โครงการ

การเรียนการสอนเพื่อเสริมประสบการณ์

ชื่อโครงการ Association between Ambient Fine Particulate Matter and Hospital Admissions for Ophthalmic Diseases in Upper Northern, Thailand: A Time-stratified, Case-crossover Study

ความสัมพันธ์ระหว่างฝุ่นละอองขนาดเล็กและการเข้ารับการตรวจโรคตาและส่วนประกอบของตาในพื้นที่ ภาคเหนือตอนบน ประเทศไทย: การศึกษาแบบไทม์-สตราติฟายด์ เคส-คอร์สโอเวอร์

ชื่อนิสิต ณิชาพรรณ กสิกรรม **เลขประจำตัว** 6033319423

ภาควิชา วิทยาศาสตร์สิ่งแวดล้อม

ปีการศึกษา 2563

คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

SENIOR PROJECT

Project Title	Association between Ambient Fine Particulate Matter and Hospital Admissions for Ophthalmic Diseases in Upper Northern, Thailand: A Time-stratified, Case-crossover Study

Student Name Nichaphan Kasikam **Student ID** 6033319423

Department Environmental Science

Academic Year 2020

Faculty of Science, Chulalongkorn University

Association between Ambient Fine Particulate Matter and Hospital Admissions for Ophthalmic Diseases in Upper Northern, Thailand: A Time-stratified, Case-crossover Study

ความสัมพันธ์ระหว่างฝุ่นละอองขนาดเล็กและการเข้ารับการตรวจโรคตาและส่วนประกอบของตาในพื้นที่ภาคเหนือตอนบน ประเทศไทย: การศึกษาแบบไทม์-สตราติฟายด์ เคส-คอร์สโอเวอร์

Miss Nichaphan Kasikam

A Senior Project Submitted in Partial Fulfillment of the Requirement for the Degree of Bachelor of Science Program in Environmental Science, Department of Environmental Science, Faculty of Science, Chulalongkorn University, Academic Year 2020

Title	Association between Ambient Fine Particulate Matter and Hospital Admissions for Ophthalmic Diseases in Upper Northern, Thailand: A Time-stratified, Case-crossover Study
Student Name	Nichaphan Kasikam **Student ID** 6033319423
Project Advisor	Assistant Professor Sitthichok Puangthongthub, Ph. D.
Faculty of Science	Department of Environmental Science
Academic Year	2020

Accepted by Department of Environmental Science, Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for the Degree of Bachelor of Science

.... Head of Department of Environmental Science

(Assistant Professor Pasicha Chaikaew, Ph.D.)

SENIOR PROJECT COMMITTEE

.... Chairman

(Jatuwat Sangsanont, Ph.D.)

.... Committee

(Sumeth Wongkiew, Ph.D.)

.... Committee

(Chidsanuphong Chart-asa, Ph.D.)

.... Project Advisor

(Assistant Professor Sitthichok Puangthongthub, Ph. D.)

หัวเรื่อง	ความสัมพันธ์ระหว่างฝุ่นละอองขนาดเล็กและการเข้ารับการตรวจโรคตาและส่วนประกอบของตาในพื้นที่ ภาคเหนือตอนบน ประเทศไทย: การศึกษาแบบไทม์-สตราติฟายด์ เคส-คอร์สโอเวอร์		
ชื่อนิสิต	นางสาว ณิชาพรรณ กสิกรรม	**รหัสนิสิต**	6033319423
อาจารย์ที่ปรึกษา	ผู้ช่วยศาสตราจารย์ ดร.สิทธิโชค พวงทองทับ		
คณะวิทยาศาสตร์	ภาควิชาวิทยาศาสตร์สิ่งแวดล้อม		
ปีการศึกษา	2563		

บทคัดย่อ

ฝุ่นละอองขนาดเล็ก ($PM_{2.5}$) ก่อให้เกิดปัญหามลพิษทางอากาศทั่วโลก รวมถึงภาคเหนือตอนบน ประเทศไทย ในขณะเดียวกัน แม้ว่าดวงตาจะเป็นอวัยวะที่สัมผัสกับมลพิษทางอากาศโดยตรงและผลกระทบต่อสุขภาพสามารถแสดงให้เห็นได้ชัดเมื่อ $PM_{2.5}$ เพิ่มขึ้นอย่างเฉียบพลัน งานวิจัยเกี่ยวกับ $PM_{2.5}$ ที่เกี่ยวข้องกับโรคตาและส่วนประกอบของตาในประชากรไทยยังคงไม่ได้รับการสืบค้น ข้อมูลการเข้ารับการตรวจของผู้ป่วยโรคตาและส่วนประกอบของตา (รหัส H00-H59) จากโรงพยาบาล 118 แห่ง ใน 9 จังหวัดภาคเหนือตอนบนของประเทศไทย ระหว่างปี พ.ศ. 2559 ถึง พ.ศ. 2563 โดยศูนย์เทคโนโลยีสารสนเทศและการสื่อสาร กระทรวงสาธารณสุข (n = 192,545) ถูกวิเคราะห์ความสัมพันธ์กับการได้รับค่าเฉลี่ยรายวัน $PM_{2.5}$ ตั้งแต่ 0 ถึง 7 วันให้หลัง (lag 0-7) จากสถานีวัดฝุ่นที่ใกล้โรงพยาบาลมากที่สุด จากทั้งหมด 15 สถานีตรวจวัดมลพิษทางอากาศและตัวชี้วัดอุตุนิยมวิทยารายชั่วโมง โดยกรมควบคุมมลพิษ ความสัมพันธ์ดังกล่าวถูกวิเคราะห์ตามฤดูกาล เพศ อายุ และโรคย่อยตาและส่วนประกอบของตา โดยวิธีทางสถิติการออกแบบแบบแบ่งช่วงของเวลาและแบบจำลองการถดถอยโลจิสติกแบบหลายตัวแปรและมีเงื่อนไขซึ่งปรับค่าด้วย PM_{10}, O_3, อุณหภูมิ และ ความชื้นสัมพัทธ์ ดำเนินการโดยโปรแกรม R® การศึกษานี้ยังได้วิเคราะห์หาความสัมพันธ์เมื่อได้รับ $PM_{2.5}$ ระดับต่ำกว่ามาตรฐานคุณภาพอากาศของไทยด้วย ผลการศึกษาพบว่า ค่าสัมประสิทธิ์สหสัมพันธ์อย่างมีนัยสำคัญของ $PM_{2.5}$ และตัวแปรอื่นๆ ได้แก่ PM_{10}, O_3 และความชื้นสัมพัทธ์ มีค่าเท่ากับ 0.92 ($p < 0.001$), 0.71 ($p < 0.001$) และ -0.62 ($p < 0.001$) ตามลำดับ ความเสี่ยงที่ตัดผลจากตัวแปรอื่นและระดับนัยยะสำคัญ (ORs and CIs) ถูกคำนวณว่ามีความสัมพันธ์อย่างมีนัยยะสำคัญกับความเข้มข้นรายวันของ $PM_{2.5}$ ที่เพิ่มขึ้น 26 $\mu g/m^3$ ต่อช่วงพิสัยระหว่างควอไทล์ (IQR) การเพิ่มขึ้นของความเข้มข้นของ $PM_{2.5}$ มีความสัมพันธ์อย่างมีนัยสำคัญกับการเพิ่มขึ้นของการเข้ารับการตรวจของผู้ป่วยโรคตาและส่วนประกอบของตา (1.04, 95% CI: 1.02 - 1.07, $p < 0.001$, lag 6) ปริมาณความเสี่ยงที่เพิ่มมากขึ้นพบในช่วงฤดูร้อน (1.23, 95% CI: 1.17 - 1.29, $p < 0.001$, lag 6) และฤดูฝน (1.10, 95% CI: 1.08 - 1.12, $p < 0.001$, lag 0) และไม่พบความเสี่ยงใด ๆ ระหว่างฤดูหนาว ความเสี่ยงต่อโรคตาและส่วนประกอบของตาควรคำนึงถึงอย่างมากในประชากรผู้ชาย (1.05, 95% CI: 1.03 - 1.07, $p < 0.001$, lag 6) และประชากรที่อายุน้อยกว่า 65 ปี (1.05, 95% CI: 1.01 - 1.09, $p = 0.010$, lag 6) ความเสี่ยงของโรคตาและส่วนประกอบของตาหลายโรคควรได้รับการสนใจ ทั้งความผิดปกติของสายตาและการเพ่งมอง (1.63, 95% CI: 1.16 - 2.29, $p = 0.005$, lag 6), เยื่อบุตาอักเสบ (1.34, 95% CI: 1.21 - 1.48, $p < 0.001$, lag 2), กระจกตาอักเสบ (1.22, 95% CI: 1.00 - 1.47, $p = 0.043$, lag

6), โรคตาอื่น ๆ (1.13, 95% CI: 1.01 - 1.25, p = 0.026, lag 1), ต้อกระจก (1.05, 95% CI: 1.02 - 1.09, p = 0.003, lag 6), และตาบอด (1.03, 95% CI: 1.02 - 1.05, p < 0.001, lag 6) การวิเคราะห์อายุและโรคย่อยพบความเสี่ยงที่เพิ่มของโรคต้อหิน (aged > 50y, 1.10, 95% CI: 1.00 - 1.21, p = 0.040, lag 1) และตาเหล่ (aged < 50y, 95% CI: 1.01 - 1.62, p = 0.038, lag 7) การวิเคราะห์กรณีที่ $PM_{2.5}$ ต่ำกว่ามาตรฐานชี้ให้เห็นว่าผลกระทบต่อสุขภาพจาก $PM_{2.5}$ ยังคงมีอยู่ การป้องกันและลดการรับสัมผัส $PM_{2.5}$ แม้ว่า $PM_{2.5}$ มีความเข้มข้นต่ำเป็นเรื่องสำคัญ ผลจากการศึกษานี้เสนอแนะว่าควรบังคับใช้มาตรการลดการรับสัมผัส $PM_{2.5}$ ให้มีประสิทธิภาพและใช้ได้จริงมากขึ้นตามช่วงเวลาและกลุ่มประชากรที่เหมาะสมในบริเวณภาคเหนือตอนบนของประเทศไทย การวิจัยทางระบาดวิทยาสำหรับมลพิษทางอากาศและโรคตาและส่วนประกอบของตายังควรได้รับการศึกษามากขึ้นในอนาคต

คำสำคัญ: ฝุ่นละอองขนาดเล็ก, $PM_{2.5}$, โรคตาและส่วนประกอบของตา, ภาคเหนือตอนบนประเทศไทย, การเข้าโรงพยาบาล

Title	Association between Ambient Fine Particulate Matter and Hospital Admissions for Ophthalmic Diseases in Upper Northern, Thailand: A Time-stratified, Case-crossover Study		
Student name	Nichaphan Kasikam	**Student ID**	6033319423
Project Advisor	Assistant Professor Sitthichok Puangthongthub, Ph. D.		
Faculty of Science	Department of Environmental Science		
Academic Year	2020		

Abstract

Fine particulate matter poses problematic worldwide pollution and has been a major health concern in upper northern Thailand. The eye and its adverse effects are one of the most obvious complaints as a frontline organ is directly exposed especially when ambient $PM_{2.5}$ is acute. Yet, epidemiological studies to investigate the acute association between $PM_{2.5}$ and the eye and adnexa diseases have been lacking. This work analyzed inpatient cases (n = 192,545) of the eye and adnexa diseases (code H00 - H59) in 118 hospitals across 9 upper north provinces of Thailand, 2016 to 2020, given by the Information and Communication Technology Center, Ministry of Public Health. For $PM_{2.5}$ exposure assessment, 15 monitoring stations of the Pollution Control Department were acquired for air pollutants and meteorological indicators. Their hourly measurements were then aggregated to daily average lagged days 0 - 7 and were assigned to their neighborhood hospitals for inpatient exposure. A time-stratified case-crossover design controlling for the day of the week and season trend and multivariate conditional logistics regression adjusted for PM_{10}, O_3, temperature, and relative humidity were performed by the R® program. The associations were analyzed and stratified for the season, sex, age, and sub-diseases. The association of $PM_{2.5}$ exposure below the daily standard was also examined. Results showed significant correlation coefficients of $PM_{2.5}$ and others: PM_{10}, O_3, and relative humidity at 0.92 ($p < 0.001$), 0.71 ($p < 0.001$) and -0.62 ($p < 0.001$) respectively. Adjusted odds ratios and their confidence intervals (ORs and CIs) disclosed statistically significant risk for the increase in $PM_{2.5}$ level per interquartile range (IQR) rising of 26 $\mu g/m^3$. An increase in $PM_{2.5}$ was found associated with the increment of the eye and adnexa inpatient visits (1.04, 95% CI: 1.02 - 1.07, $p < 0.001$, lag 6). The association was riskiest in the hot (1.23, 95% CI: 1.17 - 1.29, $p < 0.001$, lag 6) following by the wet raining season (1.10, 95% CI: 1.08 - 1.12, $p < 0.001$, lag 0) and no positive association observed in the cold season. For the subgroup, risks of the eye and adnexa diseases were slightly higher in males (1.05, 95% CI: 1.03 - 1.07, $p < 0.001$, lag 6) than females and also in younger cases (≤65 y)

(1.05, 95% CI: 1.01 - 1.09, $p = 0.010$, lag 6) than older cases (>65y). Sub-disease risks were elevated significantly such as disorders of refraction and accommodation (1.63, 95% CI: 1.16 - 2.29, $p = 0.005$, lag 6), conjunctivitis (1.34, 95% CI: 1.21 - 1.48, $p < 0.001$, lag 2), keratitis (1.22, 95% CI: 1.00 - 1.47, $p = 0.043$, lag 6), other diseases of the eye and adnexa (1.13, 95% CI: 1.01 - 1.25, $p = 0.026$, lag 1), cataract (1.05, 95% CI: 1.02 - 1.09, $p = 0.003$, lag 6), and blindness (1.03, 95% CI: 1.02 - 1.05, $p < 0.001$, lag 6). For age-sub disease analysis, the increased risk was observed for glaucoma (aged > 50y, 1.10, 95% CI: 1.00 - 1.21, $p = 0.040$, lag 1) and strabismus (aged < 50y, 95% CI: 1.01 - 1.62, $p = 0.038$, lag 7). For exposure below the $PM_{2.5}$ standard, there was no threshold for exposure level to $PM_{2.5}$. Thus, $PM_{2.5}$ exposure prevention is essential to alleviate the vulnerability of the upper-northern population. Stratified risk result is an indication for $PM_{2.5}$ abatement strategy development in upper northern Thailand for the season- and identified sensitive population-specificity. Future research is still in great need for bettering control of other co-pollutants when more available and for estimating other inpatient risk factors.

Keywords: Fine particulate matter, $PM_{2.5}$, The eye and adnexa diseases, Hospitalization, Upper northern Thailand

ACKNOWLEDGMENTS

I would like to express my special thanks of gratitude to my project advisor, Assistant Professor Sitthichok Puangthongthub, Ph. D. as well as the chairman, Jatuwat Sangsanont, Ph.D., and the committee, Sumeth Wongkiew, Ph.D. and Chidsanuphong Chart-asa, Ph.D., who gave me the golden opportunity to do this project on the topic: “Association between Ambient Fine Particulate Matter and Hospital Admissions for Ophthalmic Diseases in Upper Northern, Thailand: A time-stratified, case-crossover study”, which also advocated guidance toward the completion of the project.

I am intensely thankful to the pollution control department, ministry of natural resources and the environment and the information and communication technology center, ministry of public health who supported in gathering information, collecting and directing data to me in making this project, despite their busy schedules. And any attempt at any level cannot be satisfactorily completed without the support and guidance of Mr. Prayad Kenyota.

I would appreciate the useful and accessible websites: cran.r-project.org, .rstudio.com, rdocumentation.org, stackoverflow.com, r-bloggers.com which gave enormous tools, examples, solutions, discussions, and suggestions that allow me understanding and achieving the progression of data analysis in R software.

I would like to deeply thank my parents and friends who always encourage me endlessly throughout this time. Ultimately, many thanks to Taylor Swift and Yorushika, who always make wonderful music that helps me get through this hard-working time, and Gin-san, who always delights me and makes me feel I am not the most reckless one.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1 INTRODUCTION

1.1 PROBLEM STATEMENT

Particulate matter (PM) with a diameter of less than 2.5 micron poses problematic worldwide pollution. Being a widespread air pollutant, consisting of a mixture of solid and liquid particles suspended in the air, the minimum concentration of $PM_{2.5}$ specified by the World Health Organization's (WHO's) air quality guidelines is 10 and 25 μg/m^3 for long-term and short-term exposure, respectively (World Health Organization, 2006). Particles can either be directly emitted into the air or be formed in the atmosphere from gaseous precursors, primary and secondary PM respectively. Primary PM and precursor gases can have both anthropogenic and non-anthropogenic sources (World Health Organization, 2013). Apart from an escalating surge of $PM_{2.5}$ emitting nowadays, and outreaching its recommended level by WHO, these particles contain various detrimental substances, such as metals, polycyclic aromatic hydrocarbons (PAH), water-soluble ions, and other chemicals (Q. Y. Liu et al., 2020; World Health Organization, 2013) which can cause adverse health effects. Riskier, $PM_{2.5}$ particles are smaller than $PM_{10\text{-}2.5}$ particles. But they have a larger surface area to volume ratio, thus $PM_{2.5}$ can carry more those toxic pollutants, and then possibly pass through the lung into the bloodstream and leach to acute health effects (Y. G. Wei et al., 2019). Ambient $PM_{2.5}$ is increasingly recognized as a major contribution to PM-associated health impacts.

The numbers of hospital admissions for respiratory conditions such as asthma, pneumonia have been indicated by numerous studies that are a significant outcome of short-term exposure to $PM_{2.5}$ (Yee, Cho, Yoo, Yun, & Gwak, 2021). Studies also have linked $PM_{2.5}$ to hospital admissions for non-respiratory conditions, such as cardiovascular diseases, diabetes mellitus, skin infections, among others (Y. G. Wei et al., 2019; Zhu et al., 2019). Nearly all the systems of the human body can be affected, including neurological disorders. There has been substantial evidence pointing out that air pollutants can cause serious consequences in a human's neurological health system (Shou et al., 2019; Zanobetti, Dominici, Wang, & Schwartz, 2014). As part of the central nervous system (CNS), the retinal tissue and optic nerve are involved because their development is the protuberance of an embryological brain (Sebastian, 2010). Meanwhile, the eye, one of the few organs directly exposed to the external environment, is only protected by a thin layer of the tear film is very sensitive to external factors. If the toxins' concentration in the air is high, it can cause clinical manifestation even on the same day (Łatka, Nowakowska, Nowomiejska, & Rejdak, 2018). Involving disorders of eyelid, conjunctiva, cornea, lens, and glaucoma, there are some researches existed in epidemiology and toxicology that has insisted on these eye and adnexa effects of fine particulate matter and their chemical components (Chang & Yang, 2020; Łatka et al., 2018; Liang et al., 2017). Exposure to high concentrations of particulate matter in a short period may complain of primarily acute eye conditions: eye irritation, discomfort, conjunctivitis, red eye syndrome, dry eye syndrome, and meibomian gland dysfunction, burning, and itching (Chang & Yang, 2020). Examining the influence and mechanisms of $PM_{2.5}$ on the ocular surface both in vivo and in vitro, studies determined that it induces human corneal epithelial cells (HCECs) death by triggering autophagy (Kashiwagi & Iizuka, 2020), promotes stress and systemic inflammation in various cells (Gao et al., 2016; Kashiwagi & Iizuka, 2020; A. A. Torricelli, Novaes, Matsuda, Alves, & Monteiro, 2011), and other abnormal cell developments (Zeng et al., 2021).

Globally, up to a million people are affected by these eye and adnexa health burdens, and the numbers are expected to increase over time because of the aging population: dry eye disease (Smith et al., 2007), age-related macular degeneration (Wong et al., 2014), cataract (Khairallah et al., 2015), glaucoma (Tham et al., 2014). Research added that Asia was expected to see a substantial increase in the number of older persons in the next few decades, including Thailand (Balachandran, de Beer, James, van Wissen, & Janssen, 2020). In Thailand, public health records showing the incidence of the eye and adnexa diseases that the rate of an eye and adnexa illness has still been an essential health problem which in the top 10 major causes for outpatient visits since 2013. The hospital admission rate was higher in the upper northern areas. Plus, a disorder of cataracts and other disorders of the lens was reported to be the third of principal inpatient visits and the first among the elderly (Strategy and Planning Division, 2018, 2019, 2020). Along with association with fine particulate matter exposure, eye illness has become primarily prevalent in older Thai citizens. However, a comprehensive study in $PM_{2.5}$ levels associated with the eye and adnexa diseases among susceptible targets is still limited in Thailand.

In upper northern, Thailand, the concentrations of $PM_{2.5}$ have experienced high-profile air pollution episodes for decades, commonly affected by open agricultural burning practices, forest fires, and seasonal transboundary impacts from neighboring provinces and countries (Moran, NaSuwan, & Poocharoen, 2019). It is getting worse in the dry season, from January to April. $PM_{2.5}$ concentration levels (average of > 150 μg/m³) have been rising to 7 – 10 times higher than WHO $PM_{2.5}$ Target (IQAir, 2020, 2021) and have exceeded the air quality Thai standards. Yet the state of $PM_{2.5}$ across the upper northern area has been a hazard problem in

Thailand (Pollution Control Department, 2019). With a distinctive climate and terrain, there have been few epidemiology studies clarifying the influence of $PM_{2.5}$ exposure on either short-term or long-term health effects in the upper northern region. These null studying health effects of forest fire-related air pollutants exemplify slightly epidemiology researches of short-term exposure to $PM_{2.5}$ in upper northern Thailand: hospital mortality due to pulmonary fibrosis, cardiac involvement, renal involvement, and cancer (Foocharoen, Peansukwech, Pongkulkiat, Mahakkanukrauh, & Suwannaroj, 2021; Zhang & Tripathi, 2018). No epidemiological study of $PM_{2.5}$ effects on eye and adnexa in Thailand was found, involving analysis stratification by age and sex subgroup. Epidemiology studies in a different territory with individual geography, weather, people characteristics, and activity are essentially dependent on those factors. The health effect of particulate matter on Thai people could not consider its association with other unrelated climate and national resident researches. Thus, a deeper understanding of the epidemiology of the eye and adnexa diseases among the Thai-north population stratified by sex and age is essential to better project future demands for air pollution- and eye disease-related management.

To fill these gaps, this study aims to investigate the associations of short-term exposure to ambient $PM_{2.5}$ with the eye and adnexa diseases inpatient visits; to stratify the risk of hospital admission for the eye and adnexa diseases by season, inpatient's age, sex, and sub-diseases using a time stratified, case-crossover analyses with a conditional logistic regression model. Furthermore, the association below the Thai air quality standard will also be revealed. The results would clarify the effect of $PM_{2.5}$ on the eye and adnexa organs, specifically on the characteristics of the inpatients among Thai citizens. Plus, this research could further provide information for assessing the effectiveness of $PM_{2.5}$ standard interventions; and would be also shared the findings with larger audiences, including members of the public, patients, and other organizations.

1.2 RESEARCH OBJECTIVES

i. To inspect the prevalence of eye and adnexa diseases in the upper north population of Thailand.

ii. To investigate the characteristics of air pollutants and meteorological factors in upper northern Thailand.

iii. To assess the risks of hospital admission for eye and adnexa diseases associated with short-term exposure to $PM_{2.5}$ in upper northern Thailand, and stratify the risks by season, sex, age, and sub-diseases.

iv. To investigate short-term exposure to $PM_{2.5}$ and hospital admission for eye and adnexa diseases when data were restricted to days with a daily $PM_{2.5}$ concentration below the Thai air quality standard.

1.3 SCOPE OF THE RESEARCH

i. This study is a retrospective study.

ii. The fine particulate matter exposure sites are represented by all 15 stations located across 9 provinces in upper northern, Thailand, recording between 2016 - 2020.

iii. The studied population was inpatient with every age and sex and admitted to a selected hospital in upper northern, Thailand during 2016 – 2020.

iv. The studied diseases were the eye and adnexa adverse outcomes (code H00 - H59).

1.4 EXPECTED OUTCOMES

i. This study would encourage to reward more information and consideration of air pollution effects to the Thai territory and review regional environmental change drove by certain human activities.

ii. These pieces of knowledge would support understanding the effects of $PM_{2.5}$ on eye healths and the development of research in this field.

iii. These results are expected to aid in establishing appropriate environmental standards and relevant policies for $PM_{2.5}$ in Thailand.

iv. For a larger audience, the study may benefit future hospital utility management and prevention strategies assessment for the president and administrative board.

v. The results can be reported as raising public awareness of air pollution among Thai citizens.

