

COVID-19, Mental Health, and Chronic Illnesses: A Syndemic Perspective

by
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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Statement of Contributions

The manuscripts (Chapters 1-4) presented in this thesis are the work of Kiran Saqib in collaboration with her co-authors and committee members. These manuscripts have either been published in peer-reviewed journals or are currently in the submission process.

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The study was conducted at the University of Waterloo by Kiran Saqib under the supervision of Dr. Zahid A. Butt, Dr. Joel A. Dubin, and Dr. Vivek Goel.

Kiran Saqib was responsible for framework conceptualization, data acquisition, analysis, and drafting, submitting, and revising the manuscript under the supervision of co-authors. The co-authors have contributed to the papers by offering overall theoretical and statistical guidance, critical feedback, and reflections on drafts and revisions of manuscripts.

Abstract

Introduction

The term "syndemic" refers to the interaction between two or more coexisting epidemics, where the interactions amplify the negative health outcomes. The COVID-19 pandemic can be considered a syndemic because it involves the convergence of multiple factors: the direct impact of the SARS-CoV-2 virus causing COVID-19, the exacerbation of pre-existing chronic health conditions, and the associated mental health challenges. These factors interact in complex ways, creating a situation where the combined effect is greater than the sum of its parts. The COVID-19 pandemic has triggered a surge in mental health challenges worldwide. The connection between COVID-19, mental health, and non-communicable diseases is bidirectional. Mental health issues can exacerbate existing chronic conditions, while pre-existing chronic conditions can increase the vulnerability to severe COVID-19 outcomes and also contribute to poor mental health. Recognizing the syndemic nature of the COVID-19 pandemic is crucial for holistic understanding and effective response. Approaches that solely focus on the virus itself or individual health conditions may overlook the complex interactions of other factors. A syndemic perspective not only highlights the synergy between COVID-19, chronic diseases, and mental health, but also emphasizes the need for comprehensive public health strategies that address not only the virus's spread but also consider the broader social, economic, and health implications.

Methods

This dissertation utilized secondary data acquired from the Ontario Health Database Platform (OHDP) through the Institute for Clinical Evaluation Sciences (ICES) with adult

Ontarians aged 18 years and above as the study population. The exclusion of individuals under 18 years old in the research was driven by the specific emphasis on chronic illnesses, which are typically more widespread in the 18+ age group. Despite the occurrence of COVID-19 in those under 18, the research focuses on individuals aged 18 and above, considering that younger individuals generally face milder complications compared to their older counterparts. Consequently, the inclusion of minors was deemed irrelevant to the research specific objectives. Various administrative health databases including the Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), Ontario Health Insurance Plan (OHIP), Ontario Mental Health Reporting System (OMHRS), and ICES-derived cohorts were used to identify variables of interest and address specific research objectives. The primary aim of this analysis was to evaluate the syndemic impact of COVID-19 and related anxiety and depression on health outcomes in the Ontario population. In Study I, Cox proportional hazards regression was utilized to assess the association of factors with time to anxiety and depression related health services utilization, and results were summarized using hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). For comparison of morbidity and mortality before and during the pandemic, an interrupted time series study design was adopted in study II, using a segmented regression model to assess the monthly impact of COVID-19 on overall morbidity and mortality in the Ontario population. For every assessment period (defined as month), we determined the total number of morbidity episodes and mortality per month for each year. For Study III, multiple logistic regression analysis was utilized to identify important risk factors associated with the syndemic impact of COVID-19 and co-occurring anxiety or depression on morbidity, among the adult Ontario population

Results

In the adjusted Cox proportional hazards model (Study I) for the sample, the individuals who had PCR tests had a higher risk of utilizing health services for anxiety and depression during the pandemic, (aHR, 6.37; 95% CI, 6.25-6.50 and aHR, 5.91; 95% CI, 5.87-5.95) for COVID-19 positive and COVID-19 negative respectively, as compared to those who had no PCR testing done for COVID-19. Study II noted that in the early stages of the COVID-19 pandemic's first wave in Ontario, there was a decrease in physician visits and hospitalizations among those with chronic conditions, possibly due to infection fears and disruption of health services. As time passed, there were later phases marked by significant rises in medical visits and hospitalizations. In the final adjusted regression model (Study III) for the sample, the individuals who were COVID-19 positive and had either anxiety or depression were more likely to utilize health services for chronic conditions of interest during the pandemic, as compared to those who were COVID-19 negative with mental health issues (ORs, 1.33; 95% CI, 1.12-1.58). A higher risk of morbidity was observed among males (ORs 1.28; CI, 1.16-1.41), as well as in individuals with diverse ethnic backgrounds and low socioeconomic status.

