
- Please submit "Final Report" (Form AP-Q20) to Ethics Committee after complete all study processes

Human Research Ethics Committee
Faculty of Medicine Prince of Songkla University
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Ref no. sHJK-qdtz-APCa-khP3

Appendix 2. Structured Questionnaire of Case-control Study

Canna Case-Control | REDCap

https://redcap.dida.psu.ac.th/redcap_v14.0.32/Design/data_dic..

Data Dictionary Codebook

Canna Case-Control (PID: 38)

10-30-2024 08:00

Instruments

#	Variable / Field Name	Field Label <i>Field Note</i>	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: Domain 1a Demographic Variables (domain_1a_demographic_variables)			
1	[record_id]	Record ID	text
2	[dayint]	Date of interview (วันเดือนปี พ.ศ. ที่ทำการสัมภาษณ์)	text (date_dmy)
3	[age]	Age (in years) (อายุ)	text (number, Min: 20, Max: 99)
4	[sex]	Sex (เพศ)	radio 1 Male/ชาย 2 Female/หญิง
5	[restype]	Response type <i>Non-response ID start with 88XXX</i>	radio 0 Non-response 1 Response
6	[subdis]	Sub-district (ตำบล) <i>ตัวอย่าง: ดอนหิรัญ, ควบสิ่ง</i>	text
7	[block]	Enumeration block (ชอย) <i>ตัวอย่าง: ราชพฤกษ์ 3, ภาสกร 9</i>	text
8	[edu]	Education level (ท่านจบระดับการศึกษาใด)	radio 1 < Highschool/น้อยกว่ามัธยมศึกษาตอนปลาย 2 ≈ Highschool/มัธยมศึกษาตอนปลายหรือเทียบเท่า 3 Vocational Certificate/ปวช. 4 High Vocational Certificate/ปวส. 5 Currently in college/เรียนมหาวิทยาลัยแต่ไม่จบปริญญา 6 Bachelor's degree/ปริญญาตรี 7 > Bachelor's degree/สูงกว่าปริญญาตรี
9	[occu]	Occupation (ท่านประกอบอาชีพใด)	radio 1 Government hired/ข้าราชการ 2 Private sector/พนักงานบริษัทเอกชน 3 Small business owner/ค้าขายรายย่อย

		4 Business owner/ธุรกิจส่วนตัว หรือ ผู้ประกอบการ 5 Manual laborer/ผู้ใช้แรงงาน หรือ รับจ้างทั่วไป 6 Retired,househusband,housewife/เกษียณอายุ พ่อบ้าน แม่บ้าน 7 Farmer,fishermen/เกษตรกร หรือ ชาวประมง 8 Freelance/ทำงานอิสระ 9 Student/นักศึกษา 10 Unemployed/ไม่ได้ประกอบอาชีพ 11 Other (specify)/ อื่นๆ โปรดระบุ
10	[occu_oth] Other occupation (ระบุอาชีพอื่นๆ) Show the field ONLY if: [occu] = '11'	text
11	[income] Average income (monthly) (ท่านมีรายได้เฉลี่ยต่อเดือนอยู่ที่เท่าไร) ใส่ตัวเลขไม่ลงมี ","	text (number)
12	[group] Participant group (กลุ่มของผู้ให้สัมภาษณ์)	radio, Required 0 Control 1 Case
13	[case_regist] Registration type (ชนิดของการขึ้นทะเบียน ในกรณีที่เป็นกลุ่มเคส) Show the field ONLY if: [group] = '1'	radio 1 New/ใหม่ 2 Relapse/กลับเป็นซ้ำ 3 TAF/รักษาซ้ำหลังล้มเหลว 4 TAD/รักษาซ้ำหลังขาดยา 5 Transfer in/รับโอน 6 Not registered/ไม่ได้ขึ้นทะเบียน 7 Other (specify)/อื่น ๆ โปรดระบุ
14	[hospital] Hospital (โรงพยาบาลที่ได้รับการรักษา) Show the field ONLY if: [group] = '1'	radio 1 PSU Hospital 2 Hatyai Hospital
15	[hhc] Household contacts of pulmonary TB case (อาศัยอยู่ในบ้านหลังเดียวกันกับผู้ป่วยวัณโรค 3 เดือนก่อนผู้ป่วยวัณโรคมีอาการหรือถูกวินิจฉัย)	radio 0 No/ไม่ 1 Yes/ใช่
16	[int_compa] Are there anyone else during the interview (มีญาติอยู่ด้วยหรือไม่ขณะสัมภาษณ์)	yesno 1 Yes 0 No

17	[domain_1a_demographic_variables_complete]	Section Header: <i>Form Status</i> Complete?	dropdown <table><tr><td>0</td><td>Incomplete</td></tr><tr><td>1</td><td>Unverified</td></tr><tr><td>2</td><td>Complete</td></tr></table>	0	Incomplete	1	Unverified	2	Complete			
0	Incomplete											
1	Unverified											
2	Complete											
Instrument: Domain 2b Tobacco Alcohol And Kratom Related Varia (domain_2b_tobacco_alcohol_and_kratom_related_varia)												
18	[tcurr]	Section Header: <i>Tobacco (บุหรี่)</i> Are you a smoker (ท่านสูบบุหรี่หรือไม่)	radio <table><tr><td>0</td><td>No (0 cigarette in past 6-month)/ไม่สูบ</td></tr><tr><td>1</td><td>Yes (≥ 1 cigarette in past month)/สูบ</td></tr><tr><td>2</td><td>Just quit (0 cigarette in < 6 month)/เพิ่งเลิก</td></tr></table>	0	No (0 cigarette in past 6-month)/ไม่สูบ	1	Yes (≥ 1 cigarette in past month)/สูบ	2	Just quit (0 cigarette in < 6 month)/เพิ่งเลิก			
0	No (0 cigarette in past 6-month)/ไม่สูบ											
1	Yes (≥ 1 cigarette in past month)/สูบ											
2	Just quit (0 cigarette in < 6 month)/เพิ่งเลิก											
19	[thist]	Have you ever smoked tobacco/ cigarette (เคยสูบบุหรี่มาก่อนในอดีต) <i>ถ้ามีปัจจุบันสูบบุหรี่หรือไม่เลือก "Yes"</i>	radio <table><tr><td>0</td><td>No/ไม่เคย</td></tr><tr><td>1</td><td>Yes/เคยสูบ</td></tr></table>	0	No/ไม่เคย	1	Yes/เคยสูบ					
0	No/ไม่เคย											
1	Yes/เคยสูบ											
20	[tstart] Show the field ONLY if: [thist] = '1'	How old were you when you started smoking (ท่านสูบบุหรี่ครั้งแรกเมื่ออายุเท่าไร) <i>ใส่ตัวเลข เช่น 18, 25</i>	text (number)									
21	[tquit] Show the field ONLY if: [tcurr] = '0' and [thist] = '1'	How long has it been since you quit smoking (ท่านเลิกสูบบุหรี่มาเป็นเวลากี่ปีแล้ว) <i>ใส่ตัวเลข เช่น 18, 25</i>	text									
22	[ttype] Show the field ONLY if: [thist] = '1'	What do/did you normally smoke (ชนิดของบุหรี่ที่สูบ) *เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	checkbox <table><tr><td>1</td><td>ttype__1</td><td>Cigarette/บุหรี่</td></tr><tr><td>2</td><td>ttype__2</td><td>Tobacco joint/ใบจาก</td></tr><tr><td>3</td><td>ttype__3</td><td>Other (specify) /อื่นๆ โปรดระบุ</td></tr></table>	1	ttype__1	Cigarette/บุหรี่	2	ttype__2	Tobacco joint/ใบจาก	3	ttype__3	Other (specify) /อื่นๆ โปรดระบุ
1	ttype__1	Cigarette/บุหรี่										
2	ttype__2	Tobacco joint/ใบจาก										
3	ttype__3	Other (specify) /อื่นๆ โปรดระบุ										
23	[ttype_oth] Show the field ONLY if: [ttype(3)] = '1'	Other (อื่นๆโปรดระบุ)	text									
24	[tfreq] Show the field ONLY if: [thist] = '1'	How often do you smoke (ความถี่ในการสูบ)	radio <table><tr><td>1</td><td>Daily/รายวัน</td></tr><tr><td>2</td><td>Weekly/รายสัปดาห์</td></tr><tr><td>3</td><td>Monthly/รายเดือน</td></tr><tr><td>4</td><td>Other (specify)/อื่นๆ โปรดระบุ</td></tr></table>	1	Daily/รายวัน	2	Weekly/รายสัปดาห์	3	Monthly/รายเดือน	4	Other (specify)/อื่นๆ โปรดระบุ	
1	Daily/รายวัน											
2	Weekly/รายสัปดาห์											
3	Monthly/รายเดือน											
4	Other (specify)/อื่นๆ โปรดระบุ											
25	[tfreq_oth] Show the field ONLY if:	Other (อื่นๆโปรดระบุ)	text									

	[tfreq] = '4'		
26	[tdosage] Show the field ONL Y if: [thist] = '1'	How many cigarettes do you consume monthly? (จำนวนบุหรี่ที่สูบต่อเดือน)	text (number)
27	[treplace] Show the field ONL Y if: [tcurr] = '0' and [thist] = '1'	Replacement for tobacco (ในกรณีที่เลิกบุหรี่ ท่านได้ เปลี่ยนไปสูบบุหรี่หรือใช้ยาอื่นแทนหรือไม่ เช่น กระเทียม หรือ กัญชา) *เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	checkbox 1 treplace__1 Cannabis/กัญชา 2 treplace__2 Kratom/กระเทียม 3 treplace__3 Other (specify) / อื่นๆ โปรดระบุ
28	[treplace_oth] Show the field ONL Y if: [treplace(3)] = '1'	Other (อื่นๆโปรดระบุ)	text
29	[reason_treplace] Show the field ONL Y if: [treplace(1)] = '1' or [treplace(2)] = '1' or [treplace(3)] = '1'	Reason behind replacing tobacco with _____ (เหตุผลในการใช้ _____ แทนบุหรี่)	text
30	[acurr] Section Header: Alcohol (แอลกอฮอล์) Are you currently an alcohol drinker (ท่านดื่มแอลกอฮอล์หรือไม่)		radio 0 No (0 drink in last 12 months)/ ไม่ดื่ม 1 Yes (≥ 1 drink in the last 12 months)/ดื่ม
31	[ahist] Have you drunk alcohol in the past (ท่านเคยดื่มในอดีตหรือไม่) ถ้าปัจจุบันดื่ม เลือก Yes		radio 0 No/ไม่ 1 Yes/ใช่
32	[astart] Show the field ONL Y if: [ahist] = '1'	How old were you when you started drinking (ท่านดื่มครั้งแรกเมื่ออายุเท่าไร) ใส่ตัวเลข เช่น 18, 25	text (number)
33	[aquit] Show the field ONL Y if: [acurr] = '0' and [ahist] = '1'	How long has it been since you quit drinking (ท่านเลิกดื่มมาเป็นเวลากี่ปีแล้ว) ใส่ตัวเลข เช่น 18, 25	text
34	[afreq] Show the field ONL Y if: [ahist] = '1'	How often do you drink (ความถี่ในการดื่ม)	radio 1 Daily/รายวัน 2 Weekly/รายสัปดาห์ 3 Monthly/รายเดือน 4 Other (specify)/อื่นๆ โปรดระบุ