Chapter 2 LITERATURE REVIEW

The World Health Organization (WHO) has reported an increase in the concentrations of $PM_{2.5}$ which are found to exceed standards especially in lower-middle-income countries (LMICs), including Thailand (Sharma, Chandra, & Kota, 2020). Being one of the well-known risk factors for morbidity and mortality, $PM_{2.5}$ is a global problem consisting of a mixture of solid and liquid particles suspended in the air which can cause eye and adnexa diseases. Throughout the last decade, according to the air pollution databases, Thailand has faced a critical situation, the continuedly exceeding rise of haze particulate matter levels (Pollution Control Department, 2019). So, it is important to determine whether the Thai population has eye problems due to exposure to fine particulate matter, and the extend of the problem.

2.1 FINE PARTICULATE MATTER ($PM_{2.5}$)

DEFINITION AND PRINCIPAL SOURCES

PM is a common proxy indicator for air pollution. Particulate air pollutants comprise material in solid or liquid phases suspended in the atmosphere. Such particles can be either primary or secondary and cover a wide range of sizes. Newly formed secondary particles can be as small as 1–2 nm in diameter (1 nm = 10–9 large as 100 µm (1 µm = 10–6 m), while coarse dust and sea salt particles can be as m) or 0.1 mm in diameter (World Health Organization, 2006).

Commonly used indicators describing PM that are relevant to health refer to the mass concentration of particles with a diameter of less than 10 µm (PM_{10}) and particles with a diameter of less than 2.5 µm ($PM_{2.5}$). $PM_{2.5}$, often called fine PM, also comprises ultrafine particles having a diameter of less than 0.1 µm (World Health Organization, 2013). The major components of PM are sulfate, nitrates, ammonia, sodium chloride, black carbon, mineral dust, and water. It consists of a complex mixture of solid and liquid particles of organic and inorganic substances suspended in the air. It affects more people than any other pollutant. While particles with a diameter of 10 microns or less can penetrate and lodge deep inside the lungs, the even more health-damaging particles are those with a diameter of 2.5 microns or less. $PM_{2.5}$ can penetrate the lung barrier and enter the blood system. Chronic exposure to particles contributes to the risk of developing cardiovascular and respiratory diseases, as well as lung cancer (World Health Organization, 2018).

Primary PM and precursor gases can have both man-made (anthropogenic) and natural (non-anthropogenic) sources. Anthropogenic sources include combustion engines (both diesel and petrol), solid-fuel (coal, lignite, heavy oil, and biomass) combustion for energy production in households and industry, other industrial activities (building, mining, manufacture of cement, ceramic and bricks, and smelting), and erosion of the pavement by road traffic and abrasion of brakes and tires. Agriculture is the main source of ammonium (World Health Organization, 2013).

Secondary particles are formed in the air through chemical reactions of gaseous pollutants. They are products of atmospheric transformation of nitrogen oxides (mainly emitted by traffic and some industrial processes) and sulfur dioxide resulting from the combustion of sulfur-containing fuels. Secondary particles are mostly found in fine PM. Soil and dust re-suspension is also a contributing source of PM, particularly in arid areas or during episodes of long-range transport of dust, for example from the Sahara to southern Europe (World Health Organization, 2013).

Air quality measurements are typically reported in terms of daily or annual mean concentrations of PM_{10} particles per cubic meter of air volume (m^3). Routine air quality measurements typically describe such PM concentrations in terms of micrograms per cubic meter ($\mu g/m^3$). When sufficiently sensitive measurement tools are available, concentrations of fine particles ($PM_{2.5}$ or smaller), are also reported. WHO last revised its AQG values for $PM_{2.5}$ in 2005, as 10 $\mu g/m^3$ for the annual average and 25 $\mu g/m^3$ for the 24-hour mean (not to be exceeded for more than 3 days/year) (World Health Organization, 2018).

HEALTH EFFECTS

PM_{10} and $PM_{2.5}$ include inhalable particles that are small enough to penetrate the thoracic region of the respiratory system. The health effects of inhalable PM are well documented. They are due to exposure over both the short term (hours, days) and long term (months, years) and include respiratory and cardiovascular morbidity, such as aggravation of asthma, respiratory symptoms, and an increase in hospital admissions; mortality from cardiovascular and respiratory diseases and lung cancer (World Health Organization, 2013).

There is good evidence of the effects of short-term exposure to PM_{10} on respiratory health, but for mortality, and especially as a consequence of long-term exposure, $PM_{2.5}$ is a stronger risk factor than the coarse part of PM_{10} (particles in the 2.5–10 µm range) (Beelen et al., 2008; Samoli et al., 2008; World Health Organization, 2006). To compare the above study, all-cause daily mortality increasing by 0.2–0.6% per 10 $\mu g/m^3$ of PM_{10} and long-term exposure to $PM_{2.5}$ associated with an increase in the long-term risk of cardiopulmonary mortality by 6–13% per

10 μg/m^3 of $PM_{2.5}$. Susceptible groups with pre-existing lung or heart disease, as well as elderly people and children, are particularly vulnerable. For example, exposure to PM affects lung development in children, including reversible deficits in lung function as well as chronically reduced lung growth rate and a deficit in long-term lung function (World Health Organization, 2018). There is no evidence of a safe level of exposure or a threshold below which no adverse health effects occur. The exposure is ubiquitous and involuntary, increasing the significance of this determinant of health (World Health Organization, 2013). It should be noted, however, that the evidence for the hazardous nature of combustion-related PM (from both mobile and stationary sources) is more consistent than that for PM from other sources (World Health Organization, 2013).

2.2 THE EYE AND ADNEXA DISEASES

VISION AND THE EYE'S ANATOMY

The eye is the organ that allows us to see. The eyeball itself is a sphere spanning approximately 24 mm in diameter. It is suspended in the bony socket by muscles controlling its movements and is partially cushioned by a thick layer of fatty tissue within the skull that protects it during movement. The eyes move symmetrically (in the same direction at the same time). These symmetrical movements are made possible through the coordination of the extraocular muscles (muscles outside the eye). Since the eyes are paired structures, the brain receives two slightly different images that overlap with one another. Interpretation of the different images is possible via coordinated eye movements achieved by complex neural mechanisms. Humans are also able to perceive three-dimensional images because they possess binocular vision, which enables the perception of depth and distance (Health Engine, 2007).

The eyeball consists of three main components: *the tunics*, which are three layers that make up the wall of the eyeball, *the optical components*, also known as the refractile media components, which admit and focus light, and *the neural components*, which consist of the retina and the optic nerve. The retina is also part of the inner tunic (Figure 2.1).

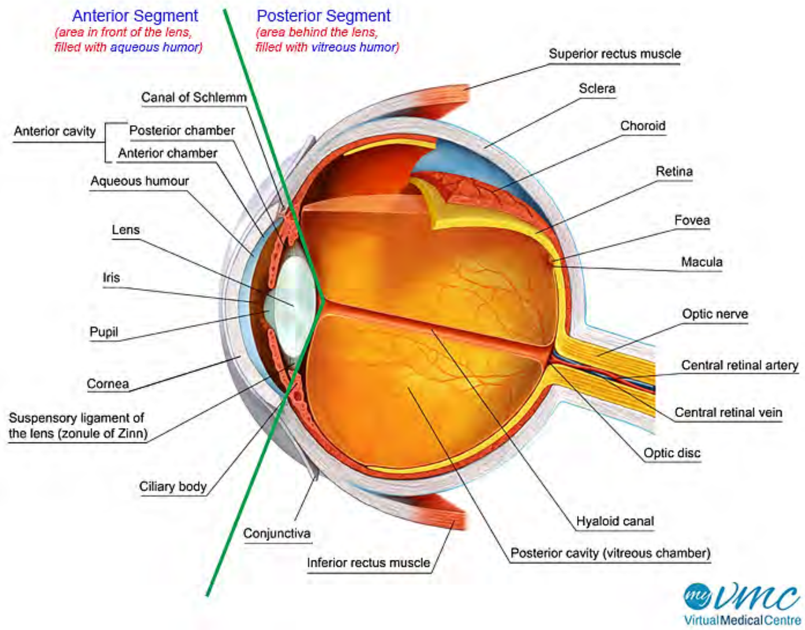

Figure 2.1 Anatomy of the eye

The tunics

Layers (tunics) of the eye, the tunics of the eye consist of the following three layers:

Tunica fibrosa: Tunica fibrosa refers to the outer fibrous layer of the eye. This includes the sclera and the cornea, which are continuous with one another.

- Sclera: The sclera is the white part of the eye, and covers most of the eye surface. It is made up of dense tissue which has a rich supply of blood vessels and nerves and provides attachment for the external muscles of the eye. The sclera tends to have a slight blue tinge during childhood because of its thinness. It also can appear yellow in the elderly due to the accumulation of a pigment associated with age-related wear and tear in the tissue.
- Cornea: The cornea allows light to enter the eye, and can be thought of as being part of the modified sclera.

Tunica vasculosa: Tunica vasculosa refers to the middle vascular layer. This is also called the uvea. The uvea is made up of the choroid, ciliary body, and iris.

- Ciliary body: The ciliary body forms a muscular ring around the lens. It secrets a fluid called the aqueous humor and supports the iris and lens. The ciliary muscle, which is a smooth muscle responsible for lens accommodation, is contained within the ciliary body. Contraction of the ciliary muscle enables the lens to focus light onto the retina by changing its shape.

- Iris: The iris is an adjustable thin muscle controlling pupil diameter. It consists of two layers – one that blocks stray light from reaching the retina, and another containing cells called chromatophores which contain a substance called melanin. The concentrations of melanin within these chromatophores give rise to eye color. High concentrations of melanin give the iris a black or brown color. When there is scarce melanin, light reflects from the epithelium of the posterior pigment, giving the iris a blue, green, or grey color.

Tunica interna: Tunica interna refers to the innermost layer. This layer is made up of the neural components – the retina and optic nerve, which are discussed later under the Neural components of the eye.

Chambers of the eye

The three layers of the eye, along with the lens, act as boundaries for the three chambers within the eye: Anterior chamber, Posterior chamber, Vitreous chamber.

The eye can also be divided into its anterior (front) and posterior (back) segments. The former consists of the cornea, as well as the anterior and posterior chambers and their contents. The posterior segment contains the vitreous chamber, the visual retina, retinal pigment epithelium (RPE), posterior sclera, and the uvea.

Optical components of the eye

The optical components are transparent elements that admit, bend, and focus light onto the cells of the retina to form images. This occurs through the process of refraction, so the optical components are also known as refractile media components. These components are:

- The cornea: the cornea acts as the main window of the eye. This is the major refractive element of the eye.

- Aqueous humor: aqueous humor is a watery fluid in the anterior and posterior chambers that is secreted by the ciliary body. Its role in refraction is relatively minor, but it is important in providing nutrients to the lens and cornea, which do not have the means to support themselves and are the two critical refractile elements.

- The lens: the lens is second-most in importance to the cornea in the refraction of light rays. It is elastic so that the shape of the lens can undergo minor changes in response to the tension of the ciliary muscle. Tension on the muscle flattens the lens, whereas it relaxes into a more spheroid shape when it is not under tension. These changes allow for accommodation to allow proper focusing on near objects.

- Vitreous body: the vitreous body contains a fluid component called the vitreous humor. The vitreous body acts as a shock absorber that protects the retina during rapid eye movements and helps to maintain the shape of the eye. In addition to refracting light, it also helps maintain the position of the lens and to keeps the neural retina in contact with the retinal pigment epithelium.

Neural components of the eye

As previously mentioned, the neural components of the eye are the retina and the optic nerve.

- Retina: the retina is a cup-shaped outgrowth of the brain. It is a thin transparent membrane attached at two points – the optic disc, where the optic nerve leaves the rear of the eye, and the ora Serrata, which is the junction between the retina and the ciliary body. It is smoothly pressed against the rear of the eyeball due to pressure coming from the vitreous body.

A detached retina can result from blows to the head or inadequate pressure from the vitreous body and can cause blurry areas in the field of vision. Since the retina normally attaches to and depends on the choroid for oxygen, nutrition, and waste removal, prolonged detachment of the retina from the choroid can lead to blindness.

- Macula lutea: A patch of cells about 3mm in diameter can be found in the retina, known as the macula lutea. In the center of this patch is a small pit called the fovea centralis, which produces finely detailed images.

The optic disc is found close to the macula lutea and is the point on which nerve fibers from all regions of the retina converge. These nerve fibers then exit the eye to form the optic nerve, so that the neural retina is continuous with the central nervous system through the optic nerve.

- Neural retina: the neural retina contains light-sensitive receptors and complex neural networks, and the retinal pigment epithelium (RPE). It consists largely of photoreceptor cells called retinal rods and cones. Visual information encoded by the rod and cones is sent to the brain via impulses conveyed along the optic nerve.

- Pupil: the pupil, which looks black because of the heavily pigmented back of the eye, changes size to control and regulate the amount of light passing through the lens to reach the retina ().

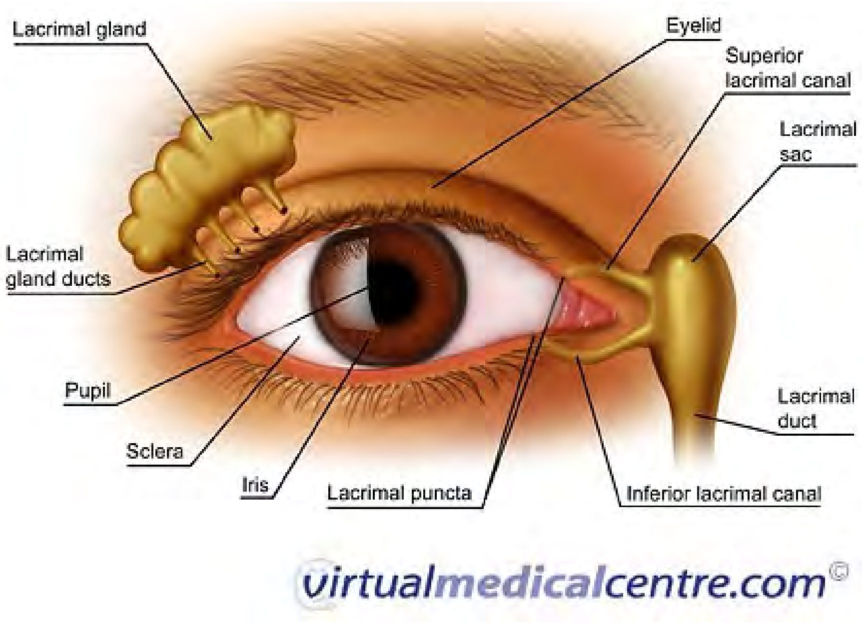

Figure 2.2 Anatomy of external eyes

Accessory structures

- Conjunctiva: The conjunctiva refers to the lining of the eye. It helps lubricate the eye by secreting mucous and tears and serves as a protective barrier again microbes. It contains many goblet cells which secrete a component of the tears that bathe the eye.
- Eyelid: the main function of the eyelid is to provide the eye with protection. The skin of the eyelids is loose and elastic, allowing for movement. There are several types of glands in the eyelids, including tarsal glands that produce a sebaceous secretion that results in an oily surface of the tear film to prevent the evaporation of the normal tear layer.
- Eyelashes: eyelashes are short stiff curved hairs that may occur in double or triple rows. They function to protect the eye from debris. Lashes may also have different lengths and diameters to one another.
- Lacrimal gland: the lacrimal glands are the sites of tear production. Tears function to keep the conjunctiva and corneal epithelium moist and wash away foreign material from the eye. The film of tears covering the corneal surface is a mixture of proteins, enzymes, lipids, metabolites, electrolytes, and drugs (secreted during therapy).
- Extraocular muscles: extraocular muscles (muscles outside the eye) allow the eye to move within its orbit. Six of these eyeball muscles attach to each eye. The actions of these muscles of both eyes are coordinated to enable the eyes to move in parallel, a phenomenon known as conjugate gaze.

Light

The amount of light entering the eye is controlled by the iris, which is a thin pigmented smooth muscle with different individual characteristics. These form a unique pattern in each individual so that it is possible to use the iris as a means of identification that is more foolproof even than fingerprinting or DNA testing.

Light enters through the pupil in the center of the iris. The size of the pupil is adjusted by variable contractions of the iris muscles to control the amount of light entering. The iris contains two sets of smooth muscle networks, one circular (in a ringlike fashion), and one radial (projecting outward).

The pupil becomes smaller when the circular muscle contracts and shortens in response to bright light, to decrease the amount of light entering the eye. Under dim conditions, the radial muscle shortens, increasing the size of the pupil.

Light rays are divergent (spreading outward) and must be bent inward to be focused back into a point, known as the focal point, on the light-sensitive retina, to produce an accurate image of the light source.

Refraction

Refraction refers to the bending of a light ray and occurs when the ray passes from a substance of one density to a substance with another density. The greater the difference in densities, the greater the degree of bending and hence refraction.

The degree of refraction also depends on the angle at which the light strikes the second substance – the greater the angle, the greater the refraction. With a curved surface such as the lens, greater curvature results in greater degrees of bending, and therefore a stronger lens.

A convex surface curves outwards while a concave surface curves inwards. Convex surfaces converge light rays, bringing them closer together. Convergence is essential for bringing an image to a focal point; therefore the refractive surfaces of the eye are convex.

Cornea and lens

The cornea and the lens are the eye’s most important refractive structures. Light first passes through the cornea, which has a curved surface. The cornea contributes the most to the eye’s total refractive ability because the difference in density at the air/corneal surface is much greater than the differences in density between the lens and the fluids surrounding it.

Rays from light sources more than about 6 meters away are considered to be parallel by the time they reach the eye, while light rays from closer objects are still diverging when they reach the eye. For a given refractive ability of the eye, it takes a greater distance behind the lens to bring the divergent rays of a near-source to a focal point than to bring the parallel rays of a far source to a focal point. However, the distance between the lens and the retina is always the same in a particular eye. The strength of the lens is therefore manipulated via a process called accommodation.

Accommodation

Accommodation refers to the ability to adjust the strength of the lens by changing its shape, which in turn is regulated by the ciliary muscle. When the ciliary muscle is relaxed, the ligaments (bands of tissue) attached to the lens pull the lens flat and therefore less curved and weakly refractive.

Contracting the ciliary muscle reduces the tension in the ligaments so that the lens assumes a more curved shape because of its elasticity. The greater curvature allows the lens to increase its strength, resulting in greater bending of the light rays. Therefore, in far vision, the ciliary muscle is relaxed and the lens is flat, but during the near vision, the muscle contracts and allows the lens to become more convex.

Phototransduction

Vision occurs through the process of phototransduction. Phototransduction is the conversion of light stimuli into neural (brain) signals by the retinal cells. The cells that perform this function are known as photoreceptors (also called rod and cone cells) and consist of three parts:

- Outer segment, which is closest to the exterior of the eye and detects the light
- Inner segment, which is in the middle and contains the components necessary for the cell’s basic functions to survive
- Synaptic terminal, which is closest to the interior of the eye. It transmits the signal, which is generated in the photoreceptor, to the bipolar cells upon light stimulation.
- The outer segment of the eye contains over a billion light-sensitive molecules. Photopigments are substances that undergo chemical alterations when activated by light. They are made up of two components, called opsin and retinene. The retina is the light-absorbing part of the photopigment.

Photopigments

There are four types of photopigments, one in the rods and one in each of three types of cones. Each type of photopigment absorbs a different wavelength of light. The pigment in the rods is called rhodopsin. Rhodopsin absorbs all visible wavelengths so that rods provide vision only in shades of grey by detecting different intensities rather than colors. The three types of cones – red, green, and blue, can respond selectively to various wavelengths of light, giving rise to color vision.

DISEASES OF THE EYE AND ADNEXA

The diseases of eye and adnexa are classified as chapter VII and H00 – H59 code by International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010. Each code will be represented the sub-diseases of the eye and adnexa (Table 2.1).

Table 2.1 ICD-10 codes the diseases of the eye and adnexa

H00-H06	Disorders of eyelid, lacrimal system, and orbit
H10-H13	Disorders of conjunctiva
H15-H22	Disorders of sclera, cornea, iris, and ciliary body
H25-H28	Disorders of lens
H30-H36	Disorders of choroid and retina
H40-H42	Glaucoma
H43-H45	Disorders of vitreous body and globe
H46-H48	Disorders of the optic nerve and visual pathways
H49-H52	Disorders of ocular muscles, binocular movement, accommodation, and refraction
H53-H54	Visual disturbances and blindness
H55-H59	Other disorders of eye and adnexa

THE INCIDENCE OF THE EYE AND ADNEXA DISEASES ACROSS THE WORLD

The trend and the burden of ocular diseases are shown in the following investigation. Visual loss, defined as either visual impairment or blindness, is a major public health problem. The global health burden of vision loss due to cataracts increased between 1990 and 2015 despite considerable efforts from the World Health Organization and VISION 2020 initiatives (He, Wang, & Huang, 2017). Asia alone accounts for approximately 60% of cases of visual impairment and blindness worldwide (Bourne et al., 2017). Globally, with a severe visual impairment from cataracts, the number of people is projected to be 220 million in 2020 (Apple, 2000). The most common eye disease diagnosed in emergency departments and affects all ages is conjunctivitis, which has caused serious health and economic burdens around the world (Chen et al., 2019). Myopia is the most common cause of distance vision impairment as well, and the condition is increasing at an alarming rate worldwide. Uncorrected myopia was estimated to affect 108 million people globally in 2013, and it is expected that one-third of the world's population (2.5 billion people) will be affected by myopia in the next decade (Morgan, 2016). Additionally, the population-based prevalence of symptomatic dry eye diseases (SDED) is estimated to be 5 - 30% and is increasing globally as a result of rapidly aging and urbanized societies (Smith et al., 2007).

For those different age subpopulations, the prevalence of several eyes and adnexa diseases is associated with age-related diseases such as glaucoma, age-related macular degeneration, vascular lesion, presbyopia, dry eyes macular degeneration, cataracts, and temporal arteritis (Cleveland Clinic, 2021; Le, Mukesh, McCarty, & Taylor, 2003; Pascolini & Mariotti, 2012). With the population aging and elongation of life expectancy, the number of people with eye and adnexa diseases was expected to continue elevating.

2.3 STUDIES OF EFFECTS OF $PM_{2.5}$ ON THE EYE AND ADNEXA

Reviewing of different epidemiological and toxicological studies revealed that exposure to fine particulate matter was associated with eye illness. In toxicology, recent studies mainly focused on the genotoxic effect of fine particulate matter on corneal epithelial cells and retinal organoids in vivo and in vitro. It illustrated the role of reactive oxygen species (ROS) formation, the process of DNA damage, cell senescence, and triggering autophagy in this process. The researches on $PM_{2.5}$ inducing cell toxicity in vivo and in vitro is shown (Table 2.2). Being investigated the association during 2017 – 2021 in the epidemiological studies, $PM_{2.5}$ is reported that can increase the burden of the eye and adnexa illness among outpatient visits and emergency department visits across the world in the UK, Africa, Canada, Russia, and Asia (Table 2.3), including all ocular diseases, a disorder of conjunctivitis, glaucoma, dry eye disease, and disorder of cataract, presbyopia, and myopia. To emphasis on the epidemiological findings, the design of studies was heterogeneous involving a time-series, case-control, a case-crossover, cohort, and cross-sectional design. The applied mathematic model to estimate risk was comprised of a correlation model, a linear mixed-effect model, the Cox proportional hazards regression model, a single-variate regression model, and a multivariate regression model. The ORs estimate of associations between $PM_{2.5}$ and diseases of the eye and adnexa was observed at approximately 1.004 – 1.19. Results were found between lag 0 to lag 7 (one week later). Characteristic of the population was observed at all ages, 40 – 69, <65, >50, and >65 years old.

2.4 $PM_{2.5}$ THAI STANDARD

In acknowledgement of the threats posed by $PM_{2.5}$, the World Health Organization set the average 1-year $PM_{2.5}$ dust standard at 10 µg/m^3 and the 24-hours average at 25 µg/m^3 (World Health Organization, 2018). However, since 11 years ago, the Pollution Control Department of Thailand set the $PM_{2.5}$ average ceiling for 1 year at 25 µg/m^3 and the average 24 hours at 50 µg/m^3 (Pollution Control Department, 2010). It's been over 10 years since Thailand has set a higher level of dust safety than international standards. Meanwhile, neighboring countries are constantly alerted to the problem of air pollution. In recent years, the Pollution Control Department of Thailand disclosed a draft document of supporting documents for improving the standard for $PM_{2.5}$ in ambient air (Pollution Control Department, 2021). It reported that the $PM_{2.5}$ Thai standard was higher than many countries, such as the USA, Canada, or other countries in the Asian continent, including Singapore, China, Taiwan, and Japan, and showed the need for $PM_{2.5}$ standard improvement in Thailand. Furthermore, many sectors argued that the $PM_{2.5}$ standard's optimum value should be reduced to match the WHO recommendation (BBC, 2019; Greenpeace, 2021).