Conclusion

The individuals who had COVID-19 testing exhibited greater utilization of healthcare resources for anxiety and depression in comparison to those who were not tested, irrespective of COVID-19 disease status. Investigating the causes of psychological distress related to COVID-19, especially among individuals undergoing PCR testing, is essential for addressing its mental health impacts and improving readiness for future pandemics. We also

noted the complex trajectory of healthcare utilization during the pandemic's waves. While the initial decline in physician visits and hospitalizations could be attributed to fear and healthcare system adjustments, subsequent periods witnessed increases in healthcare utilization and mortality rates, highlighting the evolving dynamics of the pandemic's impact. The shifts in healthcare utilization brought about by the pandemic carry significant clinical and public health implications. These include potential consequences such as missed diagnoses, delayed treatment, higher morbidity, and increased mortality. These challenges highlight the importance of healthcare system adjustments and preparedness for future pandemics. It is vital to tackle barriers to health care, ensuring that individuals, particularly those with chronic conditions, can access essential medical services, even when resources are constrained. Moreover, the individuals diagnosed with COVID-19 and co-occurring mental health issues of anxiety and depression exhibited increased healthcare service utilization. This points towards the interconnectedness of physical and mental health and emphasizes the importance of addressing both aspects for individuals' overall well-being, especially within the context of the COVID-19 pandemic. The impact of COVID-19 on mental health can be seen as a "syndemic," wherein its effects on susceptible individuals with chronic illnesses are exacerbated through synergistic interactions. This interplay underscores the significance of comprehensive public health strategies. Acknowledging this syndemic enables policymakers to develop focused measures aimed at mitigating adverse health effects among vulnerable groups.

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To the Faculty and Staff of the University of Waterloo, I would like to extend my appreciation to the entire faculty and staff of the University of Waterloo for creating an exceptional environment for research and learning.

Dedication

This dissertation is dedicated

To my beloved son, Your boundless love and endless patience have been a constant source of inspiration. Though miles may have separated us during this academic pursuit, your love, and unwavering support have bridged the distance. Your absence has been deeply felt, but your presence in my heart and thoughts has been a constant source of motivation and strength. Your understanding, patience, and the sacrifices you've made during our time apart have been a testament to your incredible character. As I pursued my studies, your love remained my anchor, guiding me through the challenges and uncertainties that come with academia. Throughout this challenging journey, your resilience and understanding have been a beacon of light, reminding me of the importance of balance in life. May everything you wish for in life come true and may you always pursue your dreams with the same determination and joy that you brought into mine.

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Chapter 1: Background

1.1. Problem Statement

The strategies implemented to combat COVID-19 have inadvertently given rise to a surge in mental health challenges. The disruption of daily routines, limited social interactions, and concerns about health and economic well-being have all played a role in exacerbating mental health issues on a global scale. Also, there has been an increasing literature on the acute and potential long-term impact of COVID-19 on psychiatric and substance use disorders, including suicidal ideation, psychosis, anxiety, and depression.⁴ The emergence of COVID-19 has impacted non-communicable diseases (NCDs) in various ways. The extensive efforts aimed at managing COVID-19 have disrupted the routine care that is often essential for patients with NCDs. People with pre-existing chronic conditions are at a heightened susceptibility to contracting COVID-19. Furthermore, if these individuals do become infected with the virus, their likelihood of facing more severe clinical consequences or even mortality is significantly elevated compared to the general population. Several research studies have indicated a direct link between chronic diseases with mental disorders like depression^{9,10} in the general population.^{11,12} The synergism between COVID-19 and Non Communicable Diseases (NCDs) is double-sided.⁵ On the one hand, existing NCDs, such as cardiovascular disease, diabetes mellitus, cancer and chronic obstructive pulmonary disease, have been associated with a higher risk of complications, higher likelihood of need of intensive care unit admissions, and poorer prognosis and increased mortality among patients with COVID-

19.⁶ On the other hand, patients who survive COVID-19 are likely to develop or have further long-term chronic and mental health conditions.⁷