35	[afreq_oth]	Other (อื่นๆโปรดระบุ)	text									
	Show the field ONL Y if: [afreq] = '4'											
36	[adosage]	How many drinks do you consume monthly? (จำนวนแอลกอฮอล์ที่ดื่มต่อเดือน) <i>นับเป็นจำนวนแก้ว เมื่อรับประทานใหญ่เท่ากับสองแก้ว</i>	text (number)									
	Show the field ONL Y if: [ahist] = '1'											
37	[areplace]	Replacement for alcohol (ในกรณีที่เลิกดื่มแอลกอฮอล์ ท่านได้ เปลี่ยนไปใช้อย่างอื่นแทนหรือไม่ เช่น กระเทียม หรือ กัญชา) *เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	checkbox <table><tr><td>1</td><td>areplace__1</td><td>Cannabis/กัญชา</td></tr><tr><td>2</td><td>areplace__2</td><td>Kratom/กระเทียม</td></tr><tr><td>3</td><td>areplace__3</td><td>Other (specify) / อื่นๆ โปรดระบุ</td></tr></table>	1	areplace__1	Cannabis/กัญชา	2	areplace__2	Kratom/กระเทียม	3	areplace__3	Other (specify) / อื่นๆ โปรดระบุ
1	areplace__1	Cannabis/กัญชา										
2	areplace__2	Kratom/กระเทียม										
3	areplace__3	Other (specify) / อื่นๆ โปรดระบุ										
38	[areplace_oth]	Other (อื่นๆโปรดระบุ)	text									
	Show the field ONL Y if: [areplace(3)] = '1'											
39	[reason_areplace]	Reason behind replacing alcohol with _____ (เหตุผลในการใช้ _____ แทนการดื่มสุรา)	text									
	Show the field ONL Y if: [areplace(1)] = '1' or [areplace(2)] = '1' or [areplace(3)] = '1'											
40	[kcurr]	Section Header: Kratom (กระเทียม) Are you currently using kratom (ท่านใช้กระเทียมอยู่หรือไม่)	radio <table><tr><td>0</td><td>No/ไม่</td></tr><tr><td>1</td><td>Yes/ใช่</td></tr></table>	0	No/ไม่	1	Yes/ใช่					
0	No/ไม่											
1	Yes/ใช่											
41	[khist]	Have you consumed kratom in the past (ท่านเคยใช้กระเทียมในอดีตหรือไม่) <i>ถ้ามีปัจจุบันใช้ เลือก Yes</i>	radio <table><tr><td>0</td><td>No/ไม่</td></tr><tr><td>1</td><td>Yes/ใช่</td></tr></table>	0	No/ไม่	1	Yes/ใช่					
0	No/ไม่											
1	Yes/ใช่											
42	[kstart]	How old were you when you started consuming kratom (ท่านใช้กระเทียมครั้งแรกเมื่ออายุเท่าไร) <i>ใส่ตัวเลข เช่น 18, 25</i>	text (number)									
	Show the field ONL Y if: [khist] = '1'											
43	[kquit]	How long has it been since you consuming kratom (ท่านเลิกใช้กระเทียมมาเป็นเวลากี่ปีแล้ว) <i>ใส่ตัวเลข เช่น 18, 25</i>	text									
	Show the field ONL Y if: [kcurr] = '0' and [khist] = '1'											
44	[ktimeline]	Kratom usage before or after diagnosed with TB (ใช้กระเทียมก่อนหรือหลังวินิจฉัย)	radio <table><tr><td>1</td><td>Before/ก่อนถูกวินิจฉัย</td></tr><tr><td>2</td><td>After/หลังถูกวินิจฉัย</td></tr></table>	1	Before/ก่อนถูกวินิจฉัย	2	After/หลังถูกวินิจฉัย					
1	Before/ก่อนถูกวินิจฉัย											
2	After/หลังถูกวินิจฉัย											
	Show the field ONL Y if: [group] = '1' and [khist] = '1'											

45	[kreason] Show the field ONL Y if: [khist] = '1'	What is the main reason behind using kratom (ในกรณีที่ใช้กระท่อม จงบอกเหตุผลหลักที่ใช้กระท่อม) *เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	checkbox 1 kreason__1 Recreational/ สันทนาการ 2 kreason__2 Health benefits/ เพื่อสุขภาพ
46	[kreason_health] Show the field ONL Y if: [kreason(2)] = '1'	In case of using kratom for health benefits, please state the seeking benefit (ในกรณีที่ใช้เพื่อสุขภาพ กรุณาระบุ อาการหรือโรคที่ใช้กระท่อมรักษา)	text
47	[ktype] Show the field ONL Y if: [khist] = '1'	How do you normally consume kratom (วิธีในการรับประทานกระท่อม) *เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	checkbox 1 ktype__1 Chew fresh leaves/ เคี้ยวใบสดแล้วคายทิ้ง 2 ktype__2 Eat fresh leaves/กิน ใบสดในคายทิ้ง 3 ktype__3 Eat fresh leaves and stem/กินทั้งใบและก้าน 4 ktype__4 Boil fresh leaves as tea/ต้มใบสดกิน 5 ktype__5 Tea from dry leaves/ ตากแห้งบดเป็นผงแล้ว ชงกิน 6 ktype__6 Cocktail mixture/สูตร ผสม 7 ktype__7 Other (specify)/อื่นๆ โปรดระบุ
48	[ktype_oth] Show the field ONL Y if: [ktype(7)] = '1'	Other (อื่นๆโปรดระบุ)	text
49	[kadditive] Show the field ONL Y if: [ktype(6)] = '1'	[In case of taking a cocktail mixture, what do you normally add in the mixture] (ในกรณีที่กินแบบสูตรผสม ท่านใส่อะไรผสมกับกระท่อมบ้าง โปรดระบุ)	text
50	[kfreq] Show the field ONL Y if: [khist] = '1'	How often do you consume kratom (ความถี่ในการรับประทานกระท่อม)	radio 1 1-3 per year/1-3 ครั้งต่อปี 2 4-7 per year/4-7 ครั้งต่อปี 3 8-11 per year/8-11 ครั้งต่อปี 4 Once a month/เดือนละครั้ง 5 2-4 per month/เดือนละ 2-4 ครั้ง 6 2-3 per week/สัปดาห์ละ 2-3 ครั้ง 7 4-6 per week/สัปดาห์ละ 4-6 ครั้ง

		8 Daily/สัปดาห์ละ 7 ครั้ง (ทุกวัน) 9 Other (specify)/อื่นๆ โปรดระบุ
51	[kfreq_oth] Show the field ONL Y if: [kfreq] = '9'	Other (อื่นๆโปรดระบุ) text
52	[kdosage] Show the field ONL Y if: [khist] = '1'	How much kratom do you consume monthly (ประมาณของกระตอมที่รับประทานต่อเดือน) นับเป็นจำนวนใบต่อเดือน, 999 = free text
53	[kcompa] Show the field ONL Y if: [khist] = '1'	Are there any companions presented during kratom consumption (จำนวนคนที่อยู่ด้วยในขณะที่รับประทาน) นับเป็นจำนวนคน ไม่มีใส่ 0 text
54	[domain_2b_tobacco_alcohol_and_kratom_related_variable_complete] Section Header: Form Status Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: Domain 3c Cannabis Related Variables (domain_3c_cannabis_related_variables)		
55	[ccurr] Show the field ONL Y if: [chist] = '1'	Are you currently using cannabis (ท่านใช้กัญชาอยู่ในปัจจุบัน) radio 0 No/ไม่ 1 Yes/ใช่
56	[chist] Show the field ONL Y if: [ccurr] = '0' and [chist] = '1'	Have you ever consumed cannabis (ท่านเคยใช้กัญชาหรือไม่) ถ้ามีปัจจุบันใช่ เลือก "Yes" radio 0 No/ไม่ 1 Yes/ใช่
57	[cstart] Show the field ONL Y if: [chist] = '1'	How old were you when you started using cannabis (ท่านใช้กัญชาครั้งแรกเมื่ออายุเท่าไร) text (number)
58	[cquit] Show the field ONL Y if: [ccurr] = '0' and [chist] = '1'	How long has it been since you quit using cannabis (ท่านเลิกใช้กัญชาเป็นเวลากี่ปีแล้ว) text (number)
59	[ctimeline] Show the field ONL Y if: [group] = '1' and [chist] = '1'	Cannabis usage before or after diagnosed with TB (ใช้กัญชาก่อนหรือหลังวินิจฉัย) radio 1 Before/ก่อนถูกวินิจฉัย 2 After/หลังถูกวินิจฉัย
60	[creason] Show the field ONL Y if:	What is the main reason behind using cannabis (ในกรณีที่ใช้กัญชา จงบอกเหตุผลหลักที่ใช้กัญชา) checkbox 1 creason__1 Recreational/สันทนาการ

[chist] = '1'	*เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	2 creason__2	Health benefits/ เพื่อสุขภาพ
61 [creason_health]	In case of using cannabis for health benefits, please state the seeking benefit (ในกรณีที่ใช้เพื่อสุขภาพ กรุณาระบุ อาการหรือโรคที่ไปก็ยารักษา)	text	
Show the field ONL Y if: [creason(2)] = '1'			
62 [ctype]	How do you normally consume cannabis (วิธีการใช้หรือรับประทานกัญชา) *เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	checkbox	
Show the field ONL Y if: [chist] = '1'		1 ctype__1	Joint/สูบแบบมวน
		2 ctype__2	Rolled in cigarette/ สูบผสมบุหรี่
		3 ctype__3	Pipe/สูบผ่านใบปี
		4 ctype__4	Water pipe/สูบผ่าน บ้อง
		5 ctype__5	Vaping/สูบผ่านบุหรี่ ไฟฟ้า
		6 ctype__6	Boil fresh leaves/ต้ม ใบสดดื่ม
		7 ctype__7	Boil dried leaves/ต้ม ใบแห้งดื่ม
		8 ctype__8	Add in food/ใส่ในอาหาร
		9 ctype__9	Other (specify)/อื่นๆ โปรดระบุ
63 [ctype_oth]	Other (specify) อื่นๆโปรดระบุ	text	
Show the field ONL Y if: [ctype(9)] = '1'			
64 [clocate]	In case of consuming through smoking, where do you generally smoke cannabis (ในกรณีที่สูบกัญชา โดยปกติแล้วท่านสูบกัญชาที่ไหน)	text	
Show the field ONL Y if: [ctype(1)] = '1' or [ctype(2)] = '1' or [ctype(3)] = '1' or [ctype(4)] = '1' or [ctype(5)] = '1'			
65 [cventi]	Ventilation status at place of consumption (สถานะการระบายอากาศของบริเวณที่สูบ)	radio	
Show the field ONL Y if: [ctype(1)] = '1' or [ctype(2)] = '1' or [ctype(3)] = '1' or [ctype(4)] = '1' or [ctype(5)] = '1'		1	Well ventilate (open door/window, outdoor)/มีการระบายอากาศ
		2	Poorly ventilate (close door/window, hotboxing)/ไม่มีการระบายอากาศ หรือ ระบายน้อย
66 [ccompa]	Are there any companions presented during cannabis consumption (จำนวนคนที่อยู่ด้วยในขณะที่ใช้หรือ	text	
Show the field ONL Y if:			