Conclusion

Literature reviews on fine particulate matter and the eye and adnexa diseases were acknowledged. It is widely recognized that outdoor air pollution can affect human health. Various chemical components that are present in ambient pollution may have an irritant effect on the mucous membranes of the body, particularly those of the respiratory tract. Much less attention has been focused on the adverse effect on the eye and adnexa, one of the most essential organs. Even though this structure is even more exposed to air pollution than the respiratory mucosa since only a very thin tear film separates the corneal and conjunctival epithelia from the air pollutants. So far, toxicological and epidemiological tools are used for assessing possible aggression to ocular health. However, the demand for studying $PM_{2.5}$ and the eye and adnexa is existing. There was no study of the effect of $PM_{2.5}$ on the total of the eye and adnexa diseases and stratified by every ocular disease, sex, and age subgroup and no study of the association of $PM_{2.5}$ with diseases of the eye and adnexa in Thailand. Plus, the argument for a safe level of $PM_{2.5}$ standard does exist.

Table 2.2 Toxicological researches on the fine particulate matter ($PM_{2.5}$) and DNA and cell disturbance

TOXICOLOGY

Article	Targets/outcomes	Type	Animal	Exposure period	Result
(Gao et al., 2016)	Corneal epithelial cells and DNA	In vitro		Short-term	– DNA damage – Cell senescence in HCECs
(Q. Fu et al., 2017)	Corneal epithelial cell	In vitro		Short-term	– HCEC death by triggering autophagy
(Cui et al., 2018)	Corneal epithelial cells	In vivo	Mice	Short-term	– Delay of corneal epithelium wound healing
(Tang et al., 2019)	Acute allergic conjunctivitis	In vivo	Mice	Long-term	– Inducing symptoms similar to clinical allergic conjunctivitis
(Kashiwagi & Iizuka, 2020)	Human corneal epithelial cells	In vitro		Short-term	– HCEC death by triggering autophagy – Releasing cytokines to involve in HCEC damage
(Zeng et al., 2021)	hESC-derived retinal organoids	In vitro		Short-term	– Contributing to abnormal human retinal development

Table 2.3 Epidemiological researches on the fine particulate matter ($PM_{2.5}$) and the eye and adnexa diseases

EPIDEMIOLOGY

Article	Location	Health outcome	Age (years)	n	Study period (years)	Method	Model	Result	
(Mimura et al., 2014)	Japan	Conjunctivitis (H10)	All	16,079	0.5	A time-series study	Pearson's two-tailed correlation model	Correlation coefficients (r) = 0.62 (0.14, 0.87)	
(Szyszkowicz, Kousha, & Castner, 2016)	Canada	Conjunctivitis (H10)	All	77,439	7	A time-stratified case-crossover study	Cox proportional hazard regression model	OR (95% CI) = 1.014 (1.005, 1.022)	Lag 07
(Q. L. Fu et al., 2017)	Hangzhou, China	Conjunctivitis (H10)	All	9,737	2	A time-stratified case-crossover study	Cox proportional hazards regression model	OR (95% CI) = 1.0092 (1.0002, 1.0183)	Lag 0
								OR (95% CI) = 1.0107 (1.0002, 1.0213)	Lag 01
(Liang et al., 2017)	Beijing, China	Ocular diseases (H00 – H59)	All	1,007	0.25	A time-stratified case-crossover study	Cox proportional hazards regression model	Percent increases = 12.6 (0.0, 26.7%)	Lag 0
(S. Y. L. Chua et al., 2019)	UK	Glaucoma (H40)	40 - 69	111,370	4	Cohort study	Multivariate regression model	OR (95% CI) = 1.06 (1.01, 1.12)	
(Lu et al., 2019)	China	Conjunctivitis (H10)	All	81,351	2	A time-stratified case-crossover study	Linear Poisson regression model	OR (95% CI) = 1.004 (1.002, 1.007)	Lag 0
(Lin et al., 2019)	China, Ghana, India, Mexico, the Russian Federation and South Africa	Presbyopia (H52.4)	≦65	36,742	3	A cross-sectional study	Linear mixed effect model	OR (95% CI) = 1.17 (1.11, 1.24)	
			>65					OR (95% CI) = 1.10 (1.02, 1.17)	
(Mo et al., 2019)	China	Dry eye disease (H16.208, H11.103)	All	1,067,441	2	A time-stratified case-crossover study	Cox proportional hazards regression model	OR (95% CI) = 1.0222 (1.0097 - 1.0348)	Lag 0
								OR (95% CI) = 1.0222 (1.0082 - 1.0364)	Lag 01
(Ruan et al., 2019)	China, Ghana, India, Mexico, the Russian Federation and South Africa	Myopia (H52.13)	50+	33,626	3	A cross-sectional study	Linear mixed-effect Poisson regression model	PR = 1.12 (1.05, 1.21)	
(Aik, Chua, Jamali, & Chee, 2020)	Singapore	Conjunctivitis (H10)	All	261,959	9	A time-series study	Multivariate regression model	IRR = 1.038, (1.029, 1.046)	Lag 01
(Kim, Choi, Kim, Paik, & Kim, 2020)	Korea	Dry eye disease (H04)	All	43	2	A prospective observational study	Linear mixed effect model	Beta = 0.378 (0.055, 0.699)	1 day
								Beta = 0.397 (0.092, 0.703)	1 week
(Sun et al., 2021)	Taiwan	Open-Angle Glaucoma (H40)	65+	2,580	5	A case–control study	Cox proportional hazards regression model	OR (95% CI) = 1.193 (1.050, 1.356)	

Chapter 3 MATERIALS AND METHODS

3.1 UPPER NORTHERN REGIONS, THAILAND

The provincial boundaries and locations of the study area are shown in Figure 3.1. The study location was 9 provinces in upper northern, Thailand, involving Chiang Mai, Lamphun, Lampang, Phrae, Nan, Phayao, Chiang Rai, Mae Hong Son, and Tak. The area of interest spans 105,474 km^2 and borders Myanmar and Laos.

Geographically the division, in conformance with the six-region system, includes most of the mountainous natural region of the Thai highlands. Upper-northern Thailand is geographically characterized by several mountain ranges, which continue from the Shan Hills in bordering Myanmar to Laos, and the river valleys which cut through them. Though like most of Thailand, it has a tropical savanna climate, its relatively high elevation and latitude contribute to more pronounced seasonal temperature variation, with cooler winters than the other regions (Department of Mineral Resources, 2013).

During the dry season, there is the air stagnation phenomenon and high air pressure has spread over in Thailand, which results in a large accumulation of air pollution in the area. In the upper northern region of Thailand, the phenomenon has been found continuously until April and air quality will improve in the monsoon season (Climatological Center, 2020).

3.2 MEDICARE DATA

Principle inpatient diagnosis record appertained to a hospital in Thailand was acquired from January 1, 2016 – December 31, 2020, from the information and communication technology center, office of the permanent secretary, ministry of public health (118 hospitals). The record was requested for inpatients admitted to hospital during 2010 – 2020 who were diagnosed with eye and adnexa diseases, whose characteristics were admission date, admitted hospital, age, sex, occupation, education, weight, and heigh. While the obtained data was only the diagnosis code, admission date from 2016 - 2020, admitted hospital, age, and sex. The official information requisition was attached in Appendix a. Without computing data, raw data had 297,791 cases. After exploring data and excluding missing data, the case was 192,545 (Appendix b). Patients who were admitted to the hospital for eye and adnexa diseases (Table 3.1) will be identified with a principle diagnosis ICD-10-TM (International Classification of Diseases and Related Health Problems, 10th Revision, Thai Modification) code (Ministry of Public Health, 2016b). The data of patients were abstracted with the following characteristic:

age, sex, date of admission, admitted hospital in which the hospital admission risk will be analyzed. The location of the hospital was obtained from the website of the health resources geographic information system, free assessment from the ministry of public health (Ministry of Public Health, 2021). Admission dates and address of admitted hospitals were consequential knowledge to detect an individual short-term exposure timeline and location respectively.

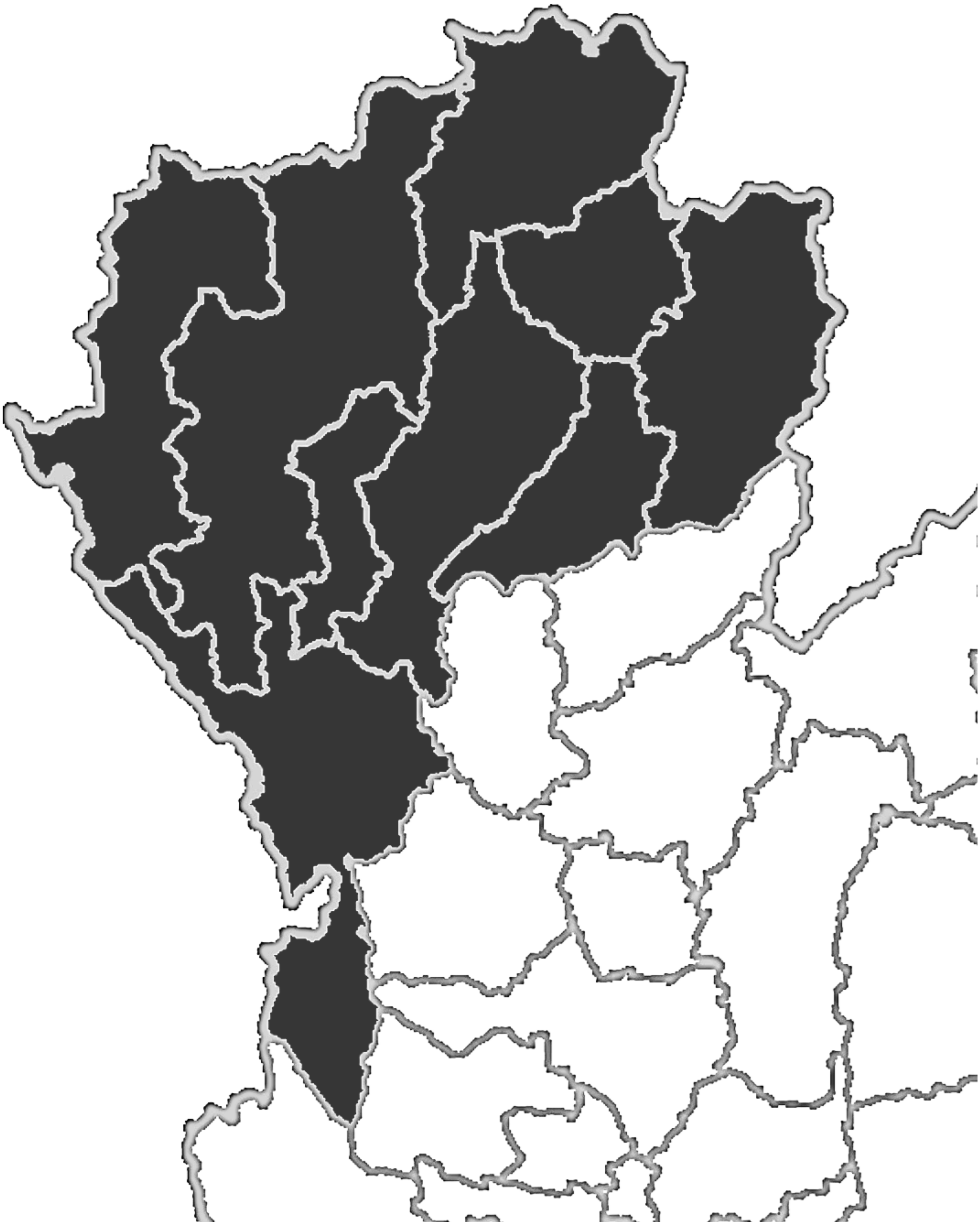

Figure 3.1 Map of the upper northern region of Thailand

Table 3.1 Lists of the eye and adnexa diseases according to ICD-10-TM

Code	Sub-diseases
130	Inflammation of eyelid (H00-H01)
131	Conjunctivitis and other disorders of the conjunctiva (H10-H13)
132	Keratitis and other disorders of sclera and cornea (H15-H19)
133	Cataract and other disorders of the lens (H25-H28)
134	Retinal detachments and breaks (H33)
135	Glaucoma (H40-H42)
136	Strabismus (H49-H50)
137	Disorders of refraction and accommodation (H52)
138	Blindness and low vision (H54)
139	Other diseases of the eye and adnexa (H02-H06, H20-H22, H30-H32, H34-H36, H43-H48, H51, H53, H55-H59)

3.3 POLLUTION AND METEOROLOGICAL DATA

Hourly $PM_{2.5}$ concentrations, apposite pollutants performing as a confounder which is PM_{10}, ozone, and meteorological parameters including temperature, relative humidity were measured at 4 monitoring stations in 2016 - 2018 (Figure 3.2) and 15 monitoring stations in 2019 – 2020 (Figure 3.3) in upper northern, Thailand by the pollution control department. Before calculating daily concentration, the low repeated value was eliminated. Data missing was imputed with available values from the nearest stations on the same day (Appendix b). The exposure level of pollutants and weathers was calculated 24-h average from hourly concentrations for $PM_{2.5}$ in $\mu g/m^3$ unit (n = 612,167 hr, NA = 45,553 hr), PM_{10} ($\mu g/m^3$), temperature (˚C), Relative humidity (%), and 8-h maximum value for O_3 (ppb) (The United States Environmental Protection Agency, 2020). The location of the monitoring station was observed from the website of the situation and air quality in Thailand (Department of Pollution Control, 2013). Individual exposure data to pollutions and weather conditions were obtained from the monitoring station nearest to the admitted hospital. The distances between the hospital and monitoring station were shown in Appendix b. Short-term exposure to fine particulate matter will be evaluated by exposure to daily average $PM_{2.5}$ on the same day of the hospital admission day to 7 days before (lag 0-7). Notably, other essential pollutants which behave as a confounder were excepted to be estimated in models according to a lack of sufficient availability, including NO_2, SO_2, and CO (Appendix b).

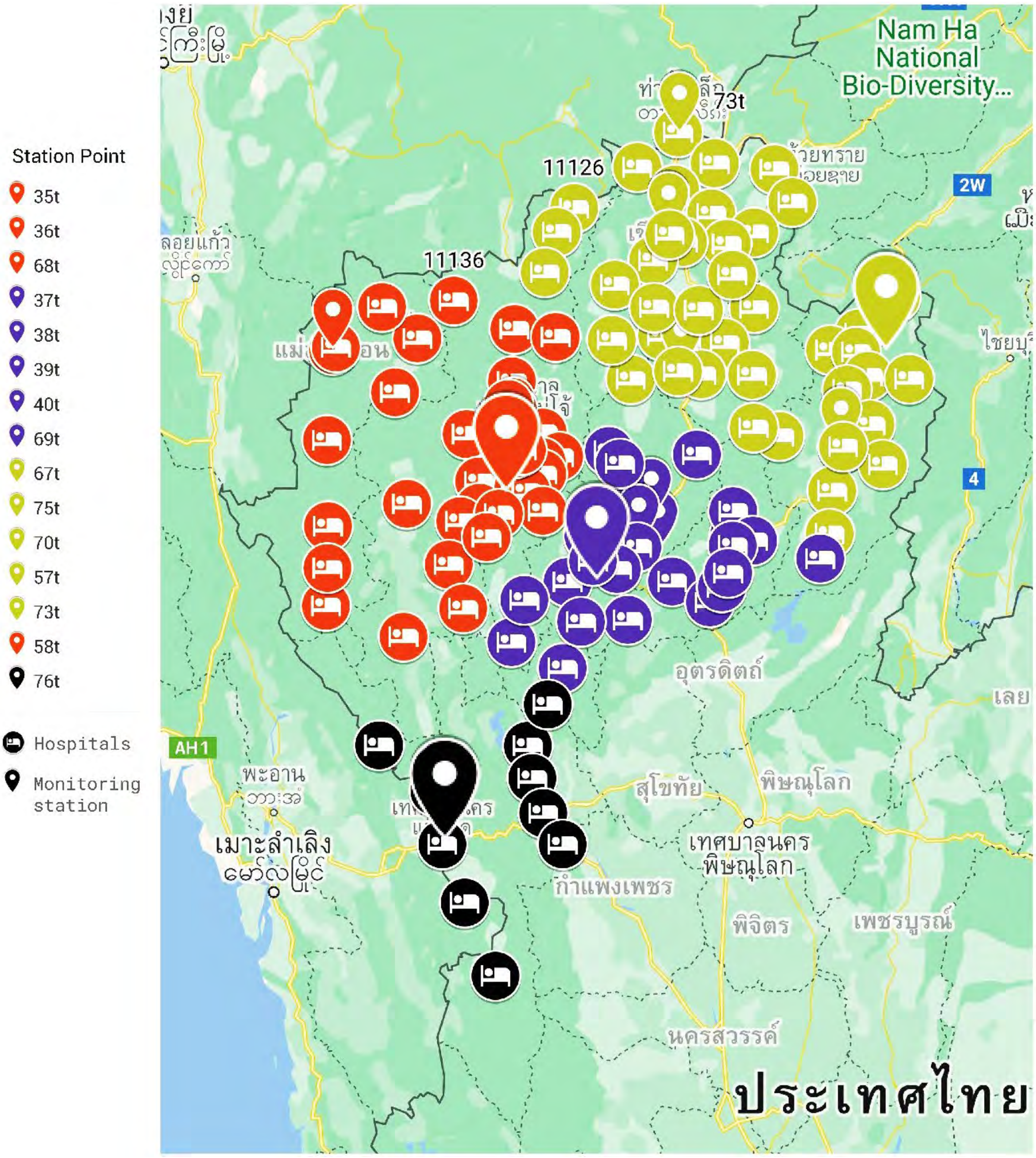

Figure 3.2 Map of monitoring stations and admitted hospitals during 2016 - 2018

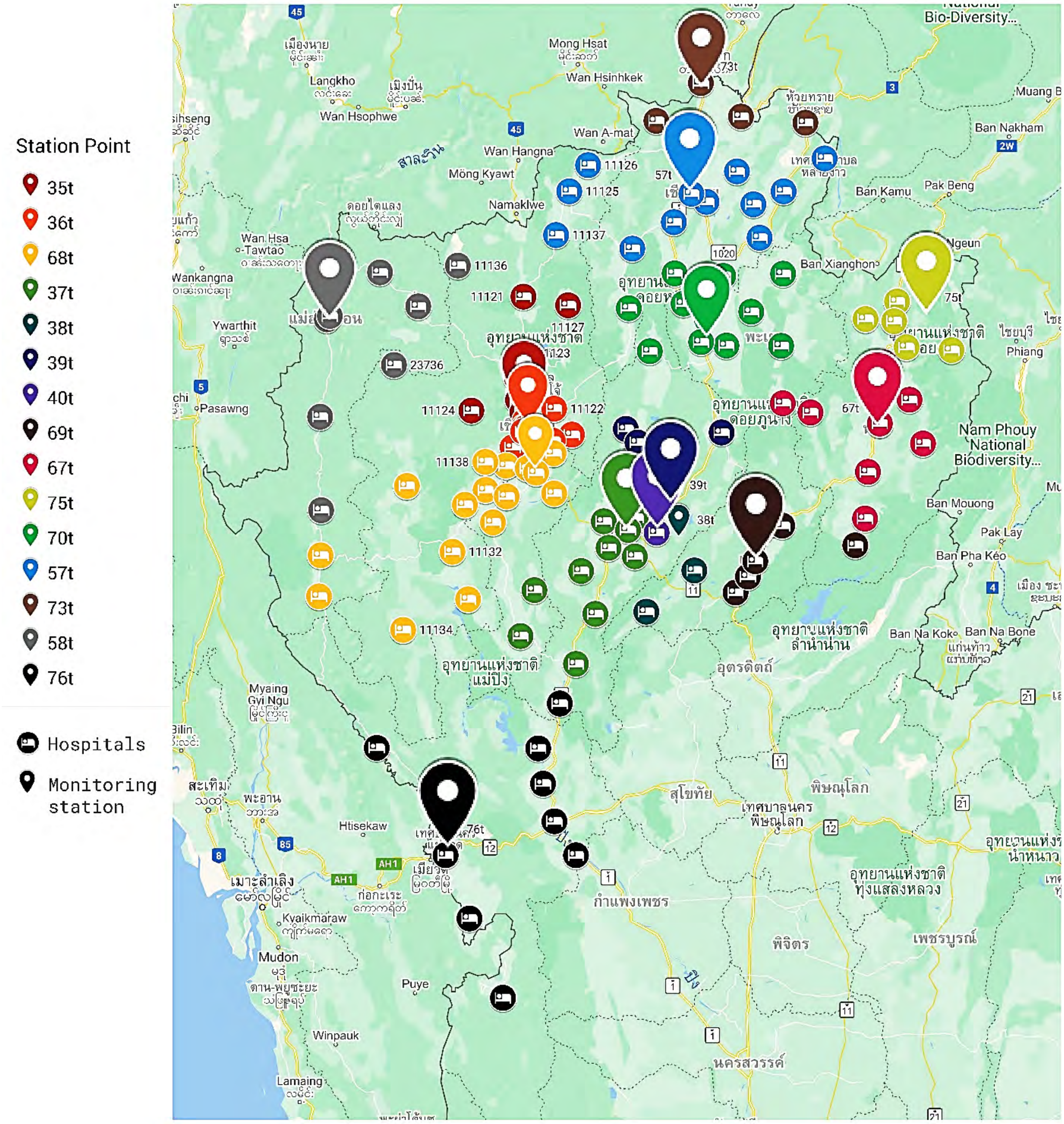

Figure 3.3 Map of monitoring stations and admitted hospitals during 2019 – 2020

3.4 STATISTICAL ANALYSIS

To investigate the association between short-term exposure to $PM_{2.5}$ and the eye and adnexa diseases, a time-stratified case-crossover design (Maclure, 2017) and a conditional logistic model will be employed. The time-stratified case-crossover design has most often proven to be the best in different simulations (Carracedo-Martinez, Taracido, Tobias, Saez, & Figueiras, 2010). This method of selecting control days could avoid overlapping exposures. This design set "case" and "control" days in the same patient to control individual time-invariant covariates such as age, gender, and habitual risk factors. Effect of time trend variable involving weather was excepted. The case day was defined as the date of the first hospital admission. The control day was one on which it will be assumed that the patient did not admit the hospital and selected from the same days of the week corresponding to the case day, in the same month of the same year, to control for long-term trends and seasonality, exposure trend bias, and confounding factors (Bateson & Schwartz, 1999). For example, if 24 March is the case day, the control days are 3, 10, 17, and 31 March. The lag 0-1 of the case day is 23 March, whereas those of the control days are 2, 9, 16, and 30 March, respectively. Before conducting the main analysis, the correlation coefficient between pollutants and weather was calculated by the Spearman correlation (non-parametric correlation) method, which uses to measures the strength and direction of monotonic association between two variables. A rank correlation sorts the observations by rank and computes the level of similarity between the rank (laerd, 2018). A rank correlation has the advantage of being robust to outliers and is not linked to the distribution of the data.

To estimate OR or odds ratio (95% confidence interval OR_{low} to OR_{high}) of hospital admission for the eye and adnexa associated with each interquartile range (IQR) unit increase in $PM_{2.5}$ concentration and exclude the effect of other covariates such O_3, and PM_{10} on $PM_{2.5}$ analysis, by fitting a conditional logistic regression (CLR) model with multivariate analysis to all pairs of case day and matched control days. The model is as follows:

$$\text{logit}(P) = \propto + \beta(PM2.5) + \beta(temp) + \beta(RH) + \beta(PM10) + \beta(O3) + \text{stratum}(id)$$

where P refers to the possibility of hospital admission; α refers to the baseline risk function; temp and RH refer to the temperature, relative humidity; β refers to the linear regression coefficients calculated from the regression model; $PM_{2.5}$, PM_{10}, O_3 refers to fine particulate matter, coarse particulate matter, ozone, respectively; id refers to an order of patient visits.

ORs and 95% confidence intervals (CIs) were calculated to show the risk of the eye and adnexa diseases associated with an increment in exposure to $PM_{2.5}$ per IQR at single 0 - 7 lag days. Testing the effect modifications of inpatient visits was stratified analysis by season (hot, wet, cold) shown as in Table 3.2, sex (male and female), age groups (≤65, >65) (Ministry of Public Health, 2016a), and sub-diseases (Table 3.1). Deeper specific analysis on each disease of the eye and adnexa, every 10 diseases of the eye and adnexa were stratified by inpatient's age (<50, ≥50) as well.

The association between short-term exposure to $PM_{2.5}$ and the eye and adnexa diseases below the Thai air quality standard for the 24-hour $PM_{2.5}$ was conducted. This analysis was used the same model in terms of independent variables specifications as the main analysis but was restricted to days with a daily $PM_{2.5}$ concentration of 50 $\mu g/m^3$ or less. An IQR was calculated separately in different periods involving the hot, wet, cold season, and below-standard phase.