The Centers for Disease Control and Prevention (CDC) defines a syndemic as "synergistically interacting epidemics."¹ A syndemic is a disproportionately increased disease burden resulting from clustering of adverse factors; the interaction between the two or more factors is synergistic rather than additive.² The COVID-19 pandemic has escalated into a syndemic due to several driving factors, such as loneliness, uncertainty, financial issues, and lack of access to health services. The syndemic nature of COVID-19 is clear; while the virus might be potentially deadly, it is a threat to livelihood and social connections that is creating a generational health crisis. Both physical and mental health are intertwined, and the interaction between the illnesses can worsen the course of both illnesses.⁸ COVID-19 is having an intense impact on both, as conditions often go undiagnosed among patients with co-occurring physical and mental illnesses, which complicates diagnosis, treatment, and disease progression. Given the inequalities in vulnerability and exposure, COVID-19 may be regarded as a syndemic. Individual factors like age, sex, and chronic conditions influence severe outcomes. Socioeconomic dynamics also drive variations in morbidity, with residents of socially deprived areas experiencing higher mortality. Low-income and ethnic-minority groups face elevated exposure risks due to factors such as living conditions and are more susceptible due to health disparities. The COVID-19 pandemic has shed light on the complex interplay between a novel and challenging infectious disease and pre-existing chronic and endemic health issues. This situation has underscored its fundamental nature as a syndemic – a synergy of various health conditions and diseases.

1.2. Literature Review: COVID-19, Mental Health, and Chronic Illnesses: A Syndemic Perspective

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1.3. Abstract

Background: The COVID-19 pandemic is an epidemiological and psychological crisis; what it does to the body is quite well known by now, and more research is underway, but the syndemic impact of COVID-19 and mental health on underlying chronic illnesses among the general population is not completely understood.

Methods: We carried out a literature review to identify the potential syndemic impact of COVID -19 and related mental health issues on underlying comorbidities that could affect the overall health of the population.

Results: The COVID-19 pandemic can be recognized as a syndemic due to; synergistic interactions among different diseases and other health conditions, increasing overall illness burden, emergence, spread, and interactions between infectious zoonotic diseases leading to new infectious zoonotic diseases; and social and health interactions leading to increased risks in vulnerable populations and exacerbating clustering of multiple diseases.

Conclusions: There is a need to develop evidence to support appropriate and effective interventions for the overall improvement of health and psychosocial well-being of at risk populations during this pandemic. The syndemic framework is an important framework that can be used to investigate and examine the potential benefits and impact of codesigning

COVID-19/Non-communicable Diseases (NCDs)/Mental Health programming services which can tackle these epidemics concurrently.

1.4. Introduction

The term "syndemic" was first conceived by Merrill Singer to describe "synergistically linked" epidemics that coalesce and emerge as a result of adverse social circumstances.¹ A syndemic is defined by the Centers for Disease Control and Prevention (CDC) as "synergistically interacting epidemics"² that result in an inordinately increased disease burden due to the clustering of adverse factors; with the interaction between two or more factors more synergistic rather than additive.³ Syndemic theory emphasizes the socio-structural determinants of health disparities by focusing on critical targets for intervention rather than individuals and connects these socio-structural conditions to synergistic health epidemics.⁴ A syndemic is composed of three components including co-occurring or clustering diseases, adverse interactions between those diseases called biological–biological interactions, and social /environmental and other factors causing or exacerbating the disease. Syndemic is distinguished from other types of epidemics by the presence of both bio–bio and bio–social interactions.⁴ In a nutshell, the syndemic approach examines the nature of disease concentrations in populations, as well as interactions, in connection with social, environmental, and economic factors driving this synergism. Furthermore, a syndemic offers predictions about how epidemic interactions add to illness burden and about how to effectively intervene to reduce this burden.¹

The COVID-19 pandemic can be recognized as a syndemic due to; 1) synergistic interactions among different diseases and other health conditions, increasing overall illness burden at

every level, 2) emergence and spread of infectious zoonotic diseases and the interactions leading to new infectious zoonotic diseases;⁵ and 3) social and health interactions leading to increased risks in vulnerable populations and exacerbating clustering of multiple diseases ⁴. There is reason to believe that COVID-19 is a syndemic, not only a pandemic, based on the available data: a term used in medical anthropology that combines the concepts of 'synergy' and 'epidemic,' and provides a philosophical backdrop for these disasters. Despite the available reporting on the infrequent fatalities of young and those without any underlying health condition, the elderly and those with preexisting comorbid health conditions continue to account for the great majority of deaths.⁶ People are disproportionately affected by the COVID-19 situation, leading to increased structural disparities not only between social groups and classes, but also between generations.⁷ Since there is an imposition of new rules, social habits, and mobilizations, it has impact at both micro and macrosystem levels.⁸