	[chist] = '1'	รับประทาน)																			
67	[cshare]	In case of consuming through smoking, have you smoked shared cannabis from others (ในกรณีที่ใช้ผ่านการสูบบุหรี่ ท่านมีการแชร์หรือเวียนกัญชาจากผู้อื่นหรือปล่าว) *เลือกได้มากกว่า 1 ข้อ/Multiple choice allow	checkbox <table border="1"> <tr><td>0</td><td>cshare__0</td><td>No/ไม่ใช่</td></tr> <tr><td>1</td><td>cshare__1</td><td>Sharing joint/แชร์มวนกัญชา</td></tr> <tr><td>2</td><td>cshare__2</td><td>Sharing bong/แชร์บ้องกัญชา</td></tr> <tr><td>3</td><td>cshare__3</td><td>Sharing pipe/แชร์ไปป์กัญชา</td></tr> <tr><td>4</td><td>cshare__4</td><td>Shotgunning/สูดควันต่อจากผู้อื่น</td></tr> <tr><td>5</td><td>cshare__5</td><td>Hotboxing/รมควันกัญชาในห้อง</td></tr> </table>	0	cshare__0	No/ไม่ใช่	1	cshare__1	Sharing joint/แชร์มวนกัญชา	2	cshare__2	Sharing bong/แชร์บ้องกัญชา	3	cshare__3	Sharing pipe/แชร์ไปป์กัญชา	4	cshare__4	Shotgunning/สูดควันต่อจากผู้อื่น	5	cshare__5	Hotboxing/รมควันกัญชาในห้อง
0	cshare__0	No/ไม่ใช่																			
1	cshare__1	Sharing joint/แชร์มวนกัญชา																			
2	cshare__2	Sharing bong/แชร์บ้องกัญชา																			
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4	cshare__4	Shotgunning/สูดควันต่อจากผู้อื่น																			
5	cshare__5	Hotboxing/รมควันกัญชาในห้อง																			
68	[pipe_hygiene]	In case of consuming via bong, how often do you clean the bong (ในกรณีที่สูบบุหรี่โดยใช้บ้อง ท่านทำความสะอาดบ้องกัญชาบ่อยแค่ไหน)	radio <table border="1"> <tr><td>1</td><td>Daily/รายวัน</td></tr> <tr><td>2</td><td>Weekly/รายสัปดาห์</td></tr> <tr><td>3</td><td>Monthly/รายเดือน</td></tr> <tr><td>4</td><td>Other (specify)/อื่นๆ โปรดระบุ</td></tr> </table>	1	Daily/รายวัน	2	Weekly/รายสัปดาห์	3	Monthly/รายเดือน	4	Other (specify)/อื่นๆ โปรดระบุ										
1	Daily/รายวัน																				
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69	[pipe_hygiene_oth]	Other (specify) อื่นๆโปรดระบุ	text																		
70	[cfreq]	How often do you consume cannabis (ความถี่ในการใช้หรือรับประทานกัญชา)	radio <table border="1"> <tr><td>1</td><td>1-3 per year/1-3 ครั้งต่อปี</td></tr> <tr><td>2</td><td>4-7 per year/4-7 ครั้งต่อปี</td></tr> <tr><td>3</td><td>8-11 per year/8-11 ครั้งต่อปี</td></tr> <tr><td>4</td><td>Once a month/เดือนละครั้ง</td></tr> <tr><td>5</td><td>2-4 per month/เดือนละ 2-4 ครั้ง</td></tr> <tr><td>6</td><td>2-3 per week/สัปดาห์ละ 2-3 ครั้ง</td></tr> <tr><td>7</td><td>4-6 per week/สัปดาห์ละ 4-6 ครั้ง</td></tr> <tr><td>8</td><td>Daily/สัปดาห์ละ 7 ครั้ง (ทุกวัน)</td></tr> <tr><td>9</td><td>Other (specify)/อื่นๆ โปรดระบุ</td></tr> </table>	1	1-3 per year/1-3 ครั้งต่อปี	2	4-7 per year/4-7 ครั้งต่อปี	3	8-11 per year/8-11 ครั้งต่อปี	4	Once a month/เดือนละครั้ง	5	2-4 per month/เดือนละ 2-4 ครั้ง	6	2-3 per week/สัปดาห์ละ 2-3 ครั้ง	7	4-6 per week/สัปดาห์ละ 4-6 ครั้ง	8	Daily/สัปดาห์ละ 7 ครั้ง (ทุกวัน)	9	Other (specify)/อื่นๆ โปรดระบุ
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9	Other (specify)/อื่นๆ โปรดระบุ																				
71	[cfreq_oth]	Other (specify) อื่นๆโปรดระบุ	text																		
72	[cdosage]	How much cannabis do you consume monthly? (ปริมาณของกัญชาที่รับประทานต่อเดือน) กัญชาต่อเดือน, 999 = free	text																		

73	[domain_3c_cannabis_related_variables_complete]	Section Header: Form Status Complete?	dropdown
			0 Incomplete
			1 Unverified
			2 Complete
Instrument: Marked For Deletion (marked_for_deletion)			
74	[delete_record]	Delete this record	yesno
			1 Yes
			0 No
75	[marked_for_deletion_complete]	Section Header: Form Status Complete?	dropdown
			0 Incomplete
			1 Unverified
			2 Complete

Appendix 3. Supplementary Table 1

Variables	Control	Case	P value
Total	117	117	
Age			0.161 ^a
Mean (SD)	55.1 (15.9)	52.2 (16.2)	
Age group			0.367
≤ 40 years old	22 (18.8)	29 (24.8)	
41 - 60 years old	59 (50.4)	49 (41.9)	
> 60 years old	36 (30.8)	39 (33.3)	
Sex			0.788 ^c
Male	71 (60.7)	74 (63.2)	
Female	46 (39.3)	43 (36.8)	
Education			0.191 ^c
< High school	54 (46.2)	65 (55.6)	
≥ High school	63 (53.8)	52 (44.4)	
Occupation			0.149 ^c
Business owner/freelance	31 (26.5)	18 (15.4)	
Laborer	32 (27.4)	33 (28.2)	
Office worker	12 (10.3)	19 (16.2)	
Retired/unemployed/student	42 (35.9)	47 (40.2)	
Monthly income (thousand baht) (n = 210)			0.576 ^b
Median (IQR)	6 (0,15)	8 (0,15)	
Ever drank alcohol			0.007 ^c
No	54 (46.2)	33 (28.2)	
Yes	63 (53.8)	84 (71.8)	
Current drinker			0.572 ^c
No	78 (66.7)	83 (70.9)	
Yes	39 (33.3)	34 (29.1)	
Monthly drink count (n = 123)			0.006 ^b
Median (IQR)	24 (10,60)	60 (16,120)	
Ever smoke			< 0.001 ^c
No	69 (59)	42 (35.9)	
Yes	48 (41)	75 (64.1)	
Current smoker			0.07 ^c
No	90 (76.9)	79 (67.5)	
Yes	27 (23.1)	38 (32.5)	
Monthly cigarette count (n = 137)			0.001 ^b
Median (IQR)	155 (55,480)	300 (157.5,600)	

^aStudent's t-test; ^bMann-Whitney U test; ^cChi-square test

Appendix 4. Supplementary Table 2

Variables	Control	Case	P value
Total	117	117	
Current user (within 1 year)			0.242 ^b
No	104 (88.9)	110 (94)	
Yes	13 (11.1)	7 (6)	
Ever used cannabis			0.008 ^b
No	95 (81.2)	76 (65)	
Yes	22 (18.8)	41 (35)	
<i>History of cannabis use</i>			
Starting age (n = 63)			0.107 ^a
Median (IQR)	22.5 (18.5,49.2)	19 (18,23)	
Year since last use (n = 41)			0.727 ^a
Median (IQR)	15 (2,38)	12.5 (2.5,28.5)	
Frequency (n = 63)			0.371 ^b
Occasionally	12 (54.5)	15 (36.6)	
Regularly	4 (18.2)	12 (29.3)	
Once or twice	6 (27.3)	14 (34.1)	
Usage via bong smoking			< 0.001 ^c
No	111 (94.9)	93 (79.5)	
Smoke only	1 (0.9)	1 (0.9)	
Smoke and share	5 (4.3)	23 (19.7)	
Usage via joint smoking			0.02 ^b
No	111 (94.9)	98 (83.8)	
Smoke only	3 (2.6)	7 (6)	
Smoke and share	3 (2.6)	12 (10.3)	
Usage via oral consumption			0.533 ^b
No	102 (87.2)	106 (90.6)	
Yes	15 (12.8)	11 (9.4)	
<i>Extra information among users</i>			
Paid for cannabis (n = 43)			
No	15 (93.8)	14 (51.9)	
Yes	1 (6.2)	13 (48.1)	
Monthly spending in THB (n = 14)			
Median (IQR)	50	200 (100,400)	
Using cannabis for health reasons (n = 11)			
To increase appetite	0 (0)	3 (50)	
To treat insomnia	1 (25)	2 (33.3)	
To freshen up	0 (0)	1 (16.7)	
For unknown medicinal benefits	2 (50)	0 (0)	
Missing	1 (25)	0 (0)	