All results were reported as odds ratio (ORs) and 95% confidence interval (95% CI) in the risks of incidence of diseases of the eye and adnexa associated with IQR increase in the daily ambient $PM_{2.5}$ concentration. All analyses were conducted using R software (version 4.0.2). We used the "survivals" package for CLR analysis. All tests were two-sided, and the effects of $p < 0.05$ were considered statistically significant.

Table 3.2 Season periods in Thailand, 2016 - 2020

Year	Hot season	Wet season	Cold season
2016	March 3rd – May 17th	May 18th - October 29th	January 1st - March 2nd, October 30th – December 31th
2017	March 3rd – May 15th	May 16th - October 22nd	January 1st - March 2nd, October 23rd – December 31th
2018	March 3rd – May 25th	May 26th - October 29th	January 1st - March 2nd, October 30th – December 31th
2019	March 3rd – May 19th	May 20th - October 16th	January 1st - March 2nd, October 17th – December 31th
2020	February 29th – May 17th	May 18th - October 19th	January 1st - February 28th, October 20th – December 31

(Climatological Center, 2021)

Chapter 4 RESULTS AND DISCUSSION

4.1 DATA DESCRIPTION

The basic characteristics of hospital admission cases for the eye and adnexa diseases in upper northern, Thailand from 2016 to 2020 are described in Table 4.1. In the 5 years of observation, a total of 192,545 eye and adnexa inpatients were investigated, nearly a half of which was hospitalized for cataract and other disorders of the lens (79,522 cases, 41.3%), and more than 1/3 of which was blindness and low vision (76,324 cases, 39.6%). About a half of patients, 53.1% were female, and 69.4% visits were elderly. It appeared that people with younger age were more rarely diagnosed than older age, and the percentage of the eye and adnexa diseases occurrences went up double with increasing age. Approximately, 43%, 39%, and 18% of hospitalization were recorded from wet, cold, and hot seasons. Sub-diseases, sex, age, and seasonal variation of diseases of the eye and adnexa occurrence seemed to be obvious. It is suggested that the occurrence of the eye and adnexa diseases may have been for sub-diseases-, age-, gender- and season-specific.

The summary statistics of air pollutants and meteorological conditions in upper northern Thailand from 2016 to 2020 are given in Table 4.2. During the study period, variables were missing under 2%. An IQR of $PM_{2.5}$ was 9.63 – 35.50 µg/ m^3 and the maximum value reached was 398.13 µg/m^3. The average daily mean concentrations of $PM_{2.5}$, PM_{10}, and O_3 were 27.13 µg/m^3, 42.75 µg/m^3, and 39.63 ppb, respectively, which were not exceeded the Thailand air quality standard. The annual average value was 25.89 °C for temperature and 73.03% for humidity represented the tropical savanna climate over the region.

The distribution of 24-h average of $PM_{2.5}$, co-pollutants concentrations including PM_{10}, O_3, and meteorological factors between January 1, 2016, to December 31, 2020, in upper northern, Thailand are presented in Figure 4.1, Figure 4.2, Figure 4.3, Figure 4.4, and Figure 4.5. In the earliest of the study period, the number of monitoring stations was slighter than 2019-2020, represented by the color of stations. The concentrations of the ambient $PM_{2.5}$ fluctuated dynamically during the study period and increased dramatically in 2019 and 2020. At the beginning of every year, from January to May, $PM_{2.5}$ concentration was above Thai air quality standards (50 µg/m^3) and was exceeding 8 times the standard concentration around March and April while temperature level increasing and percent of relative humidity dropping. It could suggest an urgent need for this portion of pollution control. Comparing to co-pollutants, the distribution of PM_{10} was corresponding evidently to $PM_{2.5}$ behaviors and escalating above the

Thailand standard (120 μg/m^3) during the summer period. In the case of ozone, its phenomenon was also running swing and risen peak within March and April.

Table 4.1 Basic characteristics of the study population in upper northern, Thailand, 2016 – 2020

Characteristics	n	Percent (%)
Total the eye and adnexa diseases	192545	100
Sub-diseases		
H00 - H01 Inflammation of the eyelid	1302	0.68
H10 - H13 Conjunctivitis and other disorders of conjunctiva	7778	4.04
H15 - H19 Keratitis and other disorders of sclera and cornea	3067	1.59
H25 - H28 Cataract and other disorders of lens	79522	41.3
H33 Retinal detachments and breaks	1752	0.91
H40 - H42 Glaucoma	10214	5.30
H49 - H50 Strabismus	618	0.32
H52 Disorders of refraction and accommodation	259	0.13
H54 Blindness and low vision	76324	39.6
Other diseases of the eye and adnexa	11709	6.08
Sex		
Male	90322	46.9
Female	102223	53.1
Age (years)		
≤ 65	58976	30.6
> 65	133569	69.4
Season of admission		
Hot	35417	18.4
Wet	82626	42.9
Cold	74502	38.7

Table 4.2 Descriptive statistics for ambient air pollutant and meteorological factors in upper northern, Thailand, 2016 – 2020

Variables	$PM_{2.5}$ (μg/m^3)	PM_{10} (μg/m^3)	O_3 (ppb)	Temperature (˚C)	Relative Humidity (%)
% Missing	0.54	1.48	0.63	1.01	1.34
Min	1.83	2.33	1.38	6.89	3.13
Mean	27.13	42.75	39.63	25.89	73.03
Max	398.13	438.88	128.50	39.76	100.00
P_{25}	9.63	19.36	23.75	23.96	64.29
P_{50}	17.08	30.71	35.50	26.01	75.58
P_{75}	35.50	54.25	53.50	27.84	83.83
Thailand air quality standards	50.00	120.00	70.00	-	-

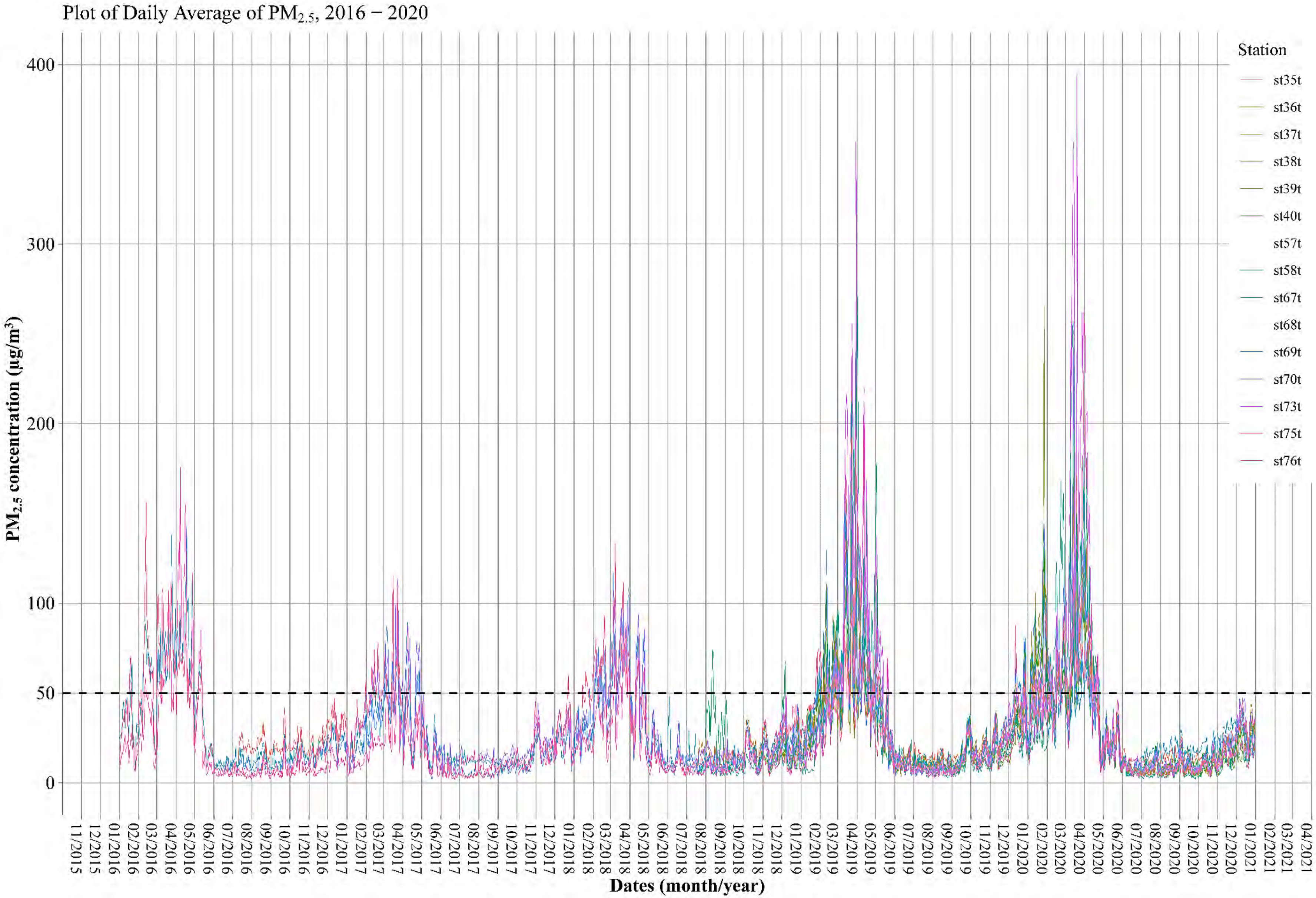

Figure 4.1 Time-series plot of daily $PM_{2.5}$ concentration during 2016 – 2020, in upper northern, Thailand

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 µm.

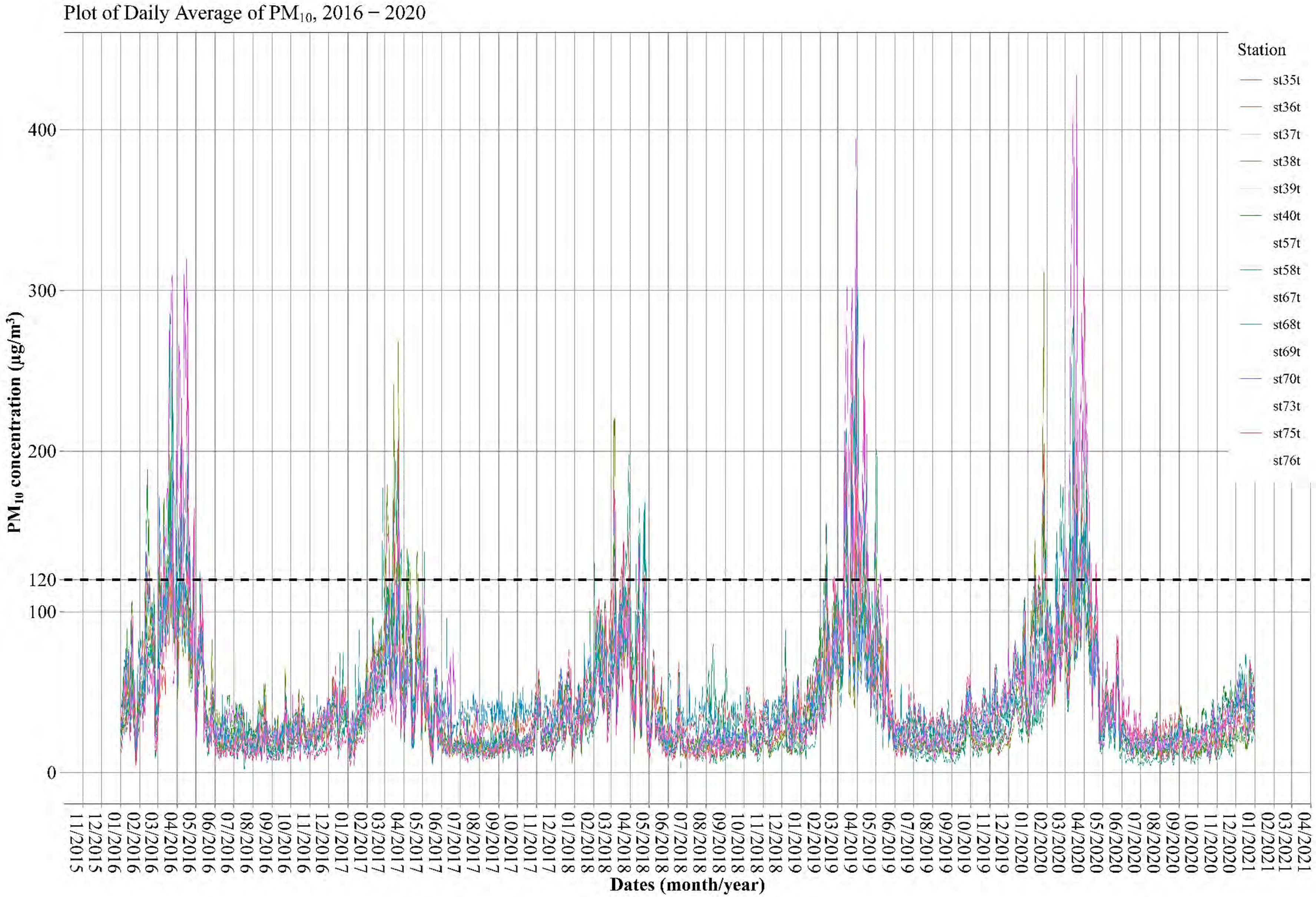

Figure 4.2 Time-series plot of daily PM_{10} concentration during 2016 – 2020, in upper northern, Thailand

Abbreviations: PM_{10}, particles with aerodynamic diameter ≤10 μm.

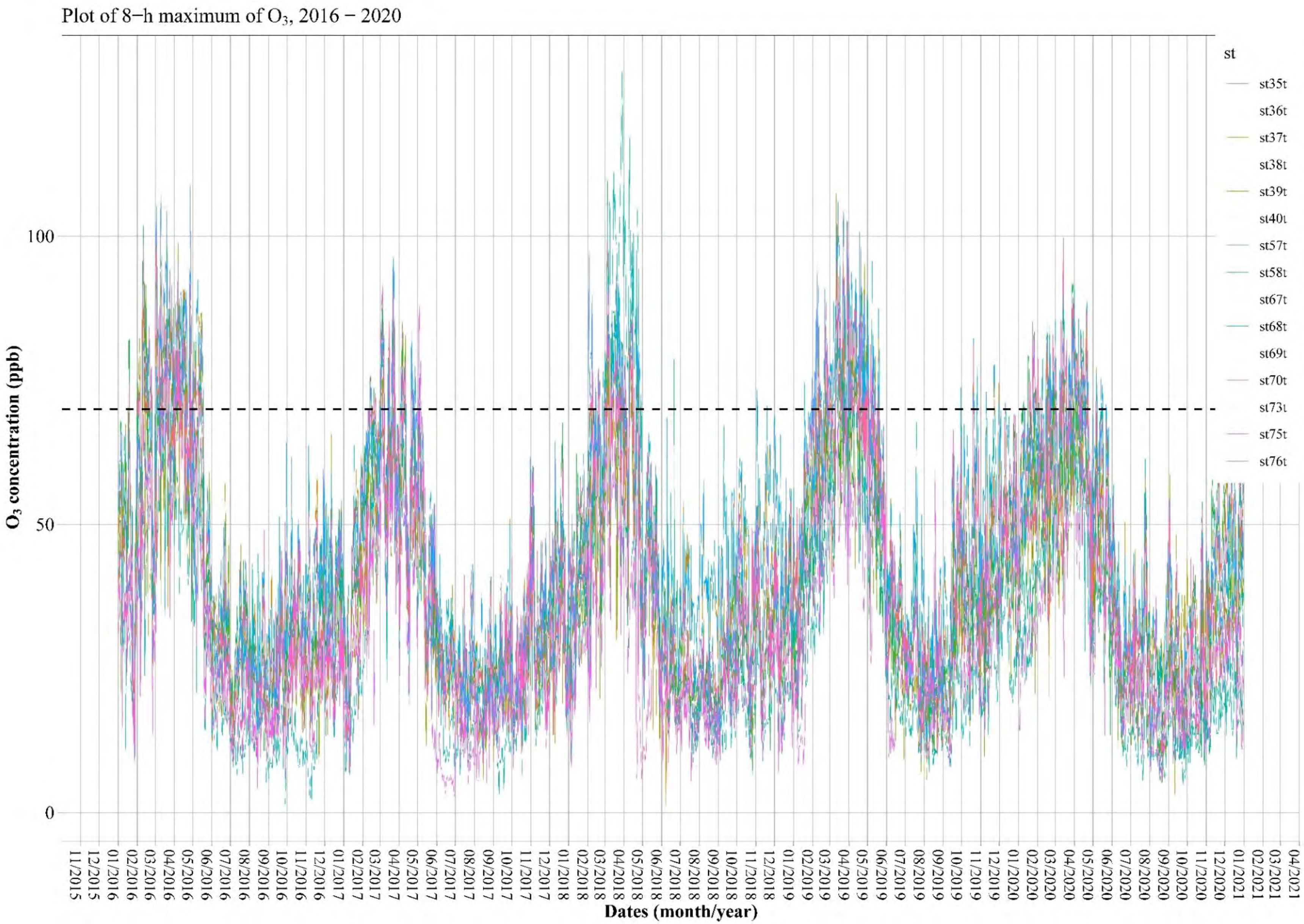

Figure 4.3 Time-series plot of 8-h maximum of O_3 concentration during 2016 – 2020, in upper northern, Thailand

Abbreviations: O_3, Ozone

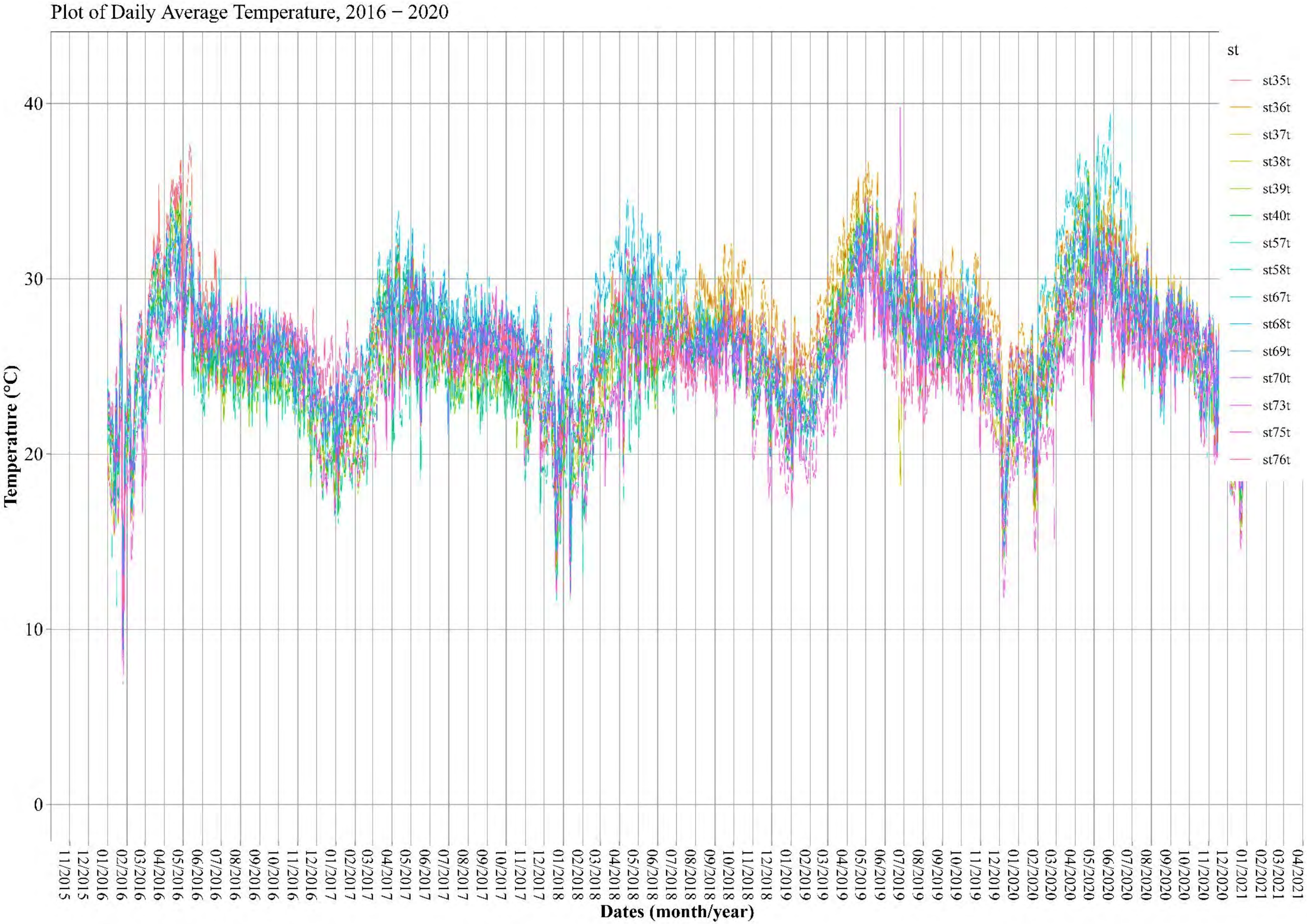

Figure 4.4 Time-series plot of daily temperature during 2016 – 2020, in upper northern, Thailand

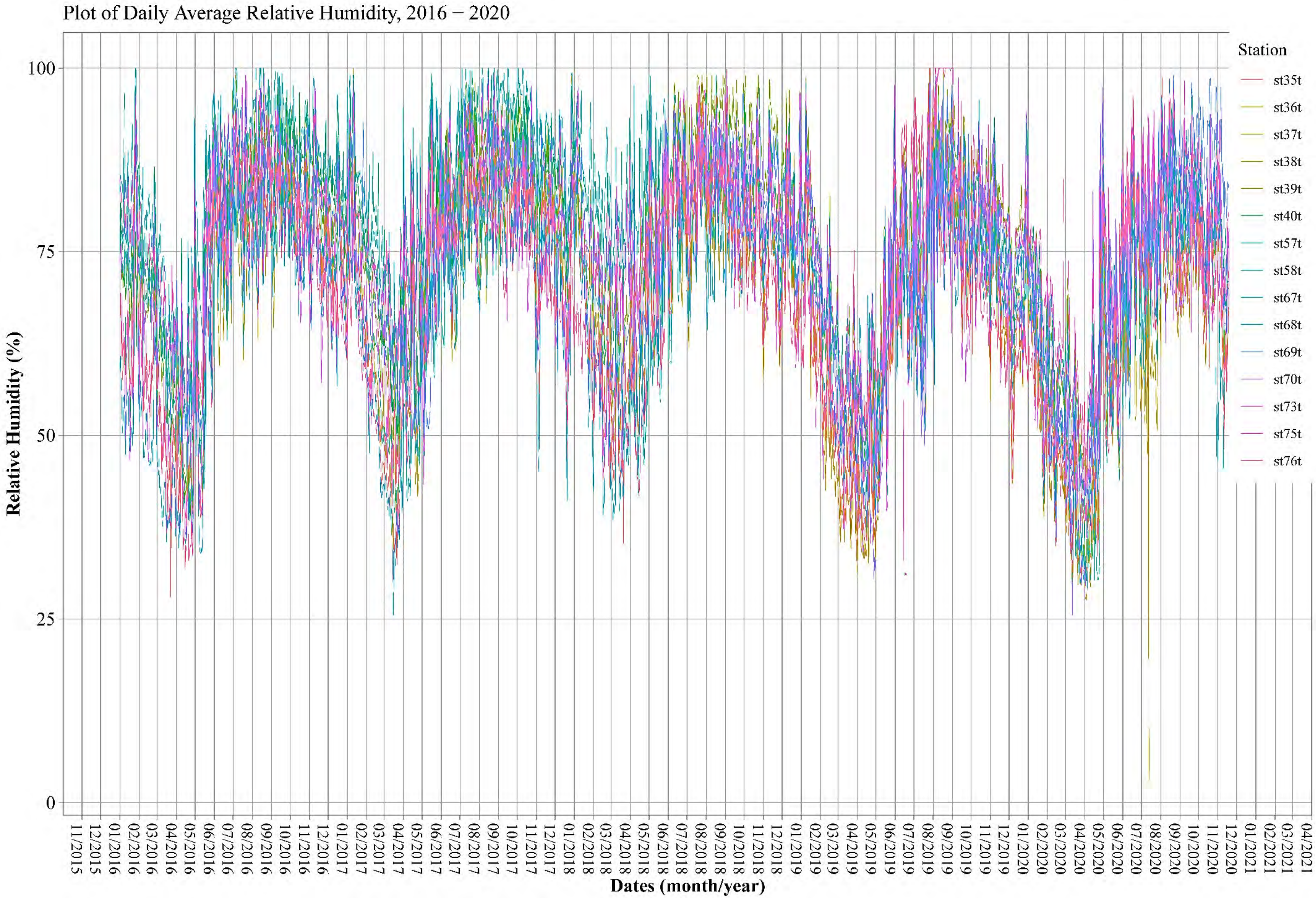

Figure 4.5 Time-series plot of relative humidity during 2016 – 2020, in upper northern, Thailand

The correlation between $PM_{2.5}$ concentration, weather, and other pollutants tested by the Spearmen correlation test is illustrated in Figure 4.6. $PM_{2.5}$ was strongly positively correlated with PM_{10} (ρ= 0.92, $p < 0.001$) and O_3 ($\rho = 0.71$, $p < 0.001$), suggesting that these particulate matters might have shared the same emission sources and O_3 might be the secondary pollutants. While negative associations were observed with humidity ($\rho = -0.67$, $p < 0.001$). The weakly correlation of PM25 with temperature was observed ($\rho = 0.20$, $p < 0.001$). A reasonable explanation may be that high humidity usually comes with a shower that washes out certain levels of ambient air pollutants.