1.5. Review Method and Search Strategy

A narrative review methodology was chosen to map the body of literature on COVID-19, chronic illnesses, and mental health during the current pandemic, including a greater range of study designs and methodologies, to provide a descriptive overview of the reviewed material. There is no standard protocol for narrative reviews in research. Therefore, a non-systematic electronic literature search was conducted using health-related research databases, including PsycINFO, PubMed, Google scholar, Web of Science and Scopus. The search period for relevant studies was conducted in November 2021-March 2022 and the search terms included variations in the terms for the following: ((chronic diseases*) OR (morbidity*) OR (mortality*) OR (deaths*) OR (Severe disease outcome*) AND (severe acute respiratory syndrome coronavirus 2* OR COVID-19* OR SARS-CoV-2* OR COVID-19

pandemic*) AND ((Psychological Stress*) OR (Anxiety*) OR (stress*), OR (Mental Health*) OR (Mental Disorders*) OR (stress disorders*) AND (mental health* OR mental illness*) AND (syndemic*) OR (COVID-19 * AND interaction*) OR (Syndemic* AND coronavirus*) OR (SARS-CoV-2* AND mental health* AND syndemic*)). The search was conducted on titles, keywords, and abstracts with " AND" entered into the database search to link different categories of search terms. We utilized forward reference searching to identify the references citing these articles and backward reference searching after reviewing the references that were cited in these articles. Non-standardized inclusion and exclusion criteria were used.

Relevant studies were selected based on following criteria; (1) focused on the COVID-19 pandemic and; (2) were contextualized to mental health in terms of anxiety and depression only, during the COVID-19; (3) Focused on chronic conditions of interest which included congestive heart failure, hypertension, chronic obstructive pulmonary diseases, asthma, and diabetes only, in terms of either severe disease outcomes or mortality during the pandemic; (4) Focused on syndemic. All relevant studies published in English, were reviewed regardless of their types or designs, and all countries of origin were eligible for inclusion. Articles were excluded if they were (1) published outside the search period; (2) did not focus on anxiety and depression during COVID-19 and reported other mental health conditions; (3) Focused on other chronic conditions; (4) irrelevant to either the COVID-19 pandemic impact on mental health, chronic conditions, and syndemic. Finally, the included articles (n=75) were peer-reviewed articles, perspectives, reviews, editorials, and commentaries. These articles were reviewed, and relevant data were extracted to report the key findings.

1.6. COVID-19 and Mental Health

COVID-19 and the mental health crisis caused by it,^{9,10} are two concurrently occurring epidemics emerging together in real time, with possible linkages with one another. Due to multiple factors, including uncertainty, loneliness, financial worries, disruption of supply chains and a lack of access to health care, the COVID-19 pandemic has evolved into a syndemic. Whether it is direct or indirect psychological and social impacts of the COVID-19 pandemic, it is obvious that they could have a long-term impact on the general population health. While the virus might be potentially deadly, it is a threat to livelihood and social connections that is creating a generational mental health crisis.^{11,12}

The COVID-19 pandemic is having an extreme impact on all aspects of society. It is believed that stress is a common factor impacting the syndemic of disease and health by influencing social, environmental, and political determinants.⁴ There is an increased incidence of fear, insecurity, anxiety disorders, depression, and suicide during these historical periods of stress.¹³ Fear-induced overreaction was reported among the general population during and after similar epidemics of SARS in 2003 and Ebola in 2014.^{14,15} Not only this, several psychiatric disorders like anxiety, depression and post-traumatic stress disorder were reported among SARS and Ebola epidemics survivors and healthcare workers.^{16–18} Changes in our daily lives and routines, job loss, loneliness, financial struggle, and grieving over the death of loved ones all are likely to negatively impact many people's mental health and well-being now and in future.