^aMann-Whitney U test; ^bChi-square test; ^cFisher's exact test

Appendix 5. Supplementary Table 3

Variable	OR (95% CI)	$P_{\text{Wald's test}}$	$P_{\text{LR-test}}$	PAF (%)
Smoking cannabis via bong (ref = no)			0.019	
Smoke only	0.88 (0.05,15.19)	0.93		0
Smoke and shared	4.12 (1.4,12.1)	0.01		11.83
Age (ref = ≤ 40 years old)			0.239	
41 - 60 years old	0.52 (0.24,1.12)	0.093		
> 60 years old	0.59 (0.24,1.42)	0.236		
Sex (ref = male)			0.045	
Female	2.19 (0.99,4.81)	0.052		
Education (ref = $\geq$ High school)			0.124	
< High school	1.64 (0.87,3.1)	0.125		
Occupation (ref = business owner)			0.209	
Laborer	1.23 (0.51,2.93)	0.645		
Office worker	2.82 (1.03,7.73)	0.044		
Retired/unemployed/student	1.55 (0.69,3.51)	0.29		
Ever smoked tobacco (ref = no)	3.62 (1.64,7.99)	0.001	< 0.001	10.13

Appendix 6. Supplementary Table 4

ICD-10 Codes	Description
Cannabis-related diagnoses	
F12	Mental and behavioural disorders due to use of cannabinoids
F120	Mental and behavioural disorders due to use of cannabinoids, acute intoxication
F121	Mental and behavioural disorders due to use of cannabinoids, harmful use
F122	Mental and behavioural disorders due to use of cannabinoids, dependence syndrome
F123	Mental and behavioural disorders due to use of cannabinoids, withdrawal state
F124	Mental and behavioural disorders due to use of cannabinoids, withdrawal state with delirium
F125	Mental and behavioural disorders due to use of cannabinoids, psychotic disorder
F126	Mental and behavioural disorders due to use of cannabinoids, amnesic syndrome
F127	Mental and behavioural disorders due to use of cannabinoids, residual and late-onset psychotic disorder
F128	Mental and behavioural disorders due to use of cannabinoids, other mental and behavioural disorders
F129	Mental and behavioural disorders due to use of cannabinoids, unspecified mental and behavioural disorder
J662	Cannabinosis
Tuberculosis diagnoses	
T407	Poisoning, cannabis (derivatives)
A15	Respiratory tuberculosis, bacteriologically and histologically confirmed
A150	Tuberculosis of lung, confirmed by sputum microscopy with or without culture
A151	Tuberculosis of lung, confirmed by culture only
A152	Tuberculosis of lung, confirmed histologically
A153	Tuberculosis of lung, confirmed by unspecified means
A157	Primary respiratory tuberculosis, confirmed bacteriologically and histologically
A158	Other respiratory tuberculosis, confirmed bacteriologically and histologically
A159	Respiratory tuberculosis unspecified, confirmed bacteriologically and histologically
A16	Respiratory tuberculosis, not confirmed bacteriologically or histologically
A160	Tuberculosis of lung, bacteriologically and histologically negative
A161	Tuberculosis of lung, bacteriological and histological examination not done
A162	Tuberculosis of lung, without mention of bacteriological or histological confirmation
A167	Primary respiratory tuberculosis without mention of bacteriological or histological confirmation
A168	Other respiratory tuberculosis, without mention of bacteriological or histological confirmation
A169	Respiratory tuberculosis unspecified, without mention of bacteriological or histological confirmation

Appendix 7. Accepted Manuscript 1

PLOS ONE

RESEARCH ARTICLE

Relationship between hospitalization from cannabis usage and pulmonary tuberculosis in Thailand from 2017 to 2022

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Abstract

In June 2022, Thailand legalized recreational cannabis. Currently, cannabis is now the most consumed drug. Cannabis usage can increase inflammatory responses in the respiratory tract. Sharing of cannabis waterpipes has been linked to increased tuberculosis risks. Using a national in-patient databank, we aimed to 1) describe the spatiotemporal correlation between cannabis-related and tuberculosis hospital admissions, and 2) compare the rate of subsequent pulmonary tuberculosis admission between those with prior admissions for cannabis-related causes and those without. Both admission types were aggregated to the number of admissions in monthly and provincial units. Temporal and spatial patterns were visualized using line plots and choropleth maps, respectively. A matched cohort analysis was conducted to compare the incidence density rate of subsequent tuberculosis admission and the hazard ratio. Throughout 2017–2022, we observed a gradual decline in tuberculosis admissions, in contrast to the increase in cannabis-related admissions. Both admissions shared a hotspot in Northeastern Thailand. Between matched cohorts of 6,773 in-patients, the incidence density rate per 100,000 person-years of subsequent tuberculosis admissions was 267.6 and 165.9 in in-patients with and without past cannabis-admission, respectively. After adjusting for covariates, we found that a cannabis-related admission history was associated with a hazard ratio of 1.48 ($P = 0.268$) for subsequent tuberculosis admission. Our findings failed to support the evidence that cannabis consumption increased pulmonary tuberculosis risk. Other study types are needed to further assess the association between cannabis consumption and pulmonary tuberculosis.

OPEN ACCESS

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Data Availability Statement: All relevant data are within the paper and [Supporting Information](#) files.

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Introduction

Pulmonary tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (MTB). Once the disease is active, prolonged treatment is necessary [1]. Since the discovery of MTB in 1882, several factors have been reported to increase TB risk. Demographic risk factors include male sex [2] and living in low socioeconomic areas with poor hygiene [3, 4] and high TB prevalence. Underlying diseases reported as TB risk factors include diabetes mellitus [5] and human immunodeficiency virus (HIV) infection [6, 7]. Behavioral TB risk factors include smoking [8–10] and sharing instruments used for substances such as tobacco and cannabis [11, 12].

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Competing interests: The authors have declared that no competing interests exist.

After the ban on opium, cannabis has become the most widely consumed and cultivated psychoactive drug for recreational and medicinal reasons worldwide. Currently, cannabis users are estimated to comprise 2.5% of the global population [13]. In 2022, cannabis was legalized in Thailand, as a result of a political campaign to use cannabis as a traditional herb to stimulate the domestic economy [14].

Several health risks have been reported from cannabis usage, including increased inflammatory responses in the respiratory system, leading to conditions such as chronic cough, chronic bronchitis, and chronic obstructive pulmonary disease [15, 16]. Pulmonary infections have also been reported to result from cannabis smoking. A case of necrotizing pneumonia originating from water contaminated with *Pseudomonas aeruginosa* in a cannabis water pipe has been reported [17].

Regarding the risk of TB from cannabis usage, a contact tracing study in Australia reported an increased risk of acquiring TB among individuals who shared water pipes with a TB index case, with the risk comparable to that observed among household contacts of patients with TB [18]. This highlighted shared substance usage as a common route of pathogen transmission. French et al. conducted a systematic review on the association between cannabis consumption and TB, comprising studies both with and without a comparison group. However, the studies with comparison groups either focused on latent TB infection or reported no association between cannabis usage and active pulmonary TB after adjusting for confounders [19]. Apart from shared cannabis smoking instruments, the potential impact of cannabis-induced inflammation on the severity of active TB development in at-risk populations remains unexplored.

To date, no systematic investigation has estimated the extent of the linkage between cannabis usage and pulmonary TB in low- and middle-income countries such as Thailand, where both issues are highly prevalent. Data mining could serve as a valuable initial approach to explore the connection between hospitalization for cannabis use and subsequent hospitalization for TB.

The Thai Health Information Portal (THIP) is a national in-patient open data warehouse established through collaborations among the National Science and Technology Development Agency (NSTDA), National Health Security Office (NSHO), and the Prince of Songkla University. THIP contains nationwide admission information of Thai inpatients who have filed for reimbursement from the NHO for medical fees. In-patient data from 2017 to 2022 have been made available for analysis [20, 21]. Therefore, using the THIP data, the study objectives were: 1) to assess the spatiotemporal correlation between cannabis-related hospital admissions and subsequent TB-related hospital admissions, and 2) to compare the incidence density rate of subsequent pulmonary TB hospital admission between in-patients previously diagnosed with cannabis-related conditions and those without such diagnoses.

Material and methods

Data source

This study was conducted using the THIP data warehouse, which comprised anonymized admission records of Thai in-patients admitted between 2017 and 2022.

Data curation

THIP data were queried using the International Classification of Diseases (ICD-10) codes. Admission records of in-patients with conditions matching the queried ICD-10 codes as either their primary or secondary diagnosis were selected for data extraction. As a proxy for cannabis user population, individuals admitted with conditions including mental and behavioral disorders due to use of cannabinoids, cannabis poisoning, and cannabinosis were queried from

THIP [22, 23]. To obtain the pulmonary TB history of these in-patients, ICD-10 codes related to TB were also used in the query processes. All ICD-10 codes utilized in this process, along with their descriptions, are detailed in [S1 Dataset](#).

Variables

Both the exposure and outcome variables were derived from the full diagnoses of the in-patients. In THIP, each admission record contains one primary diagnosis column and 21 columns for secondary diagnoses. For the exposure variable, we defined in-patients with cannabis-related conditions ([S1 Dataset](#)) listed in any diagnosis column as having a history of cannabis-related admission. A similar definition was employed for the outcome variable, which was pulmonary TB admission. Both the exposure and outcome variables were treated as binary variables in this study.

Other variables available in the databank included in this study were age, sex, province of residence, and date of admission. The date of admission was used to determine the causal relationship between the exposure and outcome variables. Age was categorized into two groups: <40 years and ≥ 40 years. For the first objective, co-diagnoses were pre-selected for estimating increased risk as a hazard ratio (HR). We selected common (>10%) co-diagnoses presented in the first admission in any diagnosis column of those who were later admitted with pulmonary TB.

Statistical analysis

For the first objective, we aggregated admission counts into monthly units and plotted a line graph to display the temporal patterns over the years. For spatial patterns, we aggregated the admission counts into province-level units for each year. The counts were subsequently divided by the population of each province and presented as the incidence rate (IR) per 100,000 population. To visualize the spatial patterns, we plotted choropleth maps of the IRs for both admission types from 2017 to 2022.

Regarding the second objective, we matched in-patients admitted for cannabis-related causes with general in-patients from the THIP data based on selected variables, including age, sex, year of admission and superdistrict. We calculated the incidence density rate (IDR) by dividing the number of subsequent TB admissions in each group by the cumulative person-years. The person-year was defined as the time between the patient's first admission entry in the THIP data and their endpoint, which was either the last admission entry if pronounced dead or the 30th of September 2022, which was the last date of entry of THIP data for alive in-patients.

We then statistically compared the matched populations using univariate analysis to assess the matching balance and differences in demographic and outcome-related variables. The pre-selected common co-diagnoses from those who later developed subsequent TB admission were also included in this univariate process. We used the Mann-Whitney *U* test, chi-squared test, and Poisson Exact test to assess non-normally distributed continuous variables, categorical variables, and comparison between IDRs, respectively.

To assess the increased risk of subsequent pulmonary TB admission while adjusting for covariates, we performed a Cox regression between the matched populations for the outcome of the first subsequent TB admission. We displayed the result of the Cox regression as an adjusted hazard ratio (HR) table.