2.5 PM-HOSPITALIZATION ASSOCIATIONS

the ORs of hospitalization for total eye and adnexa diseases at single lag 0 to 7 days associated with per IQR increase in exposure to particulate air pollutants are estimated in Figure 4.7. Detailed ORs estimates could be found in the appendix. Significant adverse effects of $PM_{2.5}$ were observed both at single 0 - 7 lag. The peak of ORs was detected at lag 6 which was 1.04 (95% CI: 1.02 to 1.07, $p < 0.001$).

The association between lag 6 exposure to per IQR increase in $PM_{2.5}$ with exceeded risk of hospital admission for the eye and adnexa diseases with 95% confident interval in the multivariate regression models is shown in Figure 4.8. The prediction of the relationship between per IQR increase in $PM_{2.5}$ and risks of hospital admission at lag 6 days was significant greatly around 20 – 40 $\mu g/m^3$ concentration of $PM_{2.5}$. While smaller and higher $PM_{2.5}$ concentration, risks were estimated less significant.

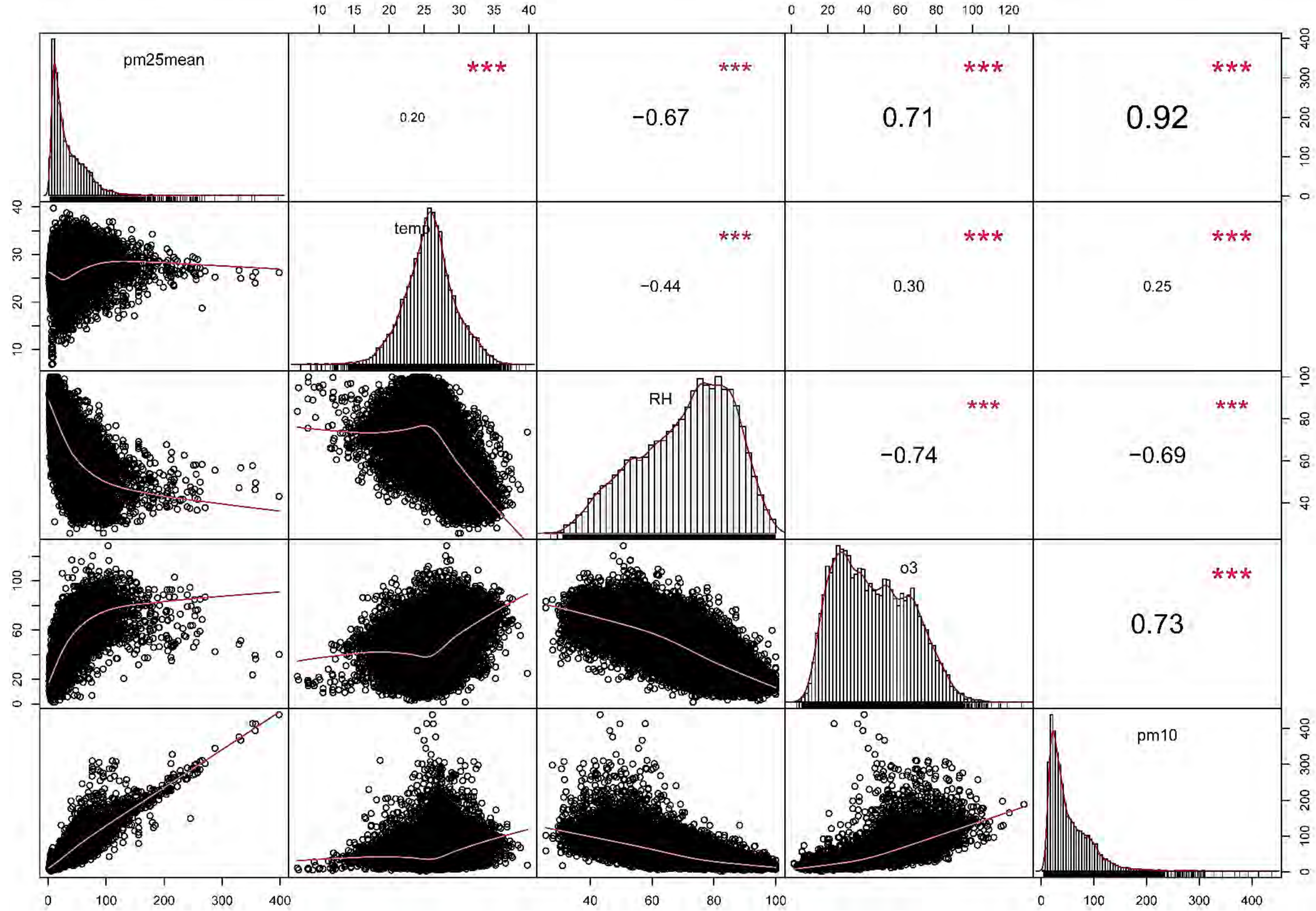

Figure 4.6 Spearman correlation coefficients between daily air pollutant concentrations and weather conditions

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 µm; temp, temperature; RH, relative humidity; O_3, Ozone; PM_{10}, particles with aerodynamic diameter ≤10

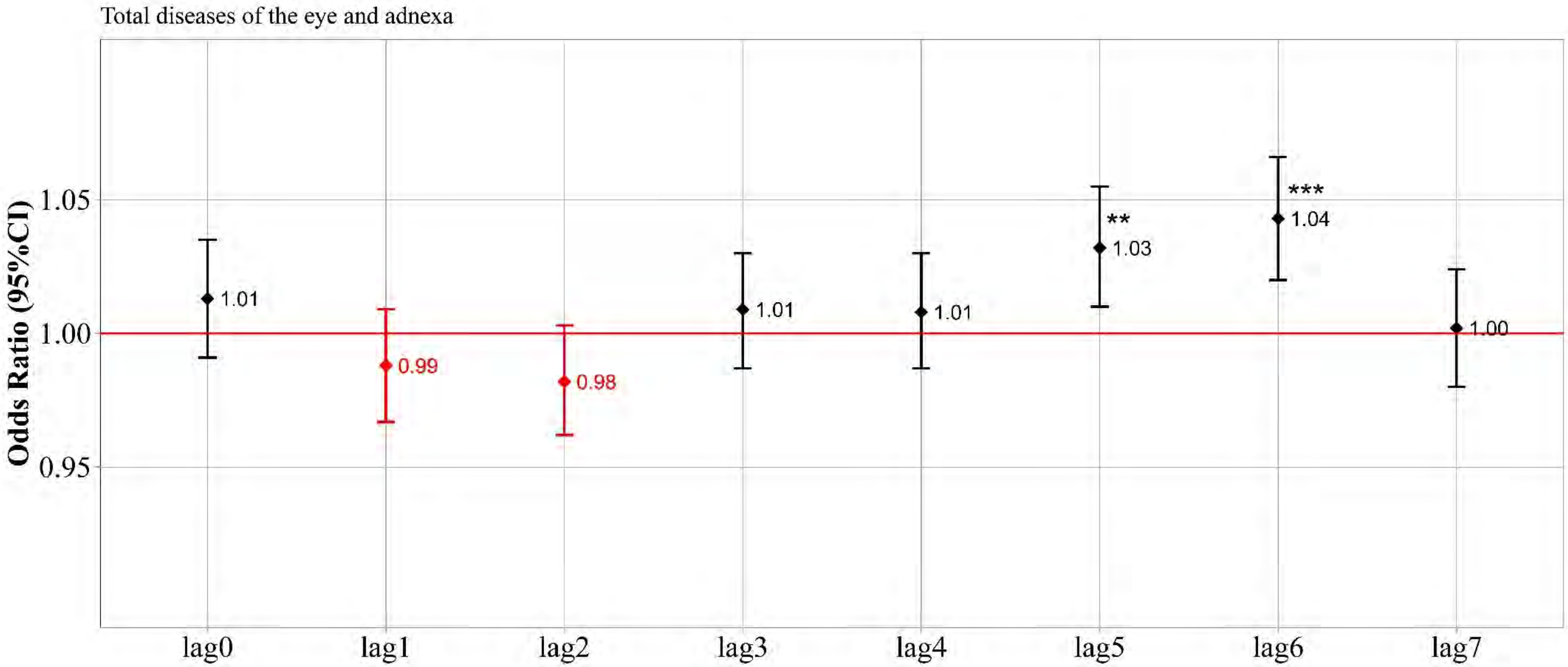

Figure 4.7 Odds ratios (with 95% CIs) adjusted for PM_{10}, O_3, temperature, and RH of hospitalization for total the eye and adnexa diseases associated with per IQR increase in exposure to $PM_{2.5}$ concentration at single 0 - 7 lag day

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 μm.

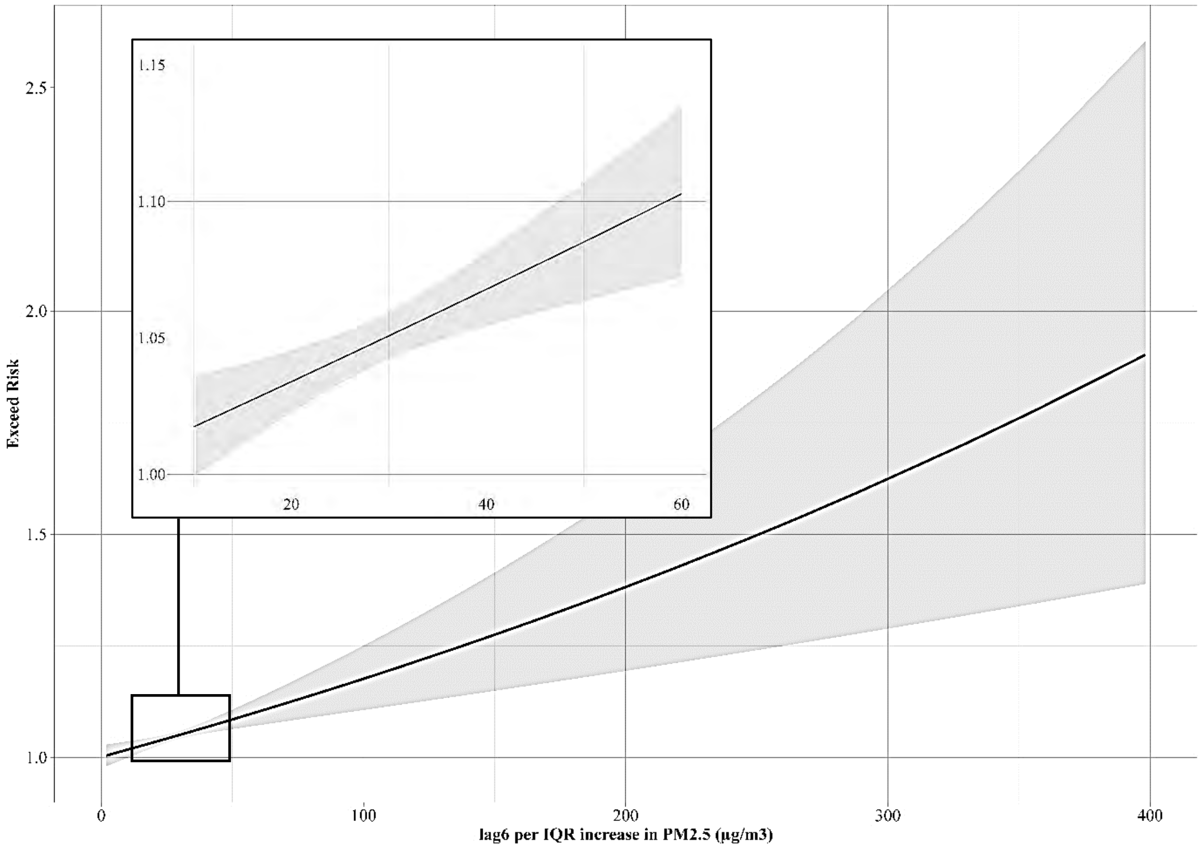

Figure 4.8 Concentration-response curve between ambient particulate matter and risk of hospital admission for the eye and adnexa diseases at lag 6 day

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 µm

2.6 SUBGROUP ANALYSES

The associations between $PM_{2.5}$ exposure and the eye and adnexa diseases inpatient visits in single lag 0 - 7 days by the effects modification of season are demonstrated in Figure 4.9. In the hot season (mid-February to mid-May), each IQR increase of $PM_{2.5}$ at lag 6 days was significantly associated with a 23% (Odds ratio = 1.23, 95% CI: 1.17 to 1.29, $p < 0.001$) increase in the eye and adnexa diseases inpatient visits. Plus, significance associations also were found at every lag day in the hot season, excepting lag 1 and lag 2. Risk estimates were significant exceedingly at lag 0 days in the wet season, with ORs of 1.10 (95% CI: 1.08 to 1.12, $p < 0.001$). At lag 1 – 3 days, risks of hospitalization for the eye and adnexa were also estimated significantly within the wet season. The pattern of risk estimates in the hot season was similar to the analysis of total eye and adnexa diseases, while in the cold season, the pattern was different from the main analysis according to a combination of risks of several eyes and adnexa diseases. In contrast, all results within the cold season were non-association significantly.

Subgroup-specific ORs estimate for the association between hospitalization for the eye and adnexa diseases and ambient exposures to $PM_{2.5}$ at single 0 - 7 lag days is summarized in Figure 4.10. Subgroup results were represented by stratification by sex and age. Between male and female subgroups, the highest risks were determined both at lag 6 days. A comparable risk estimate were observed between male and female, significantly with ORs of 1.05 (95% CI: 1.03 to 1.07, $p < 0.001$) and 1.03 (95% CI: 1.00 to 1.04, $p = 0.002$). With the strongest risks at lag 6 days, among age subgroup, there was the significant odds ratio observed in the age younger than 65 subgroups greater than the elderly, which was 1.05 (95% CI: 1.01 to 1.09, $p = 0.010$). Among older inpatients (> 65 years), ORs were detected peak at 1.04 (95% CI: 1.01 to 1.06, $p = 0.009$) at lag 6 day. The different pattern of association in subgroups aged more than 65 was observed due to the co-effect of multiple eyes and adnexa diseases.

Subgroup-specific ORs estimate represented by sub-disease s stratification for the association between hospitalization for the eye and adnexa diseases and ambient exposures to $PM_{2.5}$ at single 0 - 7 lag days is illustrated in Figure 4.11. Corresponding to per IQR rise in exposure to $PM_{2.5}$, risks of hospital admission for the eye and adnexa diseases: conjunctivitis and other disorders of the conjunctiva, keratitis and other disorders of sclera and cornea, cataract and other disorders of the lens, disorders of refraction and accommodation, blindness and low vision, and other diseases of the eye and adnexa were significantly increasing at different lag days, with ORs of 1.34 (95% CI: 1.21 to 1.48, $p < 0.001$) at lag 2 days, 1.22 (95% CI: 1.00 to 1.47, $p = 0.043$) at lag 6 days, 1.05 (95% CI: 1.02 to 1.09, $p = 0.003$) at lag 6 days, 1.63 (95% CI: 1.16 to 2.29, $p = 0.005$) at lag 6 days, 1.03 (95% CI: 1.02 to 1.05, $p < 0.001$) at lag 6 days, 1.13 (95% CI: 1.01 to 1.25, $p = 0.026$) at lag 1 day, respectively. Most diseases of the eye and adnexa were shown the greatest risk around lag 5 and 6 days. While risks of disorders of conjunctiva were revealed since the first of the lag day, and not at lag 5-6. No clear evidence was identified for informative risk increasing among inpatients stratified by other sub-diseases.

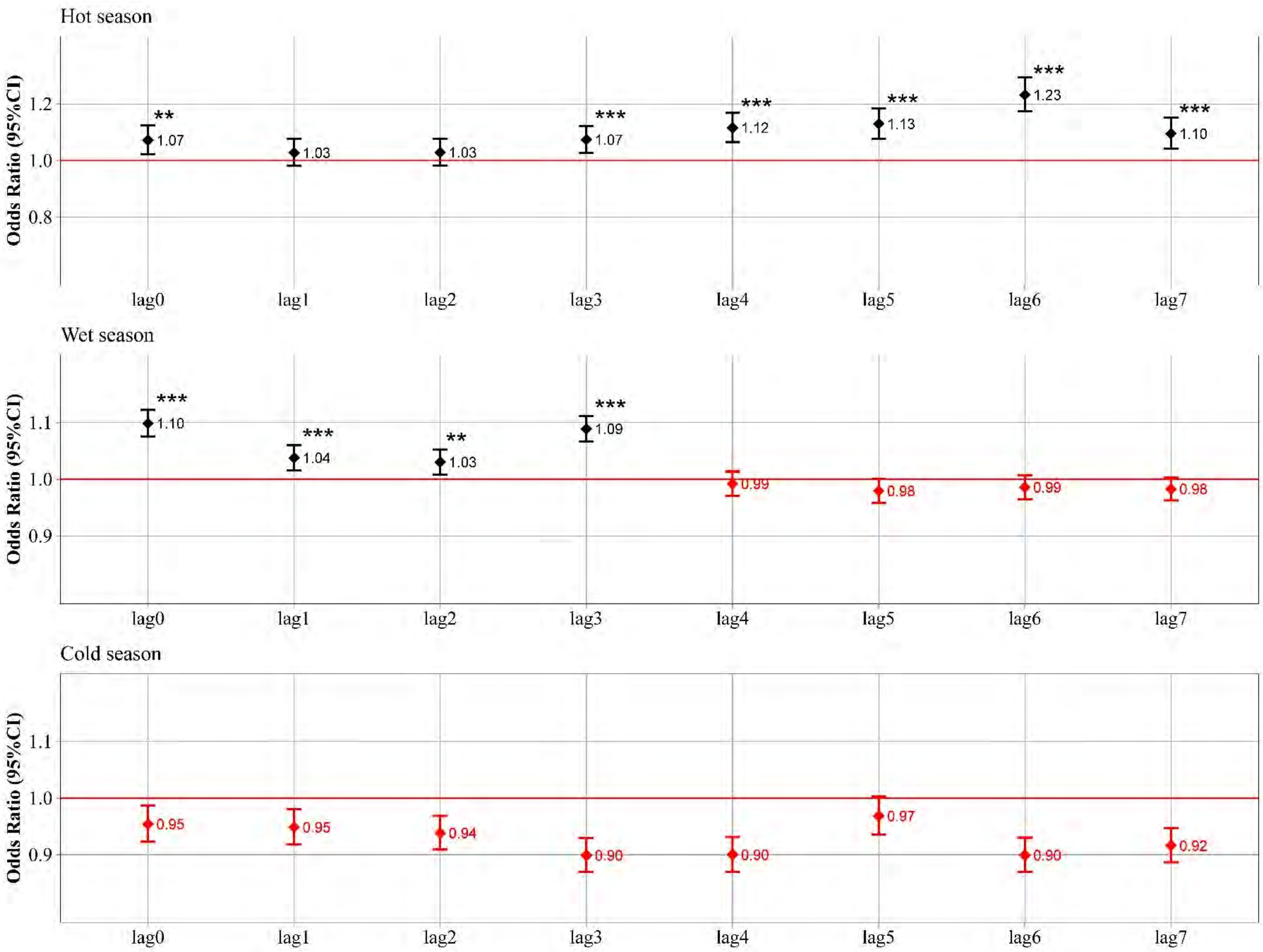

Figure 4.9 Odds ratios (with 95% CIs) adjusted for PM_{10}, O_3, temperature, and RH of hospital admission for total the eye and adnexa diseases associated with per IQR increase in exposure to $PM_{2.5}$ concentration at single 0 - 7 lag days by season (hot, wet, cold)

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 μm

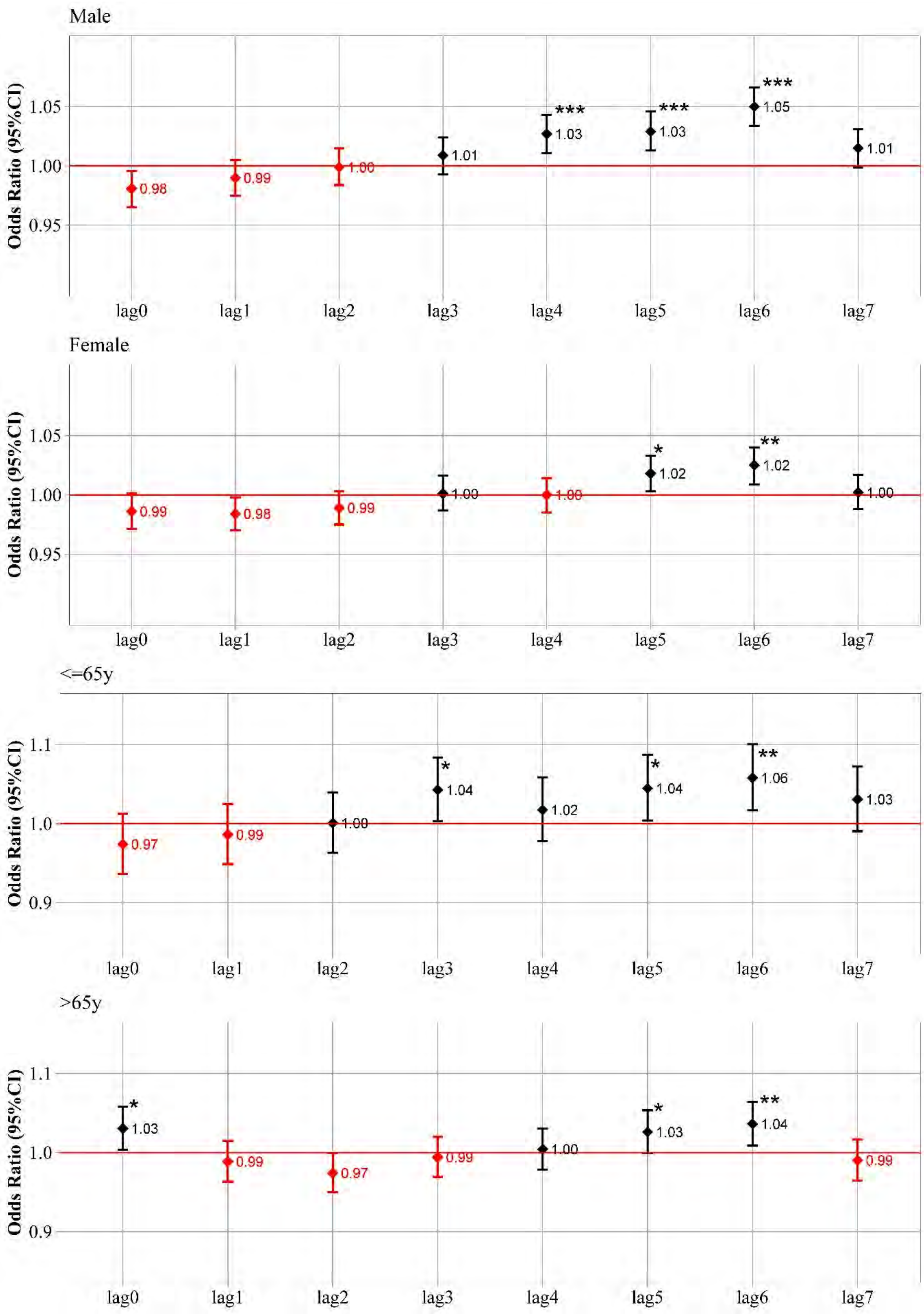

Figure 4.10 Odds ratios (with 95% CIs) adjusted for PM_{10}, O_3, temperature, and RH for hospitalization among subgroups stratified by sex and age-associated with per IQR increase in exposure to $PM_{2.5}$ concentration at single 0 - 7 lag days