The COVID-19 pandemic is having an acute and long-term negative impact on anxiety, depression, psychosis, and suicidal ideation, among other clinical and drug use disorders.¹⁹

It is evident that the emotional and mental health impact of COVID-19 and quarantine is far much more than the fear of contracting the virus.²⁰ A study reported that 34.1% of participants with an experience of quarantine reported psychological symptoms like stress, anxiety, insomnia, and depression as compared to those who did not experience quarantine (27.3%), indicating the adverse impact of COVID-19 and quarantine measures on mental health.²¹ Many of the expected outcomes of quarantine, as well as the associated social and physical separation measures, are important risk factors for mental health problems.²² A few of these examples include self-harm, suicidal ideation, addiction, substance abuse, domestic and child abuse, and psychosocial risks due to loneliness, financial stress and unemployment.^{23,24} Uncertainty, boredom, loneliness, loss of freedom and separation from loved ones, can create dramatic effects.^{25,26} During such extraordinary circumstances, it is expected to witness anxiety and coping responses to stress, but at the same time, it is suspected that prevalence of anxiety, depression, and the number of people engaging in harmful behaviors will rise in future.

The public health measures implemented to limit the spread of COVID-19 have affected all segments of the population. Globally, surveys documenting COVID-19's mental health repercussions have specified certain groups who may be more vulnerable to the pandemic's psychological consequences. Women, younger age cohorts, those with economic instability or lower income, those who have lost income owing to the pandemic, those who live with others, and those who perceive a higher risk of COVID-19 infection are among the at-risk groups.²⁷⁻²⁹ Because of the scope of the COVID-19 pandemic, it may be difficult to extrapolate results from previous studies to the present. Prior infectious disease outbreak research has tended to focus on specific populations (e.g., affected patients, health care workers, and

persons who have been quarantined), with fewer studies focusing on broader general-population samples.³⁰⁻³² Despite the fact that the effects of COVID-19 on mental health have not been studied systematically yet, it is expected to have an adverse impact on mental health necessitating immediate action.^{33,34}

1.7. COVID-19 and Chronic Diseases

COVID-19 impacts almost every system of the human body, including the respiratory, neurological, cardiovascular, renal, gastrointestinal, musculoskeletal, and hematological systems.³⁵ People with existing health conditions, the elderly, and those with weak immune systems, are facing a considerable risk from COVID-19.³⁶ Co-occurrence of physical health conditions and mental conditions may muddle diagnosis, treatment, and disease progression. For example, heart failure as well as chronic obstructive pulmonary disorder (COPD) may either disguise or reflect symptoms of anxiety, depression, and post-traumatic stress disorder, making their diagnosis improbable.³⁷ Furthermore, there is an increased risk of mental health issues, stress and functional impairment due to underlying physical health conditions.³⁸ Likewise, higher rates of chronic conditions, including diabetes and hypertension are reported in those suffering from severe mental disorder.³⁹ Several research studies have indicated a direct link between chronic diseases with mental health issues like depression^{40,41} in the general population.^{42,43}

It is acknowledged that the interaction between physical and mental health is convoluted, which can worsen the course of both illnesses.⁴⁴ Similar interactions have been identified in acute and severe cases of COVID-19, diabetes and depression. It appears that diabetes promotes viral entry into human cells through certain pathways, while COVID-19 worsens

diabetes by stimulating an aggressive damaging immune response.⁴⁵ On one hand, co-existence of diabetes and depression cause adverse effects on both morbidity and mortality⁴⁶; while on the other hand, there is a 1.5-fold increase in mortality in people with diabetes due to coexisting depression.⁴⁷

COVID-19 also poses a threat to those suffering from cardiopulmonary disease⁴⁸ causing hypoxemia in approximately 15–20% of the patients requiring ventilator support in critical conditions.⁴⁹ Though COVID-19 infections are not directly linked to asthma, patients with moderate-to-severe or uncontrolled asthma are more likely to be hospitalized from COVID-19⁵⁰, indicating that asthma may be an important risk factor for COVID-19 severity and hospitalization. Smokers who are asthmatic and elderly, in particular, are at an increased risk of severe disease if infected with COVID-19.⁵¹ In individuals suffering from obesity and hypertension, the immune responses are activated and aggravated by chronic stress and biological aging processes.^{52–54} A high case fatality is connected to patients suffering from COVID-19 and uncontrolled high blood pressure.⁵⁵ A Chinese study had reported a 6% case fatality rate (CFR) in 23% of hypertensive COVID-19 cases, and the number continued to increase due to pandemic anxiety.⁵⁶ There is a risk of developing acute coronary syndrome in cardiovascular disease (CVD) patients with COVID-19. It is still not clear about the direct relationship and the mechanism of interaction between COVID-19 and CVD but chronic diseases exhibit common traits with infectious disorders, including a persistent proinflammatory state and a weakened immune response.⁵⁷