$P < 0.05$ was considered statistically significant in all performed analyses. Estimations of increased TB risk (HR) were accompanied by 95% confidence intervals (CI). All data were managed and analyzed using R program version 4.2.3 [24].

Ethical approval

This study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC 66-479-18-5). As this study was conducted using anonymized secondary data, the need for informed consent was waived.

Results

Spatiotemporal relationships

Fig 1 illustrates the dynamics of monthly admissions from cannabis-related causes and those from pulmonary TB. From month 1 to 27, the frequency of cannabis-related admissions was relatively low (below 55 admissions per month), whereas that of TB admission was relatively high (above 4500 admissions per month). During the coronavirus disease 2019 (COVID-19) pandemic, from months 28 to 65, the number of monthly cannabis-related admissions was distributed along the middle of the X axis (ranging from 82 to 213 admission per month), while pulmonary TB admissions were widely distributed on the Y axis. Finally, during months 66 to 69, the number of cannabis-related admissions reached its peak, in contrast to that of pulmonary TB admissions.

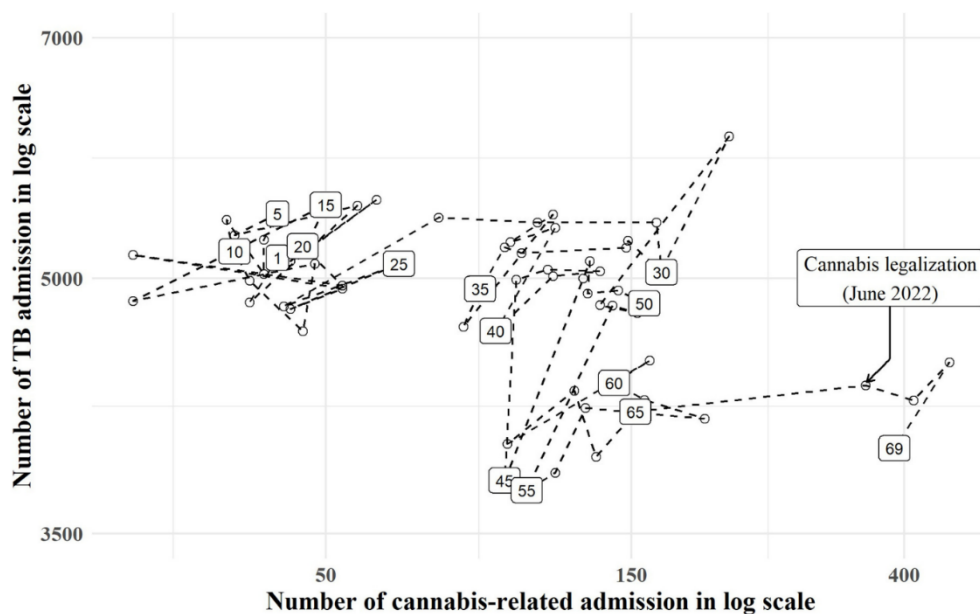


Fig 1. Chronological line plot of admission frequencies of cannabis-related and pulmonary TB diagnoses. The X-axis denotes the number of cannabis-related cases and the Y axis denotes that of pulmonary TB admissions in the same month. The number in the points denotes the number of months of follow up: month 1 denotes January 2017 and month 5 denotes May 2017, stepping up at 5-month intervals until month 69, denoting September 2022.
<https://doi.org/10.1371/journal.pone.0312139.g001>

Fig 2 illustrates the spatiotemporal changes of IR of cannabis-related admissions (**2A**), TB admissions (**2B**), and their combination (**2C**). Distinct increases in cannabis-related admissions were observed in the northern regions of Thailand, eventually overtaking the initial relatively high IR in Surat Thani province in the middle of Southern Thailand. Conversely, TB admission incidence remained the highest in the Northeastern region throughout the years, although the incidence tended to decline over time in all regions.

Matched cohort results

The flow diagram of data curation and cohort matching processes is shown in **Fig 3**. Throughout the 6-year period, 7,313 in-patients were admitted with cannabis-related causes recorded

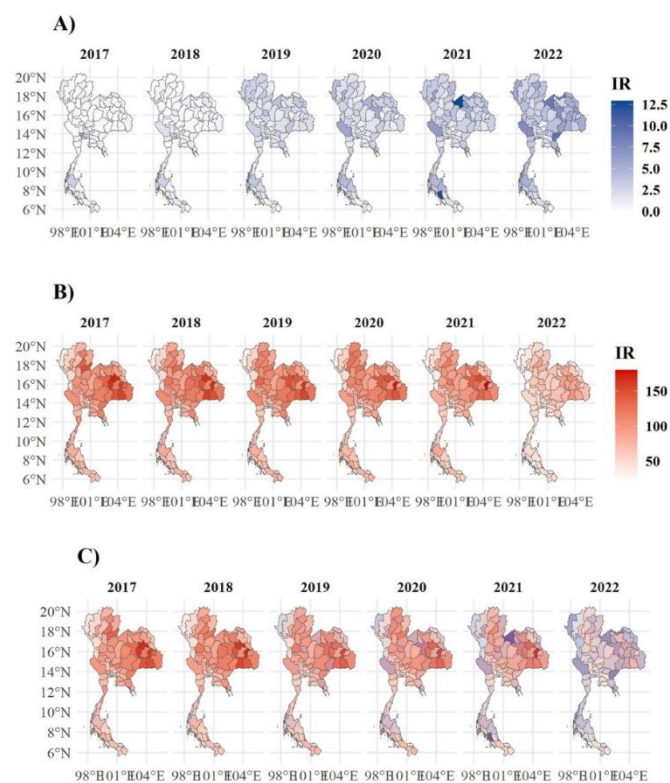


Fig 2. Thailand choropleth map based on the admission incidence rate per 100,000 population. A) cannabis-related causes, B) pulmonary TB, and C) the combination of both gradients in blue, red, and combined tones, respectively. Shapefile from GADM database (<https://gadm.org>) was used as the map's polygon under a CC-BY license. The map was created using the R program version 4.2.3 [24]. <https://doi.org/10.1371/journal.pone.0312139.g002>

in their first data entry. The most common cannabis-related causes were “Mental and behavioral disorders due to use of cannabinoids” (83.5%) and “Poisoning, cannabis (derivatives)” (23%), with the diagnoses not being mutually exclusive. After excluding those co-diagnosed with pulmonary TB, 7,272 in-patients remained. Of these, 80 (1.1%) in-patients were deceased at the time of their first admission records.

We identified 37 subsequent pulmonary TB admissions among 23 in-patients, with 6 of these in-patients having more than one sequential TB admission. More than half (52.1%) of the 23 in-patients were admitted for TB within 10 months of their initial cannabis-related admission. Among the 23 in-patients, 78.26% were diagnosed with “Mental and behavioral disorders due to use of cannabinoids” on first admission, while “Poisoning, cannabis (derivatives)” was found in 26.09% of the patients. Other co-diagnoses occurring in > 10% of these in-patients included “Mental and behavioral disorders due to use of alcohol” (17.39%), “Intentional self-poisoning by and exposure to narcotics and psychodysleptics” (13.04%), “Mental and behavioral disorders due to use of other stimulants, including caffeine” (17.39%), “Hypo-osmolality and hyponatremia” (17.39%), “Hypokalemia” (17.39%), “Pneumonia, unspecified” (13.04%), “Poisoning by and exposure to narcotics and psychodysleptics” (13.04%), and “Type 2 diabetes mellitus without complications” (13.04%).

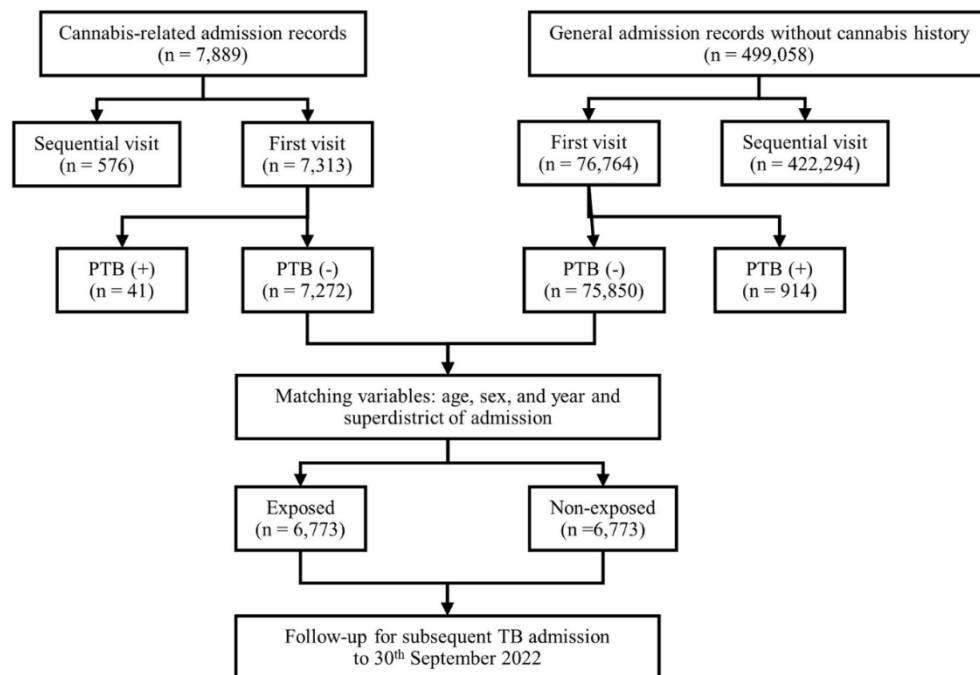


Fig 3. Flow diagram of data curation and matching process.

<https://doi.org/10.1371/journal.pone.0312139.g003>

For the control group, we obtained admission records of 75,850 general in-patients with no prior history of cannabis-related admission or co-diagnoses indicating pulmonary TB. Among these, 560 (0.7%) were deceased at the time of their first admission record. Regarding the matching of the two cohorts, we successfully matched 6,773 (93.1%) of the 7,272 in-patients diagnosed with cannabis-related causes with the general in-patients without a cannabis-related admission history or pulmonary TB in their first admission.

Table 1 summarizes the background information of the cannabis-related admission cohort with their matched pairs. The distributions of age and sex were well-matched, with a pre-dominance of young adults and male sex. The control participants were less likely to have metabolic comorbidities, such as diabetes mellitus, hypo-osmolality and hypokalemia, but were more likely to have pneumonia.

Table 2 presents various follow-up outcome variables in the univariate analysis format. The univariate analyses revealed a shorter interval between the first admission and the subsequent TB admission and higher IDR in the case group. However, none of these differences reached statistical significance ($P < 0.05$) in any of the analysis methods used.