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 μm

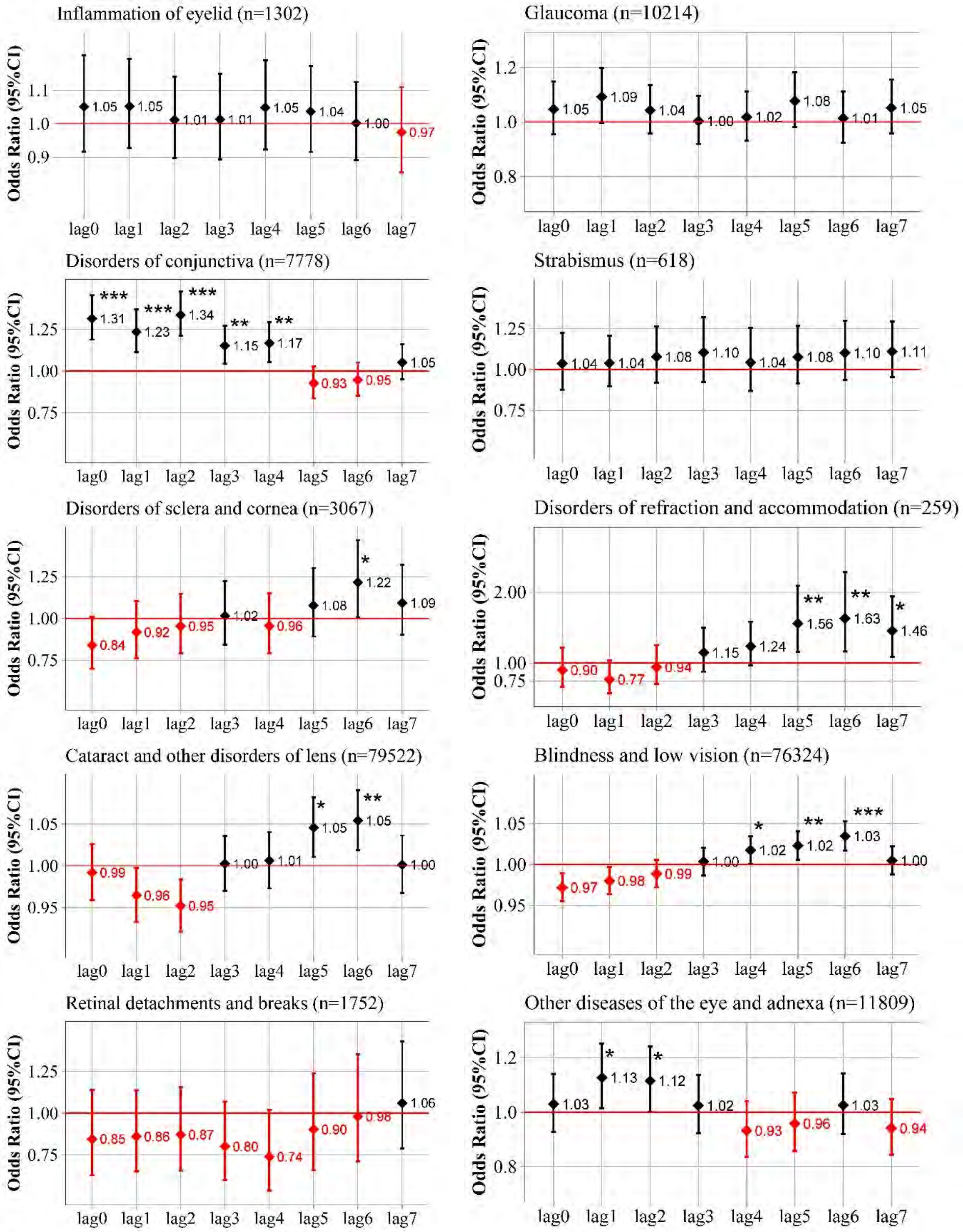

Figure 4.11 Odds ratios (with 95% CIs) adjusted for PM_{10}, O_3, temperature, and RH for hospitalization among subgroups stratified by sub-diseases associated with per IQR increase in exposure to $PM_{2.5}$ concentration at single 0 - 7 lag days

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 μm

Risks estimate with 95% CIs of hospitalization for total eye and adnexa diseases stratified by sub-diseases among the aged-subgroup population, associated with per IQR increase in exposure to $PM_{2.5}$ concentration at the most significant lag day is demonstrated in Figure 4.12. Inpatient for conjunctivitis and other disorders of conjunctiva aged both under and over 50 was found to associate with $PM_{2.5}$, with ORs of 1.26 (95% CI: 1.04 to 1.53, $p = 0.019$) and 1.36 (95% CI: 1.21 to 1.52, $p < 0.001$). With keratitis and other disorders of sclera and cornea diseases, the older subgroup was perceived to be associated with per IQR rising in $PM_{2.5}$ levels, with OR of 1.41 (95% CI: 1.11 to 1.78, $p = 0.005$). Inpatients aged under and over 50 admitted to hospital for cataract and disorders of the lens were consistent significantly with per IQR increase in $PM_{2.5}$ levels, with ORs of 1.24 (95% CI: 1.02 to 1.51, $p = 0.035$) and 1.05 (95% CI: 1.01 to 1.09, $p = 0.007$). OR was calculated approximately 1.10 (95% CI: 1.00 to 1.21, $p = 0.040$) among glaucoma patients aged 50 and older. Being similar to disorders of refraction and accommodation, the risk of hospital admissions was 1.74 (95% CI: 1.13 to 2.66, $p = 0.011$) among inpatients over 50 years old. As well as blindness and low vision and other diseases of the eye and adnexa, ORs were estimated around 1.04 (95% CI: 1.02 to 1.05, $p < 0.001$) and 1.20 (95% CI: 1.05 to 1.36, $p = 0.006$) for the older subgroup. While strabismus inpatients, the risk was associated with $PM_{2.5}$ in the younger case with OR of 1.28 (95% CI: 1.01 to 1.62, $p = 0.038$). No clear evidence was identified for other sub-diseases.

2.7 BELOW-STANDARD ANALYSES

ORs (with 95% CIs) of hospitalization for total the eye and adnexa diseases associated with per IQR increase in exposure to $PM_{2.5}$ at single 0 - 7 lag in the below-standard analysis is shown in Figure 4.13. When restricting the analysis to days with daily $PM_{2.5}$ concentrations of 50 $\mu g/m^3$ or less, the risk estimation in hospital admission of the total eye and adnexa diseases demonstrated dropped ORs. A significant decrease in risk estimate was found at lag 6 days in total for the eye and adnexa diseases. While the risk of hospitalization for the eye and adnexa diseases still developed among the male population at lag 2 days, which was 1.03 (95% CI: 1.00 to 1.05, $p = 0.023$). Note that, risks of hospital admission for the eye and adnexa diseases still were not non-associated significantly for every stratified group.

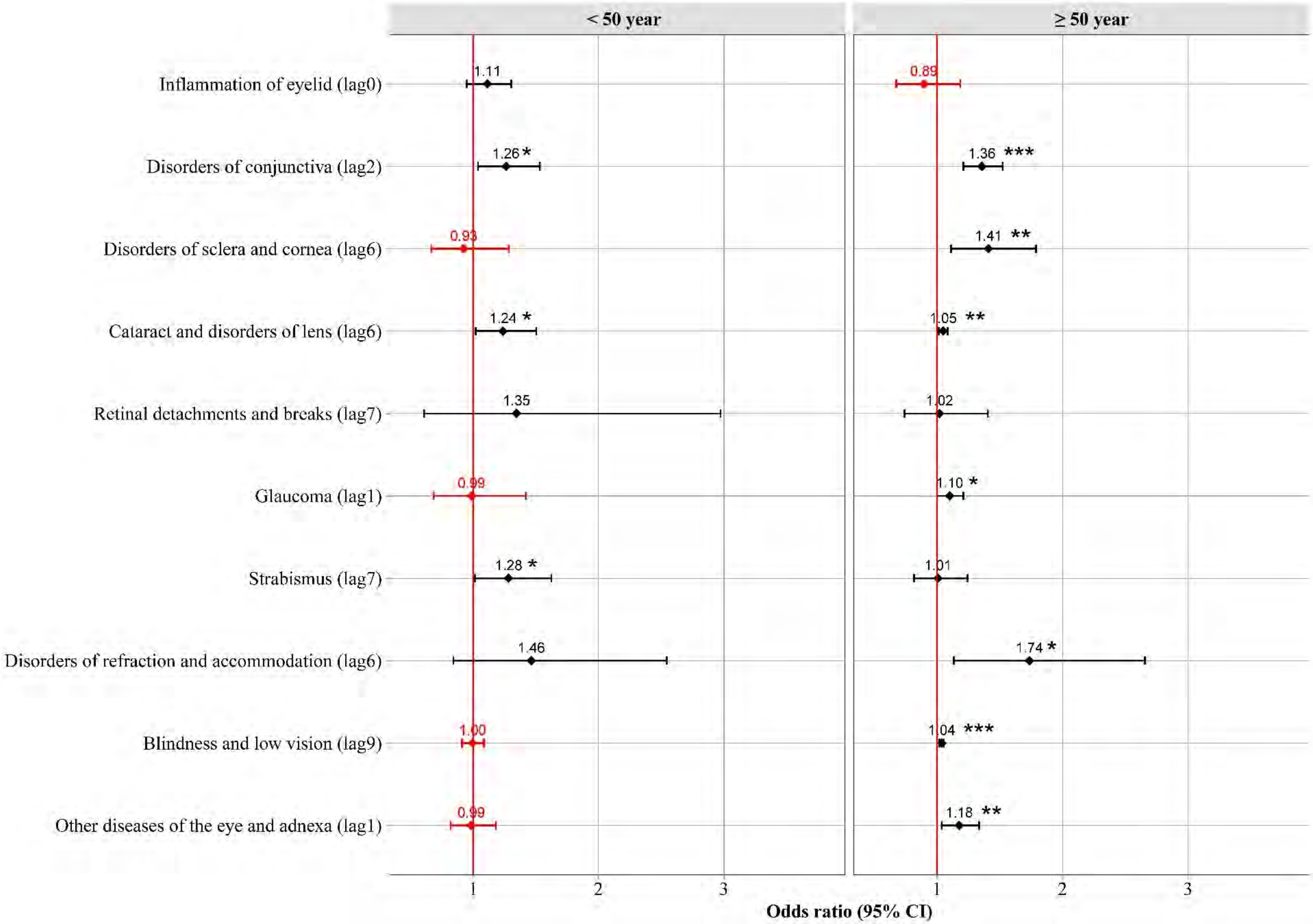

Figure 4.12 Odds ratios (with 95% CIs) adjusted for PM_{10}, O_3, temperature, and RH of hospitalization for total eye and adnexa diseases stratified by sub-diseases and age, associated with per IQR increase in exposure to $PM_{2.5}$ concentration at the most significant single lag day

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 μm

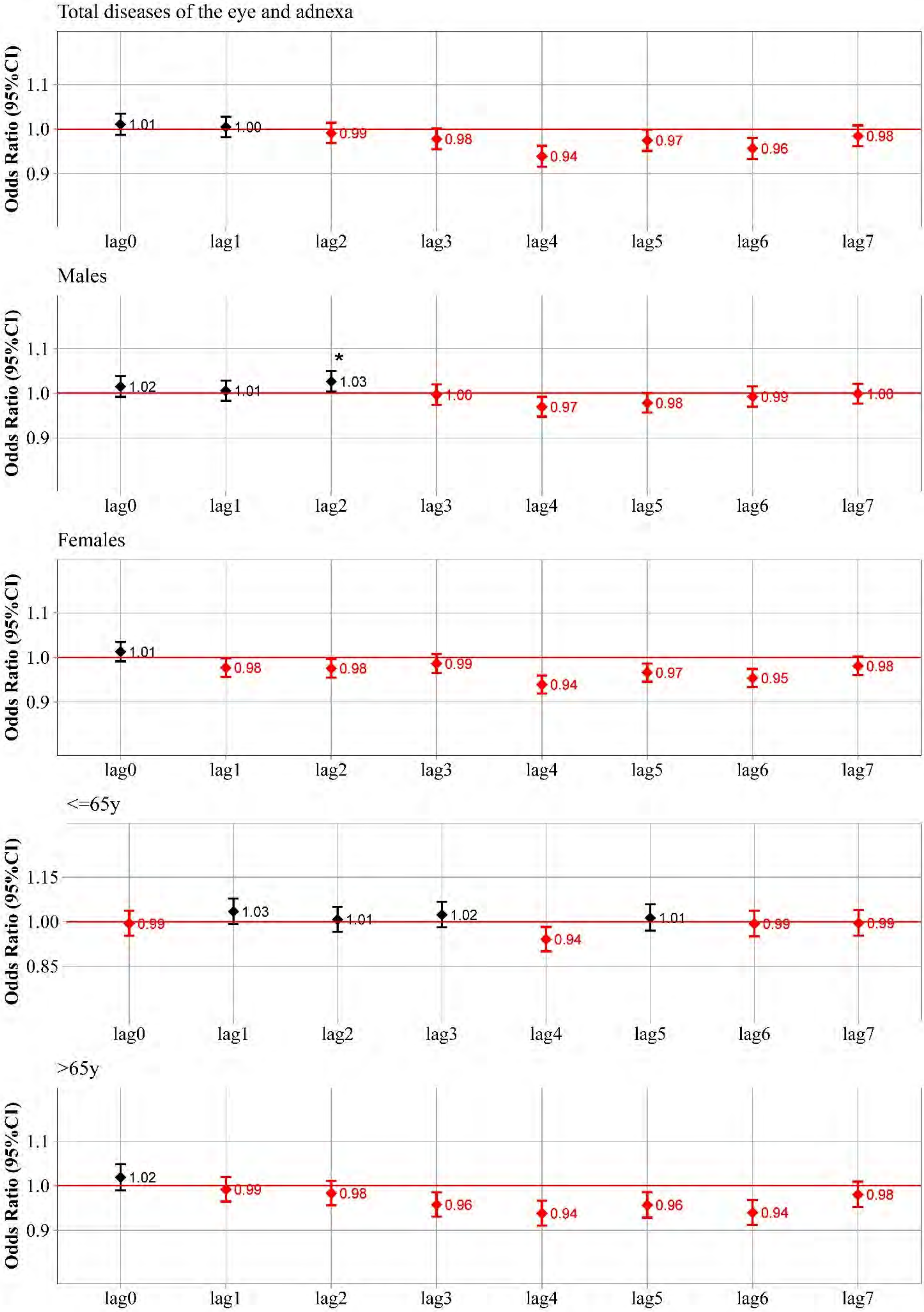

Figure 4.13 Odds ratios (with 95% CIs) adjusted for PM_{10}, O_3, temperature, and RH of hospitalization for total the eye and adnexa diseases associated with per IQR increase in exposure to $PM_{2.5}$ concentration and stratified by sex and age at single 0 - 7 lag day in the below-standard analysis

Abbreviations: $PM_{2.5}$, particles with aerodynamic diameter ≤2.5 µm

2.8 DISCUSSION

In this time-stratified, case-crossover study, short-term effects of an IQR increase in ambient $PM_{2.5}$ on daily hospital admission for eye and adnexa diseases were assessed across the area of the upper northern region of Thailand, during 2016 - 2020. Exposures to $PM_{2.5}$ were found to be associated with increased hospitalization risks at lag 6. The association between the eye and adnexa diseases and $PM_{2.5}$ was higher especially in the hot and wet season. PM-associated effects on hospital admission varied among a sex and age subpopulation, which was mainly male and younger population. Besides, each disease of the eye and adnexa has identified the association contrastingly among younger and older inpatients. The risks of hospitalization must be notably concerned for conjunctivitis and other disorders of the conjunctiva, keratitis and other disorders of sclera and cornea, cataract and other disorders of the lens, disorders of refraction and accommodation, blindness and low vision, and other diseases of the eye and adnexa. Being isolated from those daily $PM_{2.5}$ values which were above Thai air quality standard, risks of hospitalization for the eye and adnexa diseases still were existed in the male population. These findings contribute to better understandings of $PM_{2.5}$-induced health impacts in Thailand. A study of below-standard estimation informs how to set the Thai air quality standards for Thai citizens.

The basic characteristics of hospital admission cases for the eye and adnexa diseases (Table 4.1) describe that the frequency of female and elderly patients was higher for the occurrence of the eye and adnexa diseases. The following studies indicated that the incidence of hospitalization for the eye and adnexa disease was higher in older patients and females (Q. L. Fu et al., 2017; Mo et al., 2019; Ruan et al., 2019; Szyszkowicz et al., 2016; Zhong, Lee, Hsieh, Tseng, & Yiin, 2018). As for the higher prevalence in women, sex hormones are likely effective in inducing eye and adnexa diseases. A review paper reported that androgen enhanced Meibomian gland function, which secreted oils onto the ocular surface keeping the tears from evaporation, and that estrogen and progesterone might antagonize the effect of androgen on Meibomian gland function. Although the effects of estrogen and progesterone on the ocular surface are not well understood, it is suggested that estrogen may result in inflammation of the ocular surface (Truong, Cole, Stapleton, & Golebiowski, 2014). Women, especially the elderly, are therefore at a high risk of eye and adnexa diseases, as shown in this study. Further studies are required to validate this issue.

The descriptive statistics (Table 4.2) show that the average daily $PM_{2.5}$ concentration during the study period was not higher than the ambient air quality standard in Thailand (daily 50 $\mu g/m^3$). Comparing to other studies (Khalaila et al., 2021; Liang et al., 2017; C. Liu et al., 2019), the concentration was very widely distributed according to the significant gap of the annual $PM_{2.5}$ concentration during the wet and dry season which is consistent with a spatiotemporal pattern of ground-level air pollution in upper northern, Thailand (Pollution Control Department, 2019). On the one hand, studying an emergency room visit for ocular diseases associated with exposure to fine particulate matter, $PM_{2.5}$ levels were much greater during the study period, with an average of 119.8 $\mu g/m^3$ within the Beijing area (Liang et al., 2017). On the other hand, another study in China contributed to an insignificant association between exposure to $PM_{2.5}$ at lag0 and outpatient visits for the eye and adnexa diseases, the annual average concentration of $PM_{2.5}$ was 37.9 $\mu g/m^3$ (C. Liu et al., 2019). However, high levels of $PM_{2.5}$ may not the only main factor that leads to the increase of hospitalization for the eye and adnexa diseases. Further study is needed to clarify this.

The highly correlated pollutants (i.e., $PM_{2.5}/PM_{10}$ and $PM_{2.5}/O_3$) (Figure 4.6) may have shared the same sources. By definition, $PM_{2.5}$ was part of PM_{10}, and certainly, the high correlation between both was expected. Traffic emission was likely the major source of $PM_{2.5}$ and PM_{10} because they were simultaneously produced by incomplete combustion inside motor engines. However, both $PM_{2.5}$ and PM_{10} could have originated from a variety of sources, including combustion, the photochemical smog reaction (EPA, 2021b; Pollution Control Department, 2018). Coming to the controversy, meanwhile, the majority of ground-level ozone is the result of reactions of man-made VOC and NOx (EPA, 2021a). Significant sources of VOC are chemical plants, gasoline pumps, oil-based paints, autobody shops, and print shops. Nitrogen oxides result primarily from high-temperature combustion. In the multivariate conditional logistic regression analyses, the results were found that only $PM_{2.5}$ was associated with the risks of the eye and adnexa diseases. While PM_{10} and O_3 were but in opposite directions as shown in Appendix b which differed from the findings of some other studies (Aik et al., 2020; Shin, Lee, & Kim, 2020; Yu et al., 2019). Still, this study declared similar results with some other studies, no association of PM_{10}, O_3 with the eye and adnexa diseases (Kim et al., 2020; Mo et al., 2019; Szyszkowicz et al., 2016; Zhong et al., 2018).

These differences may be explained by some reasons. First, these regions differ greatly in climate and environment, which may cause divergent outcomes of each air pollutant on the eye and adnexa diseases. Second, as the time-stratified case-crossover design where each patient served as his or her control was applied in the present study, the bias of the patient's socioeconomic status, educational level, living conditions, and systemic health conditions could be avoided during the analysis, therefore, resulting in the difference in the association of each air pollutant on the eye and adnexa diseases. However, the adverse effects of air pollutants are complicated, especially when multiple factors work together. One possible explanation may involve the high levels of the other air pollutants when fitting the multiple models made the effect of PM_{10} and O_3 less apparent. Another possible explanation was that the short analysis period for PM_{10}, O_3, and the eye and adnexa diseases, like the several days seen in this study, may not be long enough to reveal the association, as PM_{10} and O_3 effects may take longer to present. Altogether, our findings at least further prove that air pollution was partially responsible for the increasing cases of diseases of the eye and adnexa. Future studies should focus on the relationship between PM_{10}, O_3, and the eye and adnexa diseases, and investigations in a longer period are needed to explain their relationship.

Meteorological factors, RH and temperature, were both found related to the risks of the eye and adnexa diseases as shown in Appendix b. Several studies have investigated the association between meteorological changes and ocular diseases (Gorski, Genis, Yushvayev, Awwad, & Lazzaro, 2016; Hu, Lin, & Chen, 2008; Khalaila et al., 2021). Studies showed that the statistically significantly higher incidence of eye and adnexa diseases in summer compared with winter suggests that higher temperatures were a risk for eye and adnexa diseases and lower temperatures were protective against the eye and adnexa disorders.

To the best of our knowledge, there was an available limitation on prior-epidemiological studies focused on associations of ambient $PM_{2.5}$ with hospitalization for the total of the eye and adnexa diseases. In this study, the risk of a total of diseases of the eye and adnexa was founded to consist with $PM_{2.5}$ exposure at lag 6 days, its increasing 4% (ORs = 1.04, 95% CI: 1.02 to 1.06, $p < 0.001$) per an IQR rise in $PM_{2.5}$ concentration (Figure 4.7). Compared with a case-crossover study in Beijing, China, it showed a 12.6 (95% CI: 0.0, 26.7%) percentage increase in risks of ocular ERV (lag0) along with an IQR increase in the $PM_{2.5}$ (Liang et al., 2017). Nevertheless, studying the short-term effect of $PM_{2.5}$ on an outpatient visit for the eye and adnexa diseases in Shennongjia, all analyses of the eye and adnexa outpatient visits were insignificant (2.18%, 95% CI: -0.68%, 5.04% at lag 0) (C. Liu et al., 2019). These comparisons showed that studies with a higher level of $PM_{2.5}$ did not calculate a higher risk of eye and adnexa diseases. Both of the above studies found the association at lag 0, which was different from this study. This could be due to the many differences between studies, such as the components, the source of $PM_{2.5}$, or even the behavior of people, all of which lead to an individual characteristic of $PM_{2.5}$ exposure. Assessing the effect of exposure to $PM_{2.5}$ on diseases of the eye and adnexa has been still needed to ensure greater consistency, especially in the study of epidemiology.

This study demonstrated the results of season modification (Figure 4.9) that risk of hospitalization of the eye and adnexa diseases associated with $PM_{2.5}$ especially in the hot season, with high temperature and low relative humidity around mid-February and mid-May. Accompanying to peak rounds of every pollutant, especially $PM_{2.5}$, concentrations across area study have risen at their maximum. Moreover, several studies pointed out the higher risks of eye and adnexa diseases during the summer period, whose characteristics are high temperature, low humidity levels, including infectious keratitis (Gorski et al., 2016), conjunctivitis (Khalaila et al., 2021; Lu et al., 2019; Szyszkowicz et al., 2016). Plus, the risk of hospitalization of the eye and adnexa diseases was greatly associated with $PM_{2.5}$ in the wet season. The study examined that with high humidity, even not that high $PM_{2.5}$ was associated with poor visibility (Tao et al., 2009). Higher relative humidity and pollutant concentration caused the lowest visibility. Because SO_4^{2-} and NO^{3-} which are the component of $PM_{2.5}$ could easily absorb liquid water to give high relative humidity in ambient. The high risk of eye and adnexa diseases during the wet season might be because of the major component of $PM_{2.5}$. Another epidemiological study claimed a significant association between relative humidity and acute otitis media visits among children (Jiang, Luo, Zhang, Ren, & Huang, 2021). Notably, the causes and characteristics of the incidence of eye and adnexa diseases between the hot and wet seasons were discrete. The risk of hospitalization for the eye and adnexa during the wet season might be affected by other factors which were specifically related to the diseases of the eye and adnexa in a high relative humidity environment and were not involved in this study, such as pathogens. This means that $PM_{2.5}$ might not be the only cause of diseases of the eye and adnexa. Further study into epidemiology and the eye and adnexa diseases during the wet season with other essential factors is needed in the future.

Among subgroup analysis (Figure 4.10), the difference in associations of air pollution with eye health among gender was observed. The result showed that the male population was estimated a higher risk of hospital admission for the total of eye and adnexa diseases than the female population. Comparing to another study, the association between elevated $PM_{2.5}$ concentrations and increments of ocular were larger in females (Liang et al., 2017). Unfortunately, the number of studies of $PM_{2.5}$ and total diseases of the eye and adnexa stratified by sex still has a ceiling.