With regards to renal disease, due to an increase in ACE-2 expression, COVID-19 disease is severe in patients with renal diseases.⁵⁸ The weak immune response is the main risk factor

for developing COVID-19 infection in those with malignancies. Factors responsible for enhanced liver damage in COVID-19 patients include drug toxicity, stress, and systematic inflammatory response, paving the pathway for severe hepatic diseases.⁵⁹ The impact of COVID-19 on the nervous system and the causes of neurological symptoms experienced by COVID-19 patients are still unknown. According to research, headaches are most common initial neurological symptom and one of the most prevalent symptom in people diagnosed with COVID-19 infections and the incidence of headaches varies and falls within a wide range of 10-70%.⁶⁰⁻⁶³

Most non-communicable diseases (NCDs) including diabetes, cardiovascular disease, hypertension, asthma, have been reported as risk factors for severe COVID-19 disease causing an increase in mortality rate.⁵⁵ Chronic disease patients have been impacted by the COVID-19 pandemic both directly and indirectly. Along with morbidity and mortality, high rates of community spread and numerous mitigation measures, such as the advice to stay at home, have disturbed lives and led to suffering in the social and economic spheres.⁶⁴ In addition, the ability to prevent or control chronic diseases has been hampered by this pandemic, which has raised concerns about the security of healthcare access ⁶⁵ as well.

1.8. COVID -19, Mental Health and Chronic Diseases

According to the World Health Organization (WHO), 71% of all deaths per year are attributed to the syndemic associated with mental health conditions and NCDs.⁶⁶ There is a connection between mental health challenges, COVID-19 pandemic related morbidity, and mortality caused by the disease itself as well as related to mitigation activities like stay-at-home orders and social distancing.⁶⁷ Despite the fact that there is not much known about the novel

coronavirus, there is evidence of multi-organ-system involvement and syndemic interactions with various NCDs in patients suffering from COVID-19.⁶⁸⁻⁷⁰ Several risk factors have been identified during the COVID-19 pandemic including pre-existing health conditions as well as adverse social determinants of health that leave many susceptible to the disease.^{71,72}

The synergism between COVID-19 and NCDs is of reciprocal nature.⁷³ On the one hand, pre-existing NCDs, including diabetes mellitus, cancer, cardiovascular disease and chronic obstructive pulmonary disease are found to be associated with poor prognosis, higher risk of complications, increase in intensive care unit admissions, and thereby increased mortality among patients with COVID-19.⁷⁴ While on the other hand, those who survive COVID-19 are more prone to develop or have further long-term chronic and mental health conditions.⁷⁵ The elevated rates of NCDs and COVID-19 suggest an inclusive syndemic health burden, pointing towards the intersection of both with social determinants of health. There is considerable evidence hinting towards NCDs as a major factor responsible for adverse outcomes as a result of COVID-19 infection ^{75,76} and vice-versa, COVID-19 also contributes to the neglect of NCDs.⁷⁵

Managing and treating COVID-19 patients is still a major challenge for health care staff as effective antiviral medications are not yet available. This is because although select antivirals have proven efficacy in improving clinical outcomes in COVID-19 patients, there are mixed results for their efficacy in reducing mortality.⁷⁷ COVID-19 in individuals with comorbidities leads to a nexus of increased morbidity and higher mortality. It causes a detrimental impact on lungs, heart and kidneys in individuals suffering from conditions like diabetes, CVDs, and

COPD. All these complications have a deleterious impact on the patient's health due to acute respiratory distress syndrome, heart failure, renal failure, multiple organ failure, shock, and ultimately mortality.^{78,79} Despite the fact that most COVID-19 patients develop mild disease, still 20% of patients require hospitalization, with 5–8% developing severe symptoms and necessitating intensive care and intensive care unit (ICU) admission.⁸⁰ There is limited accurate data about exact duration of ventilation but there is an increased need of constant mechanical ventilation for two weeks or more, to enable patients to breathe normally.⁵⁵ Factors influencing ICU admissions include predisposing factors like age and comorbidities. Data from different countries show that highest rates of ICU admissions were recorded in the USA at 81%, Italy at 5-12% and 7-26% in China.⁸¹⁻⁸³

More than half a million people have died because of the COVID-19 epidemic, which has caused severe personal and societal losses.⁸⁴ In addition to the physical cost, the emotional consequence is still not entirely clear. The effects have been especially significant for people with chronic illnesses.^{69,85} Conditions that raise the risk for COVID-19-related severe illness include heart disease, diabetes, cancer, chronic obstructive lung disease, chronic renal disease, and obesity.⁸⁶ Lastly, since February 1, 2020, more people have died from dementia, cardiovascular, and other causes in addition to COVID-19-related mortality. This increase may be attributable to COVID-19 related deaths or to the virus's unintended consequences, such as underutilization of or burden on the healthcare system.⁸⁷