Table 3 summarizes the results from the Cox regression for subsequent TB admission, including the HR and its 95% CI. The HR of the cannabis cohort was not significant (1.48, 95% CI: 0.74, 2.96). Young age (< 40 years old), having diabetes mellitus, hypo-osmolality, and pneumonia in the first admission were statistically significant predictors for subsequent pulmonary TB admission.

Discussion

While the monthly frequencies of pulmonary TB admissions declined, those that were cannabis-related increased from 2017 to 2022. The increase in cannabis-related admissions was

Table 1. Descriptive table of two cohorts.

Variable	No history of cannabis-related admission	Previously admitted from cannabis-related causes	P-value
Total	6773	6773	
Age			0.893a
Median (IQR)	30 (21, 47)	30 (21, 47)	
Sex			1 ^b
Male	5746 (84.8)	5746 (84.8)	
Female	1027 (15.2)	1027 (15.2)	
Diabetes mellitus			< 0.001b
No	6542 (96.6)	6543 (96.6)	
Yes	231 (3.4)	230 (3.4)	
Hypo-osmolality			< 0.001b
No	6610 (97.6)	6610 (97.6)	
Yes	163 (2.4)	163 (2.4)	
Hypokalemia			< 0.001b
No	6099 (90)	6099 (90)	
Yes	674 (10)	674 (10)	
Pneumonia			< 0.001b
No	6651 (98.2)	6651 (98.2)	
Yes	122 (1.8)	122 (1.8)	

^aMann-Whitney U test, and

^bChi-squared test

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Table 2. Comparison of variables related to pulmonary TB admission between the two cohorts.

Variable	No history of cannabis-related admission	Previously admitted for cannabis-related causes	P-value
Total	6773	6773	
Individual level			
Frequency of subsequent TB admission			0.392a
0	6760(99.8)	6751(99.7)	
1	8(0.1)	16(0.2)	
2	3(0)	3(0)	
3	1(0)	0(0)	
4	0(0)	1(0)	
5	1(0)	2(0)	
Time until first subsequent TB admission (in-month)			0.049b
Median(IQR)	4.1(0.4–13.5)	11.4(4.0–32.7)	
Population level			
Frequency of subsequent TB admission			0.087c
Frequency	22	36	
Follow-up person year			
Median(IQR)	1.6(0.5,3.1)	1.7(0.5,3.2)	
Incidence density rate per person year per 100,000 population			0.087c
IDR	165.9	267.6	

^aFisher's exact test

^bMann–Whitney U test

^cExact Poisson test

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classified into three time periods. From January 2017 to March 2019, the monthly admissions ranged from 25 to 75 nationally. From April 2019 to May 2022, the monthly admissions ranged from 82 to 213 nationally. In June 2022, recreational cannabis was legalized; the number of admissions then further increased to over 348 national monthly admissions until the last

Table 3. Hazard ratio table.

Variable	Hazard ratio	95% CI	P-value
History of prior cannabis-related admission (ref = no)			0.268
Yes	1.48	(0.74,2.96)	
Age group (ref = < 40 years old)			0.002
◆ 40 years old	3.45	(1.6,7.43)	
Sex (ref = female)			0.055
Male	4.11	(0.97,17.51)	
Diabetes mellitus (ref = no)			0.001
Yes	4.22	(1.77,10.08)	
Hypo-osmolarity (ref = no)			0.003
Yes	4.39	(1.67,11.53)	
Hypokalemia (ref = no)			0.561
Yes	0.76	(0.29,1.94)	
Pneumonia (ref = no)			< 0.001
Yes	10.12	(3.92,26.12)	

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data point available in September of 2022. Both cannabis and TB admissions shared a geographical hotspot in the Northeastern region.

In the analysis of anonymized in-patients, the risk of subsequent TB admission among those previously admitted for cannabis-related issues was not significantly higher than that for those admitted due to other causes or diseases.

The steady decline in TB admissions during the pre-COVID-19 period may partially reflect the success of the National End TB Program [25]. The sharp decline during the COVID-19 period, however, is likely attributable to the disruption of the health care system from the pandemic. Similar declines in notified cases were reported in China [26, 27], the USA [28], and several lower-and middle income countries [1]. However, rebounds in notified cases after the pandemic subsided was also detected in several regions, including the Americas and South-East Asia [1]. In addition, several reports showed an increase in TB mortality while the notification rate declined during the pandemic [26, 29, 30].

Our data suggest that legalization of recreational cannabis may increase the incidence of hospitalization from cannabis usage. Availability of cannabis outlets was shown to lead to a higher likelihood of cannabis consumption [31], thereby increasing the chance of hospital admission. Similar findings of increased cannabis consumption after legalization have previously been reported; Martins et al. detected an increase in past-year cannabis use of 1–3.7% in the US [32]. Following the legalization of cannabis in Canada, Sandhu et al. reported that 20% of Canadians evinced an increased interest in trying cannabis [33], and the prevalence of cannabis usage increased by 5.6% [34]. Similarly, increased hospitalization rates due to cannabis were also reported in Canada after cannabis commercialization during the pandemic [35].

Both TB and cannabis-related admissions were highest in the Northeastern region of Thailand, which is well-known for its poverty and general ill health [36, 37]. These factors may potentially explain the geographical association [38, 39]. However, the opposite trend suggests a non-causal association between cannabis use and TB admissions.

When analyzing individual-level associations, we did not detect an increased risk of subsequent TB admission in patients priorly admitted for cannabis-related causes. Therefore, this study does not provide evidence to support cannabis consumption as a risk factor for pulmonary TB. In a non-hospitalized context, a contact-tracing study in Queensland [18], and a case-control study in Thailand reported an increased TB risk associated with cannabis use only among individuals who shared bong or water pipes, but not among oral cannabis consumers and non-sharing cannabis smokers [40]. Thus, so far, only bong sharing has been identified as a risk factor for TB transmission. Hypotheses related to respiratory tract damage causing depletion of local immunity remain unsupported by evidence. However, the lack of association found in this study does not provide sufficient grounds for policy implications regarding cannabis regulation, given the need to consider other adverse health effects of cannabis that are beyond the scope of this investigation.

The limitations of this study stemmed from the usage of a national in-patient data registry. We could not rule out possible past TB status; thus, the outcomes in this study were either new TB (either from new infection or from reactivation of latent TB) or relapse TB cases, with symptoms severe enough to require hospitalization. Patients in cannabis-related admission cases may exhibit different settings and behaviors compared to the general cannabis consumer population. A previous study show that bong sharing was a significant risk factor of active TB whereas oral consumption or even smoking with sharing bong were not. [40] In the current study, the use of hospitalization data based on ICD-10 codes limited us in acquiring information regarding route, type, duration, and frequency of cannabis consumption. This information is vital when assessing associations between infection and substance usage, as the pathogenesis can vary depending on how the substance was consumed. Similar limitations were also highlighted in

another study investigating the impact of cannabis consumption on primary spontaneous pneumothorax [41]. These limitations should be corrected in the future studies.

Conclusion

Both spatiotemporal and cohort analyses in this study failed to support the hypothesis that cannabis consumption increased pulmonary TB risk. Other study types are needed to further assess the association.

Supporting information

S1 Dataset. ICD-10 codes used for query process.
(CSV)

S2 Dataset. Monthly aggregated data used for Fig 1.
(XLSX)

S3 Dataset. Spatial polygon data used for Fig 2.
(ZIP)

S4 Dataset. Diagnosis frequency.
(XLSX)

S5 Dataset. Individual-level data of matched cohort results.
(XLSX)

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Appendix 8. Accepted Manuscript 2



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Increased active pulmonary tuberculosis risk from sharing bong of cannabis: a case-control study from Thailand

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Introduction: Tuberculosis (TB) is a chronic lung disease caused by *Mycobacterium tuberculosis*. Tobacco smoking and sharing of instruments have been reported to increase TB risk. In 2022, cannabis was legalized in Thailand. To address for the potential increase in cannabis use after legalization and the reported increased TB risk associated with cannabis usage, we aimed to estimate the odds ratio and population-attributable fraction (PAF) of different types of cannabis use.

Materials and methods: A matched case-control study was conducted in the Songkhla Province of Southern Thailand in 2023. Face-to-face interviews were conducted to collect information on cannabis consumption. Multivariate logistic regression was performed to estimate the odds ratios representing TB risk from the independent variables. PAF was also calculated to compare the public health impacts of the variables.

Results: Among the 148 TB cases and 117 healthy controls, we observed lower socioeconomic status and higher proportions of tobacco and alcohol use in these cases. Eleven percent of the controls were current cannabis users, while nearly 19% had ever experienced cannabis use. The proportions of ever-used, smoked, and shared cannabis use were significantly higher in these cases. After adjusting for covariates, the best-fit model showed an odds ratio of 4.22 (95% confidence interval: 1.47–12.07) for smoking and sharing a bong of cannabis. No statistical significance was found for the other types of consumption. PAF of smoked and shared bongs of cannabis was 12.16, which was slightly lower than that found in smoking tobacco (12.62).

Conclusion: Increased numbers of cannabis users, especially shared smokers, may have an impact on TB risk in lower-middle-income countries, where TB is already highly prevalent.

KEYWORDS
tuberculosis, cannabis, case-control, increased risk, bong

Introduction

Tuberculosis (TB) is a chronic lung disease caused by *Mycobacterium tuberculosis* (MTB). Currently, one-quarter of the world's population is estimated to be infected with MTB (1). Both physical (2, 3) and mental burdens are well-established in patients with active pulmonary TB (4). Several risk factors have been identified to increase the risk of active TB, as demonstrated in previous studies. These factors include being male (5), older age (6, 7), poverty (8–10), and pre-existing HIV infection (11, 12). Increased TB risk from smoking