However, some researchers assessed that along with exposure to $PM_{2.5}$, male patients had a higher risk of eye and adnexa diseases: dry eye diseases (Mo et al., 2019; Szyszkowicz et al., 2016). In case of risk of modification by age, the younger population aged under 65 years was found the highest risk of eye and adnexa hospitalization. To correspond with the study of associations of $PM_{2.5}$ with the ocular ERVs, $PM_{2.5}$ was associated with larger increments in inpatient for eye health in younger subjects who were younger than 65 years old (Liang et al., 2017). The studies of the association of $PM_{2.5}$ with other eye disorders were also found greater among the younger population (Lin et al., 2019; Lu et al., 2019; Mo et al., 2019; Ruan et al., 2019). The study of $PM_{2.5}$ and total diseases of the eye and adnexa stratified by age still has a limitation as well. Nevertheless, each ocular disease has specifically occurred in a different age range. Among the elderly, arose $PM_{2.5}$ and eye health was associated notably as well. Following studies found that eye health was connected with the rising of daily $PM_{2.5}$ concentration greater in elders: glaucoma (Sun et al., 2021), conjunctivitis (Lu et al., 2019).

There were apparent differences in health outcomes in the male vs. female population and younger vs. older population. The observation that males had stronger associations of $PM_{2.5}$ exposure with eye health than females in our study suggests that factors, for example, hormonal levels, occupations, and time spent in outdoor air may contribute to observed differences in response. The toxic actions of air pollutants on different parts of the human body system and different age groups may differ. This may lead to the differences in response to $PM_{2.5}$ among age groups. The most evident factors differentiating health outcomes in different ages are dissimilar exposures (possibly due to unalike ways of active life) and different physiological sensibilities to the pollution factors affecting health (and many possible cofactors, as ultraviolet (UV) radiation, weather events, and allergens). Further studies with more cases may help to detect clearer differences between age groups.

To deeply explore the eye-health effect of risen $PM_{2.5}$ by differentiating by Sub-diseases and age (Figure 4.11, Figure 4.12), the distinctions in the relationship between $PM_{2.5}$ exposure and inpatient visits for the eye and adnexa diseases were calculated. Risks of hospital admission for conjunctivitis and other disorders of the conjunctiva were related with rising per an IQR of $PM_{2.5}$ concentration greater in both younger and older population. These findings on the effects of particulate matter associated with acute conjunctivitis were consistent with several studies which reported positive associations between ambient air particulate matter levels and conjunctivitis at a similar lag to this study (lag 0) (Aik et al., 2020; Lee et al., 2018; Lu et al., 2019; Mimura et al., 2014; Szyszkowicz et al., 2016). A multi-city study in China showed that conjunctivitis outpatient visits aged 35 - 64 years associated with per 10 mg/m^3 increase in $PM_{2.5}$ level at lag 0 (Lu et al., 2019). While a study of outpatient visits for conjunctivitis and $PM_{2.5}$ in Hangzhou, China determined the insignificant association among younger age (Q. L. Fu et al., 2017). Several plausible underlying mechanisms may explain findings. These relate to how particulate matter exposure increases ocular surface susceptibility to cellular breakdown and pathogens, thus increasing the risk of conjunctivitis (Q. Fu et al., 2017; H. Liu et al., 2018; A. A. M. Torricelli et al., 2013).

For those inpatients hospitalized for keratitis and other disorders of sclera and cornea, the association was found in the younger population. Epidemiological analysis between fine particulate matter and keratitis has been limited yet. A spatial study of PM_{10} and emergency room visits concluded the relationship between PM_{10} and the prevalence of keratitis (Lee et al., 2018) in Korea. Available toxicological researches declared the mechanisms underlying $PM_{2.5}$-induced corneal diseases, keratitis and disorders of the cornea: inhibition on the formation of primary cilia in ciliated cell types of the skin and eye (Bae et al., 2019), alteration of autophagy activity in HCECs (Q. Fu et al., 2017), triggering oxygen permeability (OP) impairment and reactive oxygen species (Ekanayaka, McClellan, Pitchaikannu, Francis, & Hazlett, 2019; Gao et al., 2016; Niu et al., 2021; Somayajulu et al., 2020; Suchecki, Donshik, & Ehlers, 2003). Plus, oxidative stress was an effect of those factors that favor damages of cornea and vision impairment.

Both of < 50 and ≥ 50 population, inpatient diagnosed as having cataract and disorders of lens linked to $PM_{2.5}$ concentration. To the best of our perception, yet there has been no epidemiological study in short-term exposure to $PM_{2.5}$ and cataracts and disorders of the lens to compare with. However, our results being in contrast to cohort studying ambient $PM_{2.5}$ and age-related cataracts, insignificant results were estimated in every analysis among population aged 50 years or older in South Korea (Shin et al., 2020). Fortunately, few pieces of evidence demonstrated the mechanism by which short-term exposure to $PM_{2.5}$ can lead to an increase in oxidative stress. The persistence of oxidative stress from reactive oxygen has been taken as one of the main mechanisms to the development of several ocular diseases, including cataracts (Chang & Yang, 2020; Joanna, Katarzyna, & Hassan, 2016). Clinical evidence in hamsters showed that exposure to ambient $PM_{2.5}$ was associated with pathogenesis (C. C. Wei et al., 2019). Moreover, there are many factors, including the subject's age, diabetes mellitus, blood pressure, medications, nutrition, and smoking activity being considered which could be related to cataract formation. Moreover, the relationship between high temperature and solid fuel smoke exposure and cataract formation has been established for decades. It's needed to determine whether this health impact was caused by heat, air pollutants, or both of the two factors.

Being a glaucoma inpatient, a link with elevated $PM_{2.5}$ emerged within a 50 and older years-old group. The following studies can compare with. Studying the relationship between $PM_{2.5}$ and glaucoma in a large community cohort also founded that greater exposure to $PM_{2.5}$ was associated with both self-reported glaucomas (S. Y. L. Chua et al., 2019) within UK residents aged 40 to 69 years. Studying in Taiwan showed that $PM_{2.5}$ was an independent factor associated with open-angle glaucoma among those aged 60 years or older (Sun et al., 2021). Many toxicological pieces of research proved the mechanism that $PM_{2.5}$ was a trigger of glaucoma. PM was proved associated with the system regulation of Endothelin-1 (ET-1) which is a vasoconstrictor secreted by endothelial cells. The increased ET-1 which can lead to vascular dysfunction was the suggested reason making primary open-angle glaucoma progressive (Cellini et al., 2012; Finch & Conklin, 2016). Plus, oxidative stress was an important risk factor in the development of primary angle-closure glaucoma as well (D. Chang et al., 2011). Yet few studies have indicated the association between glaucoma and polluted ambient air.

Being strabismus inpatient, a link with elevated $PM_{2.5}$ emerged in younger than 50 years old population. The following studies argued that air pollutions were associated with an increased risk of strabismus amongst children. Studies reviewed the eye diseases associated with exposure to air pollutants in children include strabismus (PD, 2018). A population-based study inspected the relationship between exposure to cigarette smoke during pregnancy and the development of strabismus in children (Kelly, Thornton, Edwards, Sahu, & Harrison, 2005). However, an association between fine particulate matter and the risk of strabismus needs to be assessed further.

With disorders of refraction and accommodation, a 50 years-old and older inpatient was connected to exposure to $PM_{2.5}$. There was some evidence estimated exposure to higher $PM_{2.5}$ and the increment in disorders of refraction and accommodation hospitalization including myopia (Ruan et al., 2019) and presbyopia (Lin et al., 2019). Focusing on myopia, Ruan's study assessing myopia in the elderly aged 50 years showed that long-term exposures to $PM_{2.5}$ might be important environmental risk factors of myopia in the elderly. For a study of presbyopia, Lin supported that exposures to ambient $PM_{2.5}$ might be important risk factors of presbyopia among old adults, and found the results that population aged 50 – 65 years were more sensitive to the effects of ambient $PM_{2.5}$ than older participants (> 65 years). The occurrence and progress of refraction and accommodation diseases were led by oxidative stress and systemic or local inflammation (Chang & Yang, 2020). One study showed that exposure to ambient air pollution has been associated with subclinical impairment in the ocular surface and the tear film (Gupta, Gupta, Joshi, & Tandon, 2002), which might discomfort eyes and lead to vision impairment. To pinpoint more differences among populations was showed, as presbyopia usually began to occur around 50 years of age, and was sensitive to the effects of the external environment at that age period (Fisher, 1973). However, the underlying mechanisms of the associations of airborne $PM_{2.5}$ and O_3 concentrations with these disorders remain largely unknown.

In the case of blindness and low vision, within < 50 and ≥ 50 population, an increase in hospital admission had linked with a rising in $PM_{2.5}$ levels. There was no epidemiological study that addressed the association between $PM_{2.5}$ with blindness and low vision hospitalization before our acknowledge. However, some toxicological researches proved the incidence of $PM_{2.5}$ impairing eye cells, corneal epithelial cells. Both in mouse and cell culture models, exposure to $PM_{2.5}$ remarkably inhibited corneal epithelial cell migration (Cui et al., 2018). Furthermore, $PM_{2.5}$ could induce DNA damage by increasing DNA double-stand breaks, altering cell ultrastructure after treatment with $PM_{2.5}$, and promoting ROS formation (Gao et al., 2016). In the condition that is delayed or sustained epithelial defect appeared, there will be an increased chance of pathogen invasion and infection, which might result in cornea ulceration, scar formation, neovascularization, and in turn lead to visual impairment or even blindness (Ma & Martins-Green, 2009). Yet few studies have indicated the association between blindness and polluted ambient air.

Hospitalization for others diseases of the eye and adnexa was associated along with $PM_{2.5}$-exposure per an IQR rising at 2 days later among the older population. Epidemiological evidence assessing elevated $PM_{2.5}$ and hospital admission for others diseases of the eye and adnexa has still scattered. But, in a good way, the examination of some diseases has been found, including disorders of the lacrimal system (Matsuda et al., 2015; A. A. Torricelli et al., 2011), dry eye disease (Kim et al., 2020; Mo et al., 2019; Tan et al., 2018; Yu et al., 2019; Zhong et al., 2018), iridocyclitis (Zheng et al., 2020), retinal disorders (S. Y. L. Chua et al., 2020; Sharon Y. L. Chua et al., 2021; Zeng et al., 2021), age-related macular degeneration (Sharon Y. L. Chua et al., 2021), and disorders of the optic nerve (Chang & Yang, 2020).

Overall, particulate matters with a diameter less than 2.5 have been proved the potential to precipitate an increment in ophthalmology health by physical attachment and many complex mechanisms. Besides, alter effects in systemic inflammation, promoting oxidative stress, and inducing cell death and DNA damage in human corneal epithelial, $PM_{2.5}$ exposure could lead to sympathetic nerve activity and then have impacts on retinal tissue and optic nerve which are regarded as part of the central nervous system (CNS) as a result. It might be showed that the characteristics and composition of $PM_{2.5}$ from multiple sources in upper northern Thailand can lead to diseases of the eye and adnexa by systematic impacts. An investigation of the properties of $PM_{2.5}$ in the upper northern area of Thailand was needed to explore further.

One interesting thing of this study is that the consistency between short-term exposure to $PM_{2.5}$ and hospital admission for eye health has been found specifically in those diseases affect by $PM_{2.5}$ according to systemic impacts such as systemic inflammation, oxidative stress, or neuro-pathways. In contrast, the ocular surface disorders including inflammation of the eyelid which is the part of the eye that is directly in contact with ambient air and are addressed in numerous studies (Chang & Yang, 2020; PD, 2018) were no clear evidence for the association with higher $PM_{2.5}$ at all. Because the 95% interval was wide, it could be that the case number of inflammation of the eyelid was too inadequate.

By excluding the above-standard $PM_{2.5}$ values (Figure 4.13), all analyses demonstrated that no ambient $PM_{2.5}$ level was a safe level for diseases of the eye and adnexa. This can suggest larger audiences, such as the government for $PM_{2.5}$ exposure protection. Even during low $PM_{2.5}$ concentrations, it was necessary that upper-northern Thai citizens be aware of the health effects of $PM_{2.5}$. Particularly, the associations between $PM_{2.5}$ and hospitalization for eye and adnexa were found to be significant during the wet season, when daily $PM_{2.5}$ concentrations were low and other critical factors were lacking. It might be that these associations were not solely related to $PM_{2.5}$.

One strength of this investigation is the time-stratified case-crossover study, using a method that has been rarely applied in prior studies on all diseases of the eye and adnexa and exposure to ambient air pollution. In this study, each inpatient served as his or her control to avoid the bias effects of the patients' socioeconomic status, educational level, living conditions, and systemic health conditions.

Some limitations of this study should be noted. First, the 24-hour average of fine particulate matter concentration data from fixed 15 monitoring stations was used, rather than measuring individual exposures. This might lead to measurement errors in the assessment of the dose-response relationship, but these errors are generally to be random (Guo et al., 2013). Secondly, this study was lack of the obligated factors being considered which could be related to the formation of the eye and adnexa diseases, including the subject’s diabetes mellitus, blood pressure, medications, nutrition, smoking activity, or occupation. The impacts of these factors were unsolved. The third of the cons is that other air pollutions were not estimated as covariates in this study because of the high data missing (37% for SO_2, 6% for NO_2, and 1.5% for CO). Lastly, the data missing rate of air pollutant concentration still exists with a possibility to introduce bias to the results. Therefore, further investigations are needed.

Chapter 5 CONCLUSION AND SUGGESTION

In conclusion, increases in ambient $PM_{2.5}$ concentration were significantly associated with the increment of the eye and adnexa inpatient visits in upper northern Thailand. The situation was getting more hazardous in the summer and wet seasons. The risk of eye and adnexa diseases should concern substantially amongst males and younger people. By sub-diseases and age stratification, the association was heterogeneous and very specific to the age range. The elderly should be mindful of the risks of hospitalization for conjunctivitis and other disorders of the conjunctiva, keratitis and other disorders of the sclera and cornea, cataract and disorders of the lens, glaucoma, disorders of refraction and accommodation, blindness and low vision, and other diseases of the eye and adnexa which were associated with ambient fine particulate matter. While younger than 65 years inpatients should keep an eye on the risks of conjunctivitis, strabismus, and other disorders of conjunctiva and disorders of the lens. This study suggested that the adverse effects of $PM_{2.5}$ were underestimated and there was no threshold for $PM_{2.5}$ exposure concentrations.

To reduce the vulnerability of the upper-northern population, $PM_{2.5}$ exposure prevention is crucial. Stringent environmental protection strategies should be practical to protect eye health from exposure to air pollution in an accurate period and population. Meanwhile, the implementation of health education should be carried out not only in high pollution periods but also in everyday life. A vast lack of information exists. Future air pollution epidemiological research still needs to target vulnerable populations, which could largely contribute to efficient public health intervention actions for policymakers.

References

Aik, J., Chua, R., Jamali, N., & Chee, E. (2020). The burden of acute conjunctivitis attributable to ambient particulate matter pollution in Singapore and its exacerbation during South-East Asian haze episodes. *Sci Total Environ, 740*, 140129. doi:10.1016/j.scitotenv.2020.140129

Apple, D. J. R., J.; Foster, A.; Peng, Q. . (2000). Cataract: Epidemiology and Service Delivery. *Survey of Ophthalmology, 45*, S32-S44. doi:https://doi.org/10.1016/S0039-6257(00)00171-5

Bae, J. E., Choi, H., Shin, D. W., Na, H. W., Park, N., Kim, J. B., . . . Cho, D. H. (2019). Fine particulate matter (PM2.5) inhibits ciliogenesis by increasing SPRR3 expression via c-Jun activation in RPE cells and skin keratinocytes. *Scientific Reports, 9*. doi:ARTN 3994 10.1038/s41598-019-40670-y

Balachandran, A., de Beer, J., James, K. S., van Wissen, L., & Janssen, F. (2020). Comparison of Population Aging in Europe and Asia Using a Time-Consistent and Comparative Aging Measure. *Journal of Aging and Health, 32*(5-6), 340-351. doi:10.1177/0898264318824180

Bateson, T. F., & Schwartz, J. (1999). Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. *Epidemiology, 10*(5), 539-544. doi:Doi 10.1097/00001648-199909000-00013

BBC. (2019). Thai doctors and environmentalists are worried about not adjusting the ceiling of PM2.5 measurements according to world standards. https://www.bbc.com/thai/46969830

Beelen, R., Hoek, G., van Den Brandt, P. A., Goldbohm, R. A., Fischer, P., Schouten, L. J., . . . Brunekreef, B. J. E. h. p. (2008). Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *116*(2), 196-202.

Bourne, R. R. A., Flaxman, S. R., Braithwaite, T., Cicinelli, M. V., Das, A., Jonas, J. B., . . . Vision Loss Expert, G. (2017). Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. *Lancet Global Health, 5*(9), e888-e897. doi:10.1016/S2214-109X(17)30293-0

Carracedo-Martinez, E., Taracido, M., Tobias, A., Saez, M., & Figueiras, A. (2010). Case-crossover analysis of air pollution health effects: a systematic review of methodology and application. *Environ Health Perspect, 118*(8), 1173-1182. doi:10.1289/ehp.0901485

Chang, C. J., & Yang, H. H. (2020). Impact on Eye Health Regarding Gaseous and Particulate Pollutants. *Aerosol and Air Quality Research, 20*(7), 1695-1699. doi:10.4209/aaqr.2020.03.0098

Chen, R. C., Yang, J., Zhang, C. L., Li, B. X., Bergmann, S., Zeng, F. F., . . . Wang, B. G. (2019). Global Associations of Air Pollution and Conjunctivitis Diseases: A Systematic Review and Meta-Analysis. *International journal of environmental research and public health, 16*(19). doi:ARTN 3652 10.3390/ijerph16193652

Chua, S. Y. L., Khawaja, A. P., Dick, A. D., Morgan, J., Dhillon, B., Lotery, A. J., . . . Consortium, U. B. E. V. (2020). Ambient Air Pollution Associations with Retinal Morphology in the UK Biobank. *Investigative Ophthalmology & Visual Science, 61*(5). doi:ARTN 32 10.1167/iovs.61.5.32

Chua, S. Y. L., Khawaja, A. P., Morgan, J., Strouthidis, N., Reisman, C., Dick, A. D., . . . Consortium, U. B. E. V. (2019). The Relationship Between Ambient Atmospheric Fine Particulate Matter (PM2.5) and Glaucoma in a Large Community Cohort. *Investigative Ophthalmology & Visual Science, 60*(14), 4915-4923. doi:10.1167/iovs.19-28346

Chua, S. Y. L., Warwick, A., Peto, T., Balaskas, K., Moore, A. T., Reisman, C., . . . Patel, P. J. (2021). Association of ambient air pollution with age-related macular degeneration and retinal thickness in UK Biobank. *British Journal of Ophthalmology*, bjophthalmol-2020-316218. doi:10.1136/bjophthalmol-2020-316218

Cleveland Clinic. (2021). Common Age-Related Eye Problems. Retrieved from https://my.clevelandclinic.org/health/articles/8567-common-age-related-eye-problems

Climatological Center. (2020). Thailand Climate. Retrieved from http://climate.tmd.go.th/map/thailand

Climatological Center. (2021). *Annual Thailand Climate Summary*. Retrieved from http://climate.tmd.go.th/content/category/17

Cui, Y. H., Hu, Z. X., Gao, Z. X., Song, X. L., Feng, Q. Y., Yang, G., . . . Pan, H. W. (2018). Airborne particulate matter impairs corneal epithelial cells migration via disturbing FAK/RhoA signaling pathway and cytoskeleton organization. *Nanotoxicology, 12*(4), 312-324. doi:10.1080/17435390.2018.1440651

Department of Mineral Resources. (2013). Geography of Northern, Thailand Retrieved from http://www.dmr.go.th/ThailandGeopark/%E0%B9%81%E0%B8%AB%E0%B8%A5%E0%B8%87%E0%B8%98%E0%B8%A3%E0%B8%93%E0%B8%A7%E0%B8%9

7%E0%B8%A2%E0%B8%B2/%E0%B8%A0%E0%B8%B2%E0%B8%84%E0%B9%80%E0%B8%AB%E0%B8%99%E0%B8%AD.html

Department of Pollution Control. (2013). Report on The Situation and Air Quality, Thailand. http://air4thai.pcd.go.th/webV2/

Ekanayaka, S. A., McClellan, S. A., Pitchaikannu, A., Francis, R., & Hazlett, L. D. (2019). Particulates Mediate Corneal Oxidative Stress, Upregulate Innate Immunity, and Enhance Keratitis. *Investigative Ophthalmology & Visual Science, 60*(9).

EPA, U. (2021a). Ground-level Ozone Pollution. Retrieved from https://www.epa.gov/ground-level-ozone-pollution

EPA, U. (2021b). Particulate Matter (PM) Basics. Retrieved from https://www.epa.gov/pm-pollution/particulate-matter-pm-basics

Fisher, R. F. (1973). Presbyopia and the changes with age in the human crystalline lens. *The Journal of Physiology, 228*(3), 765-779. doi:https://doi.org/10.1113/jphysiol.1973.sp010111

Foocharoen, C., Peansukwech, U., Pongkulkiat, P., Mahakkanukrauh, A., & Suwannaroj, S. (2021). Aerosol components associated with hospital mortality in systemic sclerosis: an analysis from a nationwide Thailand healthcare database. *Sci Rep, 11*(1), 7983. doi:10.1038/s41598-021-87114-0

Fu, Q., Lyu, D., Zhang, L., Qin, Z., Tang, Q., Yin, H., . . . Yao, K. (2017). Airborne particulate matter (PM2.5) triggers autophagy in a human corneal epithelial cell line. *Environ Pollut, 227*, 314-322. doi:10.1016/j.envpol.2017.04.078

Fu, Q. L., Mo, Z., Lyu, D. N., Zhang, L. F., Qin, Z. W., Tang, Q. M., . . . Yao, K. (2017). Air pollution and outpatient visits for conjunctivitis: A case-crossover study in Hangzhou, China. *Environmental Pollution, 231*, 1344-1350. doi:10.1016/j.envpol.2017.08.109

Gao, Z. X., Song, X. L., Li, S. S., Lai, X. R., Yang, Y. L., Yang, G., . . . Pan, H. W. (2016). Assessment of DNA Damage and Cell Senescence in Corneal Epithelial Cells Exposed to Airborne Particulate Matter (PM2.5) Collected in Guangzhou, China. *Investigative Ophthalmology & Visual Science, 57*(7), 3093-3102. doi:10.1167/iovs.15-18839

Gorski, M., Genis, A., Yushvayev, S., Awwad, A., & Lazzaro, D. R. (2016). Seasonal Variation in the Presentation of Infectious Keratitis. *Eye & Contact Lens-Science and Clinical Practice, 42*(5), 295-297. doi:10.1097/Icl.0000000000000213

Greenpeace. (2021). Different air quality measurement standards. https://www.greenpeace.org/thailand/explore/protect/cleanair/air-standard/

Guo, Y., Li, S., Tian, Z., Pan, X., Zhang, J., & Williams, G. (2013). The burden of air pollution on years of life lost in Beijing, China, 2004-08: retrospective regression analysis of daily deaths. *BMJ : British Medical Journal, 347*, f7139. doi:10.1136/bmj.f7139

Gupta, S. K., Gupta, V., Joshi, S., & Tandon, R. (2002). Subclinically dry eyes in urban Delhi: An impact of air pollution? *Ophthalmologica, 216*(5), 368-371. doi:10.1159/000066183

He, M., Wang, W., & Huang, W. Y. (2017). Variations and Trends in Health Burden of Visual Impairment Due to Cataract: A Global Analysis. *Investigative Ophthalmology & Visual Science, 58*(10), 4299-4306. doi:10.1167/iovs.17-21459

Health Engine. (2007). Vision and the eye's anatomy. Retrieved from https://healthengine.com.au/info/the-eye-and-vision#c2

Hu, C. C., Lin, H. C., & Chen, C. S. (2008). A 7-year population study of primary angle-closure glaucoma admissions and climate in Taiwan. *Ophthalmic Epidemiology, 15*(1), 66-72. doi:10.1080/09286580701771997

IQAir. (2020). *World Air Quality Report 2019*. Retrieved from http://www.indiaenvironmentportal.org.in/files/file/world-air-quality-report-2018.pdf

IQAir. (2021). World Air Quality Report 2020.