An estimated 14.9 million excess deaths directly associated with COVID-19 have been reported by the WHO between January 2020 and December 2021.⁸⁸ This calls for attention to explore excess deaths beyond those directly due to COVID-19, in assessment of the full

impact of the COVID-19 pandemic on overall mortality.⁸⁹ Along with the financial crisis due to the COVID-19 pandemic, there are also indications for mortality due to “deaths of despair”. The diseases of despair are three classes of behaviour-related medical conditions that include drug overdose, suicide, and alcoholic liver disease. These deaths are associated with a poor quality of life, including deterioration in emotional and physical health, resource constraints, and severe mental illness. Alcohol is a significant factor in mortality brought on by despair and is thought to be responsible for 15% of all drug overdoses, 26% of suicides, and 50% of liver disease deaths.⁹⁰ The pandemic mitigation strategies have also reduced social interaction due to physical distancing. Since human social connection is a strong reinforcer, a lack of it can lead to loneliness, dysphoria, despair, and general malaise. Negative emotional states have been exacerbated for many because of the ongoing COVID-19 pandemic, which has also caused social isolation, the loss of loved ones, loss of livelihood, and drinking to cope. It is possible that rising pandemic-related stress and increased drug use may fuel an increase in mortality from overdoses, suicide, and alcohol-related liver disease since the pandemic started against the backdrop of rising deaths from despair in the United States.⁹¹ These fatalities result from an increase of behavioral medical conditions in people suffering from despair due to a dreary outlook for their long-term socio-economic prospects.⁹² It is suggested that this may affect ‘at risk’ groups as well as those facing barriers to access care, having both short- and long-term implications for mental health and substance use. This is raising concerns over both cases and additional deaths, calling for action for those already-vulnerable populations at greater risk of contracting COVID-19.⁹³ Certain populations, including specific race and ethnic groups such as African Americans, Hispanics, and Native Americans, as well as those with poor socioeconomic status, suffer

from chronic diseases, COVID-19 disease, hospitalization, and mortality.⁹⁴ Due to exposure to inadequate social determinants of health (SDoH), these populations are more at risk. Where people live, work, and play has an impact on their health, and SDoH can lead to barriers that exacerbate inequalities. Numerous factors including institutional racism, lack of access to healthy food, lack of safe and cheap housing, lack of education, kind of employment, inadequate or no health care, and other factors all have an impact on a variety of health outcomes.⁹⁵⁻⁹⁷ The COVID-19 pandemic has exposed fundamental causes of health disparities and aggravated them. The current situation necessitates a holistic approach and effective coordination of health services during such health emergencies.⁹⁸