tobacco is also well established (13–15); decreased immune response and impairment of immune cell and cilia functions have been suggested to mediate this increased risk (16). In addition to the immune-mediated risk, smoking tobacco through water pipes, or shisha, has been reported as an environmental TB risk due to the act of inhaling droplet containing MTB from contaminated mouthpieces during smoking session (17, 18). Cannabis, also known as marijuana or gunja, is a flowering plant with psychoactive effects (19). According to the WHO, it is currently the most widely cultivated and consumed drug; moreover, approximately 2.5% of the global population is estimated to use cannabis (20). As a recreational drug, the popularity of cannabis lags behind that of caffeine, tobacco, and alcohol (19, 21). The collateral effects of the opioid epidemic have led to a gradual increase in interest in medicinal cannabis (22–24). Although their medicinal efficacy is not well established and several studies have reported increased cardiovascular risks from cannabis usage, such as heart failure and stroke (25, 26), cannabis and cannabinoid agents are currently used for various purposes, such as providing analgesia, alleviating cancer pain or neuropathic pain, and treating chemotherapy-induced nausea (27). Following a campaign by a political party to use cannabis to promote the domestic economy, both medicinal and recreational cannabis were legalized in Thailand in 2022 (28). A previous study conducted in US states reported an increase in the number of cannabis users after the legalization of recreational cannabis in four ethnicities including non-Hispanic black, Hispanic, non-Hispanic white and other. The increases in percentage of past-year cannabis use ranged from 1 to 3.7% (29). However, the impact of cannabis legalization in Thailand has not been well reported. Several studies have reported mechanisms that could lead to increased TB risk from cannabis use, one of which is an increased inflammatory response. Compared to tobacco-only smokers, higher risks of prolonged coughing, chronic bronchitis, and chronic obstructive pulmonary disease (COPD) were found in co-users of tobacco and cannabis (30, 31). The increased inflammation from co-use could be due to the intake of both tobacco and cannabis smoke, which were reported to have similar physical and chemical properties (32). Another aspect similar to tobacco, cannabis can be smoked using various instruments. Following the smoking cannabis joint, the water pipe, bong, and hookah were among the most reported instruments used for cannabis consumption (33–35). Several studies have linked cannabis consumption through water pipes to pulmonary infections (36, 37). A necrotizing pneumonia case was found in individuals who inhaled contaminated pipe water (36). In addition, an increased TB risk from sharing cannabis water pipes with patients with TB was also reported in a contact tracing investigation in Queensland, Australia. In the same study, the odds ratio (OR) for acquiring TB infection through sharing cannabis water pipes was 2.22, following the highest OR of 4.91 in those who were household contacts of the TB case (37). Although it has been shown that sharing bong among cannabis smokers could transmit TB (37, 38), no study at the population level has demonstrated this association, especially in lower-middle-income countries, such as Thailand, where TB and cannabis consumption are both highly prevalent. In 2021, the TB incidence in Thailand was predicted to be 143 per 100,000 individuals (39), while in the following year, a national poll regarding legalization of cannabis reported that 32% of participants ever consumed or used cannabis (40). This aimed to conduct a case–control study to estimate the OR and

population attributable fraction (PAF) of cannabis use and smoking, including sharing smoked cannabis, on active TB risk in our study population.

Materials and methods

Study setting

This study was conducted in Songkhla, southern Thailand, which is located on the coast of the Gulf of Thailand. The total population of the province is approximately 1.4 million people, with a population density of 194 per square kilometer (41). In Songkhla, the two largest hospitals responsible for TB treatment were Songklanagarind Hospital and Hatyai Hospital. The former, a university hospital, offers super-tertiary care, whereas the latter is classified as a regional hospital operated by the Ministry of Public Health. Thus, both hospitals were selected as the study hospitals. Regarding cannabis consumption, the Thailand National Poll reported a 32% prevalence of lifetime exposure to any type of cannabis. However, its prevalence at the provincial level has not been reported (40). Furthermore, this study was conducted in 2023, when both medicinal and recreational uses of cannabis were legal.

Study design

A matched case–control study was conducted to compare cannabis usage and smoking between patients with active pulmonary TB and healthy controls in the same population.

Case ascertainment

The case group was defined as active pulmonary TB patients. Patients were recruited from among outpatients diagnosed with active pulmonary TB based on bacteriological results or clinical diagnoses. Inclusion criteria comprised patients over 20 years old, residents of Songkhla Province, and those undergoing treatment at the study hospitals since January 1st, 2023. The latter criterion was placed to make sure that TB cases were diagnosed after cannabis was legalized in 2022. We excluded TB patients with diabetes mellitus, cancer, and HIV infection to prevent unnecessary heterogeneity in the exposure groups. The nursing teams at both study hospitals identified eligible cases for recruitment process. Information on the actual residential addresses of the patients who participated in the study was obtained for planning community control selection.

Control selection

Controls in this study was matched with the cases using age group, sex, and community as the matching variables. Control matching was varied between urban and rural cases due to differences in TB transmission, influenced by factors such as high population density, crowded living conditions, and low hygiene (42, 43). For rural areas, we defined a community as a village in which the patient resided. For the urban setting, we defined the study community as an alley of the

patient's home. The responsible healthcare center for each study community was approached. The study protocol was explained to the patients. The health offices were requested to invite health volunteers in charge to participate in the control selection. Information on the age group (10 year range) and sex of the patients in that community was used to match with the cases and guide the health volunteers to select controls. The exclusion criteria for controls were the same as those for the case group. Potential controls were not included if they had been diagnosed with TB. However, we did not attempt to exclude patients with TB from the control group using any tests, including chest radiography. When more than one eligible control was available for each TB case, volunteers were advised to randomly select one. Selected controls were then interviewed at a nearby community health center.

Sample size calculation

This study sample size was calculated using two independent proportion formulas. For the exposure proportion in the control group, we used the previously reported prevalence of Thai people who had ever used cannabis for medicinal purposes, which was 0.32 for P_1 .

We assumed the proportion of cannabis consumption among the cases (P_2) to be 0.49, which was sufficient to generate an OR of 2.

With a confidence interval of 0.8, and a 1:1 case-to-control ratio, the required total sample size was 148 cases and 148 controls.

We started recruiting participants on March 9th, 2023, and ended data collection on December 5th, 2023. Both the case and control groups provided informed consent. Participants were informed that this was a survey on cannabis use without disclosing our hypothesis of the link to TB. Face-to-face interviews were conducted using a structured questionnaire. The questionnaire contained three sections including demographic information, tobacco and alcohol consumption, and cannabis consumption.

The outcome variable was active pulmonary TB status, as described in the aforementioned protocol. Our main exposure variables were cannabis exposure, including oral consumption and smoking status. Oral cannabis consumption included drinking cannabis tea, consuming foods enhanced or mixed with cannabis derivatives, and consuming commercial drinks containing cannabis. Smoking details included the form of preparation/instrument used for the smoking session, such as rolled joint, mixed cigarette, pipe, and bong. In this study, a bong was classified as any type of water pipe used for smoking cannabis. The social aspects of smoking included whether cannabis was shared during the session, such as sharing a cannabis joint or bong. As we hypothesized that cannabis sharing would be the main mechanism of TB transmission among cannabis users, we stratified smoking cannabis levels into non-smoking, smoking, and smoking and sharing cannabis separately for both smoking via a bong and rolled joints. Timing variables of consumption included age at start and quit (among ex-users). Frequencies and reasons for consumption were also collected. Other potential confounding variables included a history of tobacco smoking and alcohol consumption, education, occupation, and monthly income.

Data management

During the interview process, data were collected directly and entered into a mobile REDCap application (44). The mobile data were transferred and securely stored in the REDCap database hosted by the Research and Development Office of Prince of Songkla University (45, 46). Data from REDCap were exported in a comma-separated value format (CSV), specifically for the analysis process, using the R program version 4.2.3 (47).

Statistical analysis

Descriptive statistics were used to summarize all independent variables and stratified by the outcome variable. Frequency and percentage were used as categorical variables, whereas continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR) based on their distribution. Univariate association analysis was conducted using either the chi-square test or Fisher's exact test for small expected cell counts, while the Student's t-test or Mann-Whitney U test was performed for continuous variables depending on the variable's distribution. A logistic regression analysis was performed to adjust for the remaining confounding factors. The key independent variables maintained in the model were cannabis use and smoking. Other covariates included in the model as potential confounders were those that showed significantly association with the outcome in the univariate analysis (smoking tobacco is a strong confounder, a multivariate model was initially performed without it. This model was then compared with the model in which it was included. The coefficient/OR of cannabis in the model, including smoking tobacco, reflected its direct effect on TB risk. This stepwise modeling approach was used separately to analyze the effects of cannabis use and cannabis smoking. To compare the different models, we used the Akaike information criterion (AIC) values. The model with the lowest AIC was considered the best-fit model, given that the set of records was the same. In the case of collinearity between two exposure variables, the variable with the lowest AIC was selected. This model was then summarized to display the OR with a 95% confidence interval (CI) for each independent variable. In addition, the PAF based on Levin's formula was computed for modifiable risk factors, particularly cannabis use (48). The significance level (α) for multivariate analysis was set at 0.05.

Results

Demographic characteristics

Of 152 eligible TB patients, 148 patients gave their consent, a response rate of 97.4%. We obtained 117 age-sex-community matched controls from the health volunteer recruitment. As these controls were readily recruited by the health workers, we did not have the information on the number of eligible subjects and the response rate. Table 1 shows the results of the univariate analysis. The patients in the case group were generally younger than the controls,

had a lower education level, and had a higher proportion of unemployed individuals and office workers. Substance usage was

TABLE 1 Descriptive table stratified by case and control group status.

Variables	Control	Case	p value
Total	117	148	
Age			0.097a
Mean (SD)	55.1 (15.9)	51.8 (16.2)	
Age group			0.351c
≤40 years old	22	38	
41–60 years old	(18.8)	(25.7)	
>60 years old	59	64	
Sex	(50.4)	(43.2)	0.492c
Male	59	69	
Female	(50.4)	(46.5)	
Education	46	51	0.042c
n <High school	63	64	
≥High school	(46.2)	(59.5)	
Occupation	63	60	0.065c
Business owner/freelance	(53.8)	(40.0)	
Laborer	(26.5)	40 (27)	
Office worker	32	26 (17.6)	
Retired/unemployed/ student	(27.4) 42 (35.9) 12	60 (40.5)	
Monthly income (thousand baht) (n = 235)	(10.3)		0.388b
Median (IQR)	6 (0,15)	8 (0,15)	
Ever drank alcohol			0.004c
No	54	42 (28.4)	
Yes	(46.2)	106 (71.6)	
Current drinker	63		0.707c
No	(53.8)	103 (69.6)	
Yes	(66.7)	45 (30.4)	
Monthly drink count (n = 123)	39 (33.3)		0.004b
Median (IQR)	24 (10,60)	60 (16,120)	
Ever smoke			< 0.001c
No	69	49	
Yes	(59)	(33.1)	
Current smoker	48	99	0.035c
No	(41)	(66.9)	
Yes	(76.9)	(64.2)	
Monthly cigarette count (n = 137)	27 (23.1)	53 (35.8)	0.004b
Median (IQR)	155 (55,480)	300 (150,600)	

*Student's t-test.

Mann-Whitney U test.

*Chi-square test.

more common in the case group, with a significantly higher proportion of individuals reporting ever-drunk alcohol and tobacco, along with a higher prevalence of current smoker. Additionally, the

monthly cigarette dosage was significantly higher in those who had smoked tobacco.