Jiang, Y. F., Luo, W. W., Zhang, X., Ren, D. D., & Huang, Y. B. (2021). Relative Humidity Affects Acute Otitis Media Visits of Preschool Children to the Emergency Department. *Ear Nose Throat J*, 1455613211009151. doi:10.1177/01455613211009151

Joanna, K., Katarzyna, K.-K., & Hassan, Y. A.-E. (2016). The Role of Oxidative Stress in the Pathogenesis of Eye Diseases: Current Status and a Dual Role of Physical Activity. *Mini-Reviews in Medicinal Chemistry, 16*(3), 241-257. doi:http://dx.doi.org/10.2174/1389557516666151120114605

Kashiwagi, K., & Iizuka, Y. (2020). Effect and underlying mechanisms of airborne particulate matter 2.5 (PM2.5) on cultured human corneal epithelial cells. *Sci Rep, 10*(1), 19516. doi:10.1038/s41598-020-76651-9

Kelly, S. P., Thornton, J., Edwards, R., Sahu, A., & Harrison, R. (2005). Smoking and cataract: Review of a causal association. *Journal of Cataract and Refractive Surgery, 31*(12), 2395-2404. doi:10.1016/j.jcrs.2005.06.039

Khairallah, M., Kahloun, R., Bourne, R., Limburg, H., Flaxman, S. R., Jonas, J. B., . . . Vision Loss Expert Group of the Global Burden of Disease, S. (2015). A Number of People Blind or Visually Impaired by Cataract Worldwide and in World Regions, 1990 to 2010. *Invest Ophthalmol Vis Sci, 56*(11), 6762-6769. doi:10.1167/iovs.15-17201

Khalaila, S., Coreanu, T., Vodonos, A., Kloog, I., Shtein, A., Colwell, L. E., . . . Tsumi, E. (2021). Association between ambient temperature, particulate air pollution, and emergency room visits for conjunctivitis. *Bmc Ophthalmology, 21*(1). doi:ARTN 100 10.1186/s12886-021-01854-1

Kim, Y., Choi, Y. H., Kim, M. K., Paik, H. J., & Kim, D. H. (2020). Different adverse effects of air pollutants on dry eye disease: Ozone, PM2.5, and PM10. *Environ Pollut, 265*(Pt B), 115039. doi:10.1016/j.envpol.2020.115039

laerd. (2018). Spearman's Rank-Order Correlation. Retrieved from https://statistics.laerd.com/statistical-guides/spearmans-rank-order-correlation-statistical-guide.php

Łatka, P., Nowakowska, D., Nowomiejska, K., & Rejdak, R. (2018). How air pollution affects the eyes — a review. *Ophthalmology Journal, 3*, 58-62. doi:10.5603/OJ.2018.0032

Le, A., Mukesh, B. N., McCarty, C. A., & Taylor, H. R. (2003). Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. *Invest Ophthalmol Vis Sci, 44*(9), 3783-3789. doi:10.1167/iovs.03-0077

Lee, J. Y., Kim, J. W., Kim, E. J., Lee, M. Y., Nam, C. W., & Chung, I. S. (2018). Spatial analysis between particulate matter and emergency room visits for conjunctivitis and keratitis. *Annals of Occupational and Environmental Medicine, 30*. doi:ARTN 41 10.1186/s40557-018-0252

Liang, F., Tian, L., Guo, Q., Westerdahl, D., Liu, Y., Jin, X., . . . Pan, X. (2017). Associations of PM2.5 and Black Carbon with Hospital Emergency Room Visits during Heavy Haze Events: A Case Study in Beijing, China. *International journal of environmental research and public health, 14*(7). doi:10.3390/ijerph14070725

Lin, H., Guo, Y., Ruan, Z., Yang, Y., Chen, Y., Zheng, Y., . . . Wu, F. (2019). Ambient PM2.5 and O3 and their combined effects on the prevalence of presbyopia among the elderly: A cross-sectional study in six low- and middle-income countries. *Science of The Total Environment, 655*, 168-173. doi:https://doi.org/10.1016/j.scitotenv.2018.11.239

Liu, C., Liu, Y., Zhou, Y., Feng, A., Wang, C., & Shi, T. (2019). Short-term effect of relatively low-level air pollution on outpatient visits in Shennongjia, China. *Environmental Pollution, 245*, 419-426. doi:https://doi.org/10.1016/j.envpol.2018.10.120

Liu, H., Zhang, X., Zhang, H., Yao, X. W., Zhou, M., Wang, J. Q., . . . Hu, B. L. (2018). Effect of air pollution on the total bacteria and pathogenic bacteria in different sizes of particulate matter. *Environmental Pollution, 233*, 483-493. doi:10.1016/j.envpol.2017.10.070

Liu, Q. Y., Lu, Z. J., Xiong, Y., Huang, F., Zhou, J. B., & Schauer, J. J. (2020). Oxidative potential of ambient PM2.5 in Wuhan and its comparisons with eight areas of China. *Science of The Total Environment, 701*. doi:ARTN 134844 10.1016/j.scitotenv.2019.134844

Lu, P., Zhang, Y. M., Xia, G. X., Zhang, W. Y., Li, S. S., & Guo, Y. M. (2019). Short-term exposure to air pollution and conjunctivitis outpatient visits: A multi-city study in China. *Environmental Pollution, 254*. doi:UNSP 113030 10.1016/j.envpol.2019.113030

Ma, C., & Martins-Green, M. (2009). Second-hand cigarette smoke inhibits wound healing of the cornea by stimulating inflammation that delays corneal reepithelialization. *Wound Repair and Regeneration, 17*(3), 387-396. doi:https://doi.org/10.1111/j.1524-475X.2009.00478.x

Maclure, M. (2017). The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. *American Journal of Epidemiology, 185*(11), 1174-1183. doi:10.1093/aje/kwx105

Matsuda, M., Bonatti, R., Marquezini, M. V., Garcia, M. L. B., Santos, U. P., Braga, A. L. F., . . . Monteiro, M. L. R. (2015). Lacrimal Cytokines Assessment in Subjects Exposed to Different Levels of Ambient Air Pollution in a Large Metropolitan Area. *PLOS ONE, 10*(11), e0143131. doi:10.1371/journal.pone.0143131

Mimura, T., Ichinose, T., Yamagami, S., Fujishima, H., Kamei, Y., Goto, M., . . . Matsubara, M. (2014). Airborne particulate matter (PM2.5) and the prevalence of allergic conjunctivitis in Japan. *Science of The Total Environment, 487*, 493-499. doi:10.1016/j.scitotenv.2014.04.057

Ministry of Public Health. (2016a). Data analysis and statistical preparation of hospitals.

Ministry of Public Health. (2016b). ICD-10-TM. Retrieved from http://www.thcc.or.th/ebook1/2016/mobile/index.html#p=1

Ministry of Public Health. (2021). Health Resources Geographic Information System. http://gishealth.moph.go.th/healthmap/gmap.php#result

Mo, Z., Fu, Q. L., Lyu, D. N., Zhang, L. F., Qin, Z. W., Tang, Q. M., . . . Yao, K. (2019). Impacts of air pollution on dry eye disease among residents in Hangzhou, China: A case-crossover study. *Environmental Pollution, 246*, 183-189. doi:10.1016/j.envpol.2018.11.109

Moran, J., NaSuwan, C., & Poocharoen, O. O. (2019). The haze problem in Northern Thailand and policies to combat it: A review. *Environmental Science & Policy, 97*, 1-15. doi:10.1016/j.envsci.2019.03.016

Morgan, I. G. (2016). What Public Policies Should Be Developed to Deal with the Epidemic of Myopia? (1538-9235 (Electronic)).

Niu, L. L., Li, L. P., Xing, C., Luo, B., Hu, C. C., Song, M. M., . . . Lei, Y. (2021). Airborne particulate matter (PM2.5) triggers cornea inflammation and pyroptosis via NLRP3 activation. *Ecotoxicology and Environmental Safety, 207*. doi:ARTN 111306 10.1016/j.ecoenv.2020.111306

Pascolini, D., & Mariotti, S. P. (2012). Global estimates of visual impairment: 2010. *British Journal of Ophthalmology, 96*(5), 614-618. doi:10.1136/bjophthalmol-2011-300539

PD, G. (2018). Minor to Chronic Eye Disorders Due to Environmental Pollution: A Review. *2*, 108.

Pollution Control Department, M. o. N. R. a. E. (2010). Announcement of the National Environment Board No. 36 (2010) Re: Standards for particulate matter with a size not exceeding 2.5 microns in the general atmosphere. Retrieved from https://www.pcd.go.th/laws/%E0%B8%9B%E0%B8%A3%E0%B8%B0%E0%B8%81%E0%B8%B2%E0%B8%A8%E0%B8%84%E0%B8%93%E0%B8%B0%E0%B8%81%E0%B8%A3%E0%B8%A3%E0%B8%A1%E0%B8%81%E0%B8%B2%E0%B8%A3%E0%B8%AA%E0%B8%B4%E0%B9%88%E0%B8%87%E0%B9%81%E0%B8%A7-2/

Pollution Control Department, M. o. N. R. a. E. (2018). Air Quality Index. Retrieved from http://air4thai.pcd.go.th/webV2/aqi_info.php

Pollution Control Department, M. o. N. R. a. E. (2019). *Booklet on Thailand State of Pollution 2018*. 15 Soi Sathon 11 Section 13, Yannawa, Sathon, Bangkok 10120 Thailand: S.Mongkon Press Limited Partnership.

Pollution Control Department, M. o. N. R. a. E. (2021). Supporting Documents: Improving the standard for dust particles up to 2.5 microns in size in the general atmosphere. Retrieved from https://www.pcd.go.th/wp-content/uploads/2021/01/pcdnew-2021-01-28_08-42-24_325315.pdf

Ruan, Z. L., Qian, Z. M., Guo, Y. F., Zhou, J., Yang, Y., Acharya, B. K., . . . Lin, H. L. (2019). Ambient fine particulate matter and ozone higher than certain thresholds associated with myopia in the elderly aged 50 years and above. *Environmental Research, 177*. doi:ARTN 108581 10.1016/j.envres.2019.108581

Samoli, E., Peng, R., Ramsay, T., Pipikou, M., Touloumi, G., Dominici, F., . . . Samet, J. J. E. h. p. (2008). Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. *116*(11), 1480-1486.

Sebastian, E. (2010). *The complexity and origins of the human eye A brief study on the anatomy, physiology, and origin of the eye*.

Sharma, S., Chandra, M., & Kota, S. H. (2020). Health Effects Associated with PM2.5: a Systematic Review. *Current Pollution Reports, 6*(4), 345-367. doi:10.1007/s40726-020-00155-3

Shin, J., Lee, H., & Kim, H. (2020). Association between Exposure to Ambient Air Pollution and Age-Related Cataract: A Nationwide Population-Based Retrospective Cohort Study. *International journal of environmental research and public health, 17*(24). doi:10.3390/ijerph17249231

Shou, Y. K., Huang, Y. L., Zhu, X. Z., Liu, C. Q., Hu, Y., & Wang, H. H. (2019). A review of the possible associations between ambient PM2.5 exposures and the development of Alzheimer's disease. *Ecotoxicology and Environmental Safety, 174*, 344-352. doi:10.1016/j.ecoenv.2019.02.086

Smith, J. A., Albeitz, J., Begley, C., Caffery, B., Nichols, K., Schaumberg, D., & Schein, O. (2007). The epidemiology of dry eye disease: Report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocular Surface, 5*(2), 93-107.

Somayajulu, M., Ekanayaka, S., McClellan, S. A., Bessert, D., Pitchaikannu, A., Zhang, K. Z., & Hazlett, L. D. (2020). Airborne Particulates Affect Corneal Homeostasis and Immunity. *Investigative Ophthalmology & Visual Science, 61*(4). doi:ARTN 23 10.1167/iovs.61.4.23

Strategy and Planning Division, P. H. D. (2018). Summary of Health Report, Thailand.

Strategy and Planning Division, P. H. D. (2019). Summary of Health Report, Thailand.

Strategy and Planning Division, P. H. D. (2020). Summary of Health Report, Thailand.

Suchecki, J. K., Donshik, P., & Ehlers, W. H. (2003). Contact lens complications. *Ophthalmol Clin North Am, 16*(3), 471-484. doi:10.1016/s0896-1549(03)00056-7

Sun, H.-Y., Luo, C.-W., Chiang, Y.-W., Li, K.-L. Y., Ho, Y.-C., Lee, S.-S., . . . Kuan, Y.-H. (2021). Association Between PM2.5 Exposure Level and Primary Open-Angle Glaucoma in Taiwanese Adults: A Nested Case-control Study. *International journal of environmental research and public health, 18*(4). doi:10.3390/ijerph18041714

Szyszkowicz, M., Kousha, T., & Castner, J. (2016). Air pollution and emergency department visits for conjunctivitis: A case-crossover study. *Int J Occup Med Environ Health, 29*(3), 381-393. doi:10.13075/ijomeh.1896.00442

Tan, G., Li, J., Yang, Q. C., Wu, A. H., Qu, D. Y., Wang, Y. H., . . . Shao, Y. (2018). Air pollutant particulate matter 2.5 induces dry eye syndrome in mice. *Scientific Reports, 8*. doi:ARTN 17828 10.1038/s41598-018-36181-x

Tang, Y. J., Chang, H. H., Chiang, C. Y., Lai, C. Y., Hsu, M. Y., Wang, K. R., . . . Lin, D. P. (2019). A Murine Model of Acute Allergic Conjunctivitis Induced by Continuous Exposure to Particulate Matter 2.5. *Invest Ophthalmol Vis Sci, 60*(6), 2118-2126. doi:10.1167/iovs.18-26214

Tao, J., Ho, K. F., Chen, L. G., Zhu, L. H., Han, J. L., & Xu, Z. C. (2009). Effect of chemical composition of PM2.5 on visibility in Guangzhou, China, 2007 spring. *Particuology, 7*(1), 68-75. doi:10.1016/j.partic.2008.11.002

Tham, Y. C., Li, X., Wong, T. Y., Quigley, H. A., Aung, T., & Cheng, C. Y. (2014). Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040 A Systematic Review and Meta-Analysis. *Ophthalmology, 121*(11), 2081-2090. doi:10.1016/j.ophtha.2014.05.013

The United States Environmental Protection Agency. (2020). Outdoor Air Quality Data. Retrieved from https://www.epa.gov/outdoor-air-quality-data/about-air-data-reports

Torricelli, A. A., Novaes, P., Matsuda, M., Alves, M. R., & Monteiro, M. L. (2011). Ocular surface adverse effects of ambient levels of air pollution. *Arq Bras Oftalmol, 74*(5), 377-381. doi:10.1590/s0004-27492011000500016

Torricelli, A. A. M., Novaes, P., Matsuda, M., Braga, A., Saldiva, P. H. N., Alves, M. R., & Monteiro, M. L. R. (2013). Correlation Between Signs and Symptoms of Ocular Surface Dysfunction and Tear Osmolarity With Ambient Levels of Air Pollution in a Large Metropolitan Area. *Cornea, 32*(4), E11-E15. doi:10.1097/ICO.0b013e31825e845d

Truong, S., Cole, N., Stapleton, F., & Golebiowski, B. (2014). Sex hormones and the dry eye. *Clinical and Experimental Optometry, 97*(4), 324-336. doi:10.1111/cxo.12147

Wei, C. C., Lin, H. J., Lim, Y. P., Chen, C. S., Chang, C. Y., Lin, C. J., . . . Wan, L. (2019). PM2.5 and NOx exposure promote myopia: clinical evidence and experimental proof. *Environ Pollut, 254*(Pt B), 113031. doi:10.1016/j.envpol.2019.113031

Wei, Y. G., Wang, Y., Di, Q., Choirat, C., Wang, Y., Koutrakis, P., . . . Schwartz, J. D. (2019). Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: time stratified, case-crossover study. *Bmj-British Medical Journal, 367*. doi:ARTN l6258

10.1136/bmj.l6258

Wong, W. L., Su, X. Y., Li, X., Cheung, C. M. G., Klein, R., Cheng, C. Y., & Wong, T. Y. (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Global Health, 2*(2), E106-E116. doi:10.1016/S2214-109x(13)70145-1

World Health Organization. (2006). *Air quality guidelines: Global update 2005 for Particulate matter, ozone, nitrogen dioxide and sulfur dioxide*.

World Health Organization. (2013). *Health Effects of Particulate Matter: Policy implications for countries in eastern Europe, Caucasus and Central Asia*. UN City, Marmorvej 51, DK-2100 Copenhagen Ø, Denmark: WHO Regional Office for Europe.

World Health Organization. (2018). Ambient (outdoor) air pollution. Retrieved from https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health

Yee, J., Cho, Y. A., Yoo, H. J., Yun, H., & Gwak, H. S. (2021). Short-term exposure to air pollution and hospital admission for pneumonia: a systematic review and meta-analysis. *Environmental Health, 20*(1). doi:ARTN 6 10.1186/s12940-020-00687-7

Yu, D. H., Deng, Q. L., Wang, J. W., Chang, X., Wang, S. X., Yang, R. R., . . . Yu, J. (2019). Air Pollutants are associated with Dry Eye Disease in Urban Ophthalmic Outpatients: a Prevalence Study in China. *Journal of Translational Medicine, 17*. doi:ARTN 46 10.1186/s12967-019-1794-6

Zanobetti, A., Dominici, F., Wang, Y., & Schwartz, J. D. (2014). A national case-crossover analysis of the short-term effect of PM2.5 on hospitalizations and mortality in subjects with diabetes and neurological disorders. *Environmental Health, 13*. doi:Artn 38 10.1186/1476-069x-13-38

Zeng, Y., Li, M., Zou, T., Chen, X., Li, Q., Li, Y., . . . Xu, H. (2021). The Impact of Particulate Matter (PM2.5) on Human Retinal Development in hESC-Derived Retinal Organoids. *Front Cell Dev Biol, 9*, 607341. doi:10.3389/fcell.2021.607341

Zhang, H. R., & Tripathi, N. K. (2018). Geospatial hot spot analysis of lung cancer patients correlated to fine particulate matter (PM2.5) and industrial wind in Eastern Thailand. *Journal of Cleaner Production, 170*, 407-424. doi:10.1016/j.jclepro.2017.09.185

Zheng, Z. H., Huang, G., Gao, T., Huang, T. Y., Zou, M. S., Zou, Y. H., & Duan, S. W. (2020). Epigenetic Changes Associated With Interleukin-10. *Frontiers in Immunology, 11*. doi:ARTN 1105 10.3389/fimmu.2020.01105

Zhong, J. Y., Lee, Y. C., Hsieh, C. J., Tseng, C. C., & Yiin, L. M. (2018). Association between Dry Eye Disease, Air Pollution and Weather Changes in Taiwan. *International journal of environmental research and public health, 15*(10). doi:ARTN 2269 10.3390/ijerph15102269

Zhu, X. J., Qiu, H., Wang, L. Y., Duan, Z. Q., Yu, H. Y., Deng, R., . . . Zhou, L. (2019). Risks of hospital admissions from a spectrum of causes associated with particulate matter pollution. *Science of The Total Environment, 656*, 90-100. doi:10.1016/j.scitotenv.2018.11.240

APPENDICES

Appendix a
Requisition document

ลำดับ	ชื่อแฟ้ม	ตัวแปร	ชื่อในระบบฐานข้อมูลแฟ้ม 43	คำอธิบาย	ช่วงข้อมูล
1*	DIAGNOSIS_IPD	รหัสสถานบริการ	HOSPCODE	*รหัสสถานพยาบาลตามมาตรฐานสำนักนโยบายและยุทธศาสตร์*	โรงพยาบาลในพื้นที่สุขภาพที่ 1 และจังหวัดตาก
2**	DIAGNOSIS_IPD	ทะเบียนบุคคล	PID	*ทะเบียนของบุคคลที่มาขึ้นทะเบียนในสถานบริการนั้นๆ ใช้สำหรับเชื่อมโยงหาตัวบุคคลในแฟ้มอื่น ๆ (สามารถกำหนดได้ตั้งแต่ 1-15 หลัก)*	
3*	PERSON	เพศ	SEX	*1 = ชาย 2 = หญิง*	ทุกเพศ
4*	PERSON	วันเกิด	BIRTH	*วันเดือนปีเกิด กำหนดเป็น ค.ศ. (YYYYMMDD) (หากไม่ทราบวันเดือนที่เกิด แต่ทราบ ค.ศ เกิด ให้กำหนดวันเกิดเป็นวันที่ 1 มกราคมของปี ค.ศ.นั้น ๆ)*	ทุกวันเกิด
5	-	อายุ	-	-	ทุกช่วงอายุ
6*	ADMISSION	วันที่และเวลารับผู้ป่วยไว้ในโรงพยาบาล	DATETIME_ADMIT	*วันเดือนปีและเวลาที่รับผู้ป่วยไว้ในโรงพยาบาล กำหนดเป็น ค.ศ. (YYYYMMDDHHMMSS)*	1 ม.ค. 2559 – 31 ธ.ค. 2563
7	ADMISSION	น้ำหนักแรกรับ	ADMITWEIGHT	*น้ำหนักผู้ป่วยแรกรับ (กิโลกรัม) จดทศนิยม 1 ตำแหน่ง*	ทุกช่วงน้ำหนักแรกรับ
8	ADMISSION	ส่วนสูงแรกรับ	ADMITHEIGHT	*ส่วนสูงผู้ป่วยแรกรับ (ซ.ม.)*	ทุกส่วนสูงแรกรับ

9*	DIAGNOSIS_IPD	รหัสการวินิจฉัย	DIAGCODE	*รหัสโรค ICD - 10 - TM*	D50-D89, I00-I99*, J00-J99, H00-H59*, N00-N99
10**	ADMISSION	ราคาทุนของบริการ	COST	*ราคาทุน ซึ่งรวมค่ายาและเวชภัณฑ์ทั้งหมด รวมทั้งค่าบริการทางการแพทย์ (รวมจุดทศนิยมและเลขหลังจุด 2 ตำแหน่ง)*	ทุกราคาทุนของบริการ
11**	ADMISSION	ค่าบริการทั้งหมด (ราคาขาย)	PRICE	*ราคาขาย ซึ่งรวมค่ายาและเวชภัณฑ์ ทั้งหมด รวมทั้งค่าบริการทางการแพทย์ (รวมจุดทศนิยมและเลขหลังจุด 2 ตำแหน่ง)*	ทุกค่าบริการทั้งหมด
12**	ADMISSION	ค่าบริการที่ต้องจ่ายเอง	PAYPRICE	*จำนวนเงินที่เรียกเก็บ เนื่องจากเป็นค่าใช้จ่ายที่เบิกไม่ได้ (รวมจุดทศนิยมและเลขหลังจุด 2 ตำแหน่ง) โดยถ้าไม่มีการเรียกเก็บให้ใส่เลขศูนย์*	ทุกค่าบริการที่ต้องจ่ายเอง
13**	ADMISSION	เงินที่จ่ายจริง	ACTUALPAY	*จำนวนเงินที่จ่ายจริง ถ้าไม่มีการจ่ายให้ใส่เลขศูนย์*	ทุกเงินที่จ่ายจริง
*แฟ้มข้อมูลที่จำเป็นต้องใช้ ได้แก่ HOSPCODE, SEX, BIRTH, DATETIME_ADMIT (เอาแค่ 3 ปี ตั้งแต่ 2561 – 2563 ได้) และ DIAGCODE (เอาแค่รหัส I00 - I99 และ H00 - H59 ได้) **แฟ้มข้อมูลใดหรือช่วงข้อมูลใด ที่รวบรวมได้ยากและใช้เวลานานสามารถเปลี่ยนแปลงหรือไม่เอาได้ ได้แก่ COST, PRICE, PAYPRICE, ACTUALPAY ***รบกวนส่งข้อมูลมาที่ toeychalala@gmail.com ***					

Appendix b
Analysis details

https://chula-my.sharepoint.com/:f:/g/personal/6033319423_student_chula_ac_th/Etpuq6956hlPu48km6gOjjcBMbcZgwodgbSVRPSoPgcwxQ

The above link is an appendix that contains:

- Partial of raw data for air pollutants, weathers and medical records
- Computation data including excluding low repeated value, imputing data, excluding the cases for the eye and adnexa diseases with 'NA'
- Location of the monitoring station and hospital
- Calculating daily concentrations of air pollutants and weathers at single and moving lag day
- Setting up a case-crossover table with a time-stratified design
- Actual results from fitting models
- Stratification analysis by season, sex, age and sub-diseases
- Summary statistics for air pollutants, weathers, medical records
- Visualizations

Appendix c
additional information

https://chula-my.sharepoint.com/:f:/g/personal/6033319423_student_chula_ac_th/Etpuq6956hlPu48km6gOjjcBMbcZgwodgbSVRPSoPgcwxQ

The above link is an appendix that contains:

- Additional multiple regression models
- Data without imputing

BIOGRAPHY

Nichaphan Kasikam was born on Saturday 8th, November 1998, in Bangkok. She was a senior at Chulalongkorn University at the faculty of science, where she was majoring in the department of environmental science with a concentration in air pollution and epidemiology. She graduated from the science-specific senior high school, Princess Chulabhorn's Science High School, Pathum Thani. Her intense interest in environmental science began during the second semester of 2019 when she had the opportunity to intern in environmental management. She learned about waste and wastewater management from suppliers. Her mentor aspired to pursue a career in environmental audit and management. When starting a senior project, she searched for research papers on the association between fine particulate matter and diseases, using a case-crossover design. She intended to assess the association between $PM_{2.5}$ and eye health. When she is not busy implicating about university works, she enjoys watching anime, listening to music, and realistic sketching.