Active pulmonary TB association with cannabis usage

The details of cannabis consumption among cases and controls are summarized in Table 2. Eleven percent of the controls were current cannabis users, whereas nearly 19% had used cannabis at least once before, most commonly through oral consumption (12.8%). Cannabis consumption among cases and controls was not significantly different among current users, quitting age, usage frequency, oral consumption, and health reasons behind cannabis use. Cases were more likely to have a history of ever using cannabis and smoking cannabis via a bong or joint, especially when sharing cannabis during the session. We obtained the ventilation status from 37 out of 38 bong smokers and 30 out of 33 joint smokers. Smoking in well-ventilated areas was reported by 33 (89.2%) of bong smokers and 26 (86.7%) of joint smokers. Table 3 compares the AICs of all prediction models for active pulmonary TB from various types of cannabis use with different combinations of covariates. Owing to the collinearity between smoking via the bong and joints, they were separately analyzed and displayed. Row A displays the results from ever-used cannabis, while rows B and C display those from smoking cannabis via bong and joint, respectively. Model 1, incorporating all exposure variables, showed a significant crude increased risk that remained significant after age, sex, education and occupation were included (Model 2). Of all the models, model 3B yielded the lowest AIC value and was therefore used to calculate the ORs and population-attributed fractions.

Table 4 displays the ORs (95% CI) of variables in model 3B. The effects from smoking and sharing cannabis via a bong were independently significant, as were the effects from tobacco smoking. The levels of ORs between smoking and sharing cannabis via a bong and tobacco smoking were similar (4.22; 95% CI: 1.47–12.07 and 4.36; 95% CI: 1.97–9.65, respectively). The percentages of PAF were 12.16 and 12.62 for the respective categories. Based on the likelihood ratio tests, all other independent variables in the model, except age, were also statistically significant.

Discussion

Our TB cases were more likely to have a lower SES than community-matched controls in terms of education. They were also more likely to consume alcohol and tobacco. Univariate analysis showed that both bong and joint sharing were associated with the disease. However, multivariate analysis suggested that bong sharing was a stronger risk factor, with an OR and PAF close to those of smoking tobacco. Our study conformed with most previous research that found that low SES (49–51) and tobacco smoking were risk factors for TB (13). These factors are associated with addiction, including cannabis use, particularly in Thailand. Therefore, it is important to adjust for these factors when assessing the effects of cannabis in increasing pulmonary TB risk.

TABLE 2 Comparison of cannabis use details among cases and controls.

Variables	Control	Case	<i>p</i> value
Total	117	148	
Current user (within 1 year)			0.303b
No	104 (88.9)	138 (93.2)	
Yes	13 (11.1)	10 (6.8)	
Ever used cannabis			0.002b
No	95	94	
Yes	(81.2)	(63.5)	
History of cannabis use	22	54	
Starting age (<i>n</i> = 76)	(18.8)	(36.5)	0.064a
Median (IQR)	22.5 (18.5,49.2)	19 (18,21)	
Year since last use (<i>n</i> = 49)			0.736a
Median (IQR)	15 (2,38)	10 (3,26.5)	
Frequency (<i>n</i> = 76)			0.366b
Occasionally	12 (54.5)	20 (37)	
Regularly	4 (18.2)	15 (27.8)	
Once or twice	6 (27.3)	19 (35.2)	
Usage via bong smoking			< 0.001c
No	111 (94.9)	116 (78.4)	
Smoke only	1 (0.9)	1 (0.7)	
Smoke and share	5 (4.3)	31 (20.9)	
Usage via joint smoking			0.005b
No	111 (94.9)	121 (81.8)	
Smoke only	3 (2.6)	11 (7.4)	
Smoke and share	3 (2.6)	16 (10.8)	
Usage via oral consumption			0.390b
No	102 (87.2)	135 (91.2)	
Yes	15 (12.8)	13 (8.8)	
Extra information among users			
Paid for cannabis (<i>n</i> = 51)			
No	15 (93.8)	20	
Yes	1 (6.2)	(57.1)	
Monthly spending in THB (<i>n</i> = 16)			
Median (IQR)	5	306 (100,450)	
Using cannabis for health reasons (<i>n</i> = 11)			
To increase appetite	0 (0)	4	
To treat insomnia	1 (25)	(57.14)	
To freshen up	0 (0)	2	
For unknown medicinal benefits	2 (50)	(28.57)	
Missing	1 (25)	0 (0)	

^aMann-Whitney U test.

^bChi-square test.

^cFisher's exact test.

In this study, we tested the effects of different forms of cannabis. Oral consumption was not a risk factor, although it was the most common form of consumption. Leaves are commonly added to food

TABLE 3 Comparison of AIC values among predicting models for active pulmonary TB.

Key independent variables	Odds ratio		
	Model 1	Model 2	Model 3
Included covariates	–	Age group, sex, education, and occupation	Model 2 and history of tobacco smoking
(A)			
Ever used cannabis (ref = never)	2.48 (1.40,4.39)*	2.71 (1.47,5.01)*	2.00 (1.05,3.81)*
AIC	357.46	353.61	339.13
(B)			
Smoking cannabis via bong (ref = no)			
Smoke only	0.96 (0.06,15.49)	0.95 (0.06,16.23)	0.72 (0.04,12.38)
Smoke and shared	5.93 (2.23,15.80)*	6.35 (2.28,17.67)*	4.22 (1.47,12.07)*
AIC	351.36	349.76	336.78
(C)			
Smoking cannabis via joint (ref = no)			
Smoke only	3.36 (0.91,12.37)	4.50 (1.15,17.59)*	3.32 (0.84,13.22)
Smoke and shared	4.89 (1.39,17.24)*	5.45 (1.46,20.34)*	3.42 (0.89,13.05)
AIC	358.31	353.63	339.23

*Statistical significance at *p* < 0.05.

to enhance its flavor and appetite. No plausible mechanism linking this to the risk of pulmonary TB was evident.

Without instrument sharing, we do not have enough evidence to suggest that cannabis smoking has the same effect as tobacco smoking. Notably, non-shared cannabis smoking is uncommon. This lack of evidence is likely explained by the small sample size of the non-sharing groups. Thus, we could not test the hypothesis that cannabis causes respiratory inflammation, which leads to increased TB risk.

In our setting, bong sharing was a significant risk factor for TB, which corresponds well with that reported in a previous contact-tracing study (37). MTB can remain viable in aerosol droplets for as long as 60 min (52). Bong sharing is a socializing activity among cannabis smokers. Aerosol droplets produced by a smoker can enter the bong cavity from the coughing of a patient with active pulmonary TB and be inhaled by the sharer shortly thereafter. Conversely, although more than 85% of bong and joint cannabis smokers were reported to smoke in well-ventilated areas, the possibility of inhaling aerosol droplets without sharing remains if the smokers are seated in close proximity. Joint sharing is a common practice among cannabis smokers. Infectious MTB aerosol droplets can be transmitted to other smokers during a smoking session that is often conducted in a closed space (53). A similar mechanism has been reported for SARS-CoV-2 transmission among tobacco smokers who share the same cigarette (54). The collinearity between joint and bong sharing compelled us to report supporting only one interest. Our choice to choose bong

TABLE 4 Odds ratios of active pulmonary TB.

Variable	OR (95% CI)	PWald's test	$P_{LR-test}$	PAF (%)
Smoking cannabis via bong (ref = no)			0.011	
Smoke only	0.72	0.82		0
Smoke and shared	(0.04,12.38)	3		12.16
Age (ref = ≤ 40 years old)	4.22	0.00	0.169	
41–60 years old	(0.47,48.27)	0.07		
> 60 years old	0.5 (0.21,1.17)	7		
Sex (ref = male) Female		0.10	0.034	
Education (ref = ≥ High school)	2.28 (1.04,5.04)	0.041		
<High school	2.02 (1.1,3.72)	0.024		
Occupation (ref = business owner)			0.038	
Laborer	1.1 (0.47,2.55)	0.83		
Office worker	3.55 (1.36,9.27)	0.01		
Retired/unemployed/student	1.65 (0.75,3.61)	0.212		
Ever smoked tobacco (ref = no)	4.36 (1.97,9.65)	< 0.001	< 0.001	12.62

sharing as the main interest was due to its significant adjusted ORs (4.22; 95% CI: 1.47–12.07), compared to the non-significant OR of joint sharing (3.42; 95% CI: 0.89–13.05). Our study lacked sufficient power to demonstrate the effect of joint sharing because of the small sample size of joint sharing behavior.

Tobacco smoking had similar levels of adjusted OR and PAF as those calculated from the sharing of bongs of cannabis. Tobacco smoking causes ciliary dysfunction and reduces local immunity against MTB infection (55). Although sharing instruments for tobacco smoking increases the risk of TB transmission (56), this behavior is not as common as that observed in cannabis smokers. Therefore, at the population level, the mechanisms attributed to TB cases are different. The strengths of this study lie in the time and place where the study was conceptualized. Thailand, a high TB burden country, and also the first country in Asia to legalize cannabis. It added evidence of this association in general population setting from those derived from a TB contact tracing study (37).

A limitation of the study might come from uncommon setting that number of cases was higher than number of controls, as not all cases could have an eligible control to match with. However, their post-hoc analysis confirmed sufficient power for our hypothesis testing. In addition, sensitivity analyses using only cases with matched control (Supplementary Tables 1–3) showed similar results in both univariate and multivariate analyses, with marginal differences in proportions in the former and a slightly lower odds ratio from sharing bong of cannabis in the latter. These results suggest that not having enough controls for a 1:1 case–control ratio could slightly overestimate the association, as the incomplete control group was not a perfect representation of the matched-population. However, including cases without matched control in the analysis provided slightly higher statistical power. The collinearity between joint and bong sharing among cannabis smokers disabled us to separate these two factors well enough. Our TB cases (and thus also the matched control) were generally older than cannabis consumers in the general population. The prevalence of tobacco smoking in the control group (23.1%) was much higher than in the general population (19%), as reported in a

2017 national survey (57). This might be due to the fact that our study subjects resided in low socio-economic areas. In addition, we excluded TB patients with immunocompromised conditions. This may reduce the generalizability of our findings, as it may not reflect the general TB patient population, especially for PAF. Moreover, the time lag between policy change in 2022 and the study period in 2023 was just 1 year. The association found may not be due to the change in the policy. Therefore, the findings of this study must be interpreted with caution. Most cannabis smokers have started smoking since they were young. Recent changes in the prevalence of cannabis smoking were not observed in the present study. However, the legalization of cannabis in other countries has been followed by an increase in the number of users (29). Therefore, this policy may have an impact on TB risk in lower-middle-income countries where TB is already highly prevalent.

Data availability statement

The original contributions presented in the study are included in the Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because we collected information involved cannabis usage/consumption. To protect the confidentiality and to prevent the data being trace back to the participant, we waived for written informed consent and used verbal informed consent instead.

Author contributions

KC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. VC: Methodology, Validation, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at <https://www.frontiersin.org/articles/10.3389/fpubh.2024.1474761/full#supplementary-material>

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