1.9. Syndemic Approach: A Way Forward

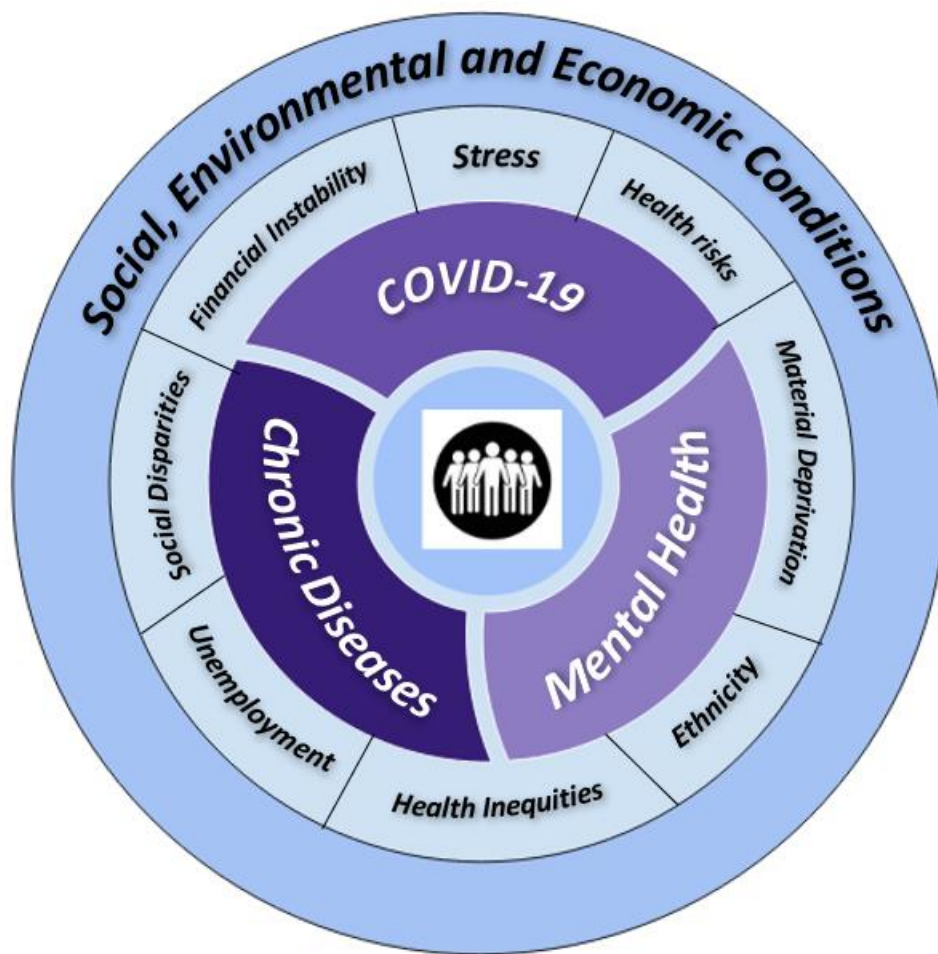
The concept of syndemic is not new; it has been applied to understand various issues, including health disparities, the dynamics of migrant health, malnutrition, violence, substance abuse, mental health, sexual health, infectious diseases like HIV/AIDS, and tuberculosis, and non-communicable diseases (such as diabetes mellitus, cardiac and pulmonary), over the years.^{46,99-101} The syndemic approach has gained popularity and has been utilized to study both global health and global mental health over the past 20 years.¹⁰² Initially the syndemic approach was focused on vulnerable communities in only high-income countries (HICs)¹⁰³, but lately, the syndemic approach has been applied to low- and middle-income countries (LMICs) as well.¹⁰⁴⁻¹⁰⁶ Researchers, such as Mendenhall et al.⁴⁶ and Irene et al.¹⁰⁷ have studied mental health conditions along with NCDs in those countries where infectious diseases or disease-specific interventions are a priority for research and policy.¹⁰⁴

Syndemic theory argues that the pandemic might exacerbate disparities in the social, political, and economic conditions that elevate the risk of disease concentration in vulnerable populations. It considers the synergistic effects of social, environmental and political factors affecting etiology and prognosis, at both the population and individual level, moving beyond comorbidity¹⁰⁸ and help us understand how these factors contribute and influence the onset and clustering of diseases.^{109,110} In addition to disease concentration, disease interaction is a dominant feature of a syndemic. These interactions are thought to worsen pandemic consequences by having multiplicative rather than additive impacts. The syndemic interaction plays a prominent role in defining the trajectories and intensification of infectious diseases.^{3,111} The significance of syndemic thinking is emphasized by the existence of synergistic effects in the short and long term.¹¹²

The COVID-19 outbreak continues to have an impact on populations, especially those living in poverty, the elderly, people with disabilities, children, and indigenous peoples. It is most harmful to those individuals who belong to the social groups that are most at risk. Early pandemic data suggests that the poor are disproportionately paying the costs of the virus's effects on their health and economic circumstances. For instance, homeless individuals are more vulnerable, in addition to, refugees and migrants, who suffer disproportionately from the epidemic and its aftermath due to restrictions on movement, and a lack of work prospects. COVID-19 teaches us that social and biological risk are closely intertwined. Viruses may infect individuals, but pandemics impact entire populations. Like previous pandemics, this disease is a reflection of political, economic, and social circumstances, and the concept of syndemic helps us grasp these interactions.¹¹³ The challenging social, economic, and power disparities, inequities in the distribution of health risks and resources,

resulting in disease concentration in specific vulnerable population, and the biological interactions point towards COVID-19 being a syndemic. (Fig 2.1).The aggregation of disease on a background of social and economic disparity exacerbates the adverse effects of already existing comorbidities.¹¹⁴ People infected with COVID-19 have suffered severe outcomes due to pre-existing diseases including hypertension, diabetes, and respiratory problems., while the virus spread has been fueled by the existing social and health inequalities, and a fragmented health-care system. Synergistic failures have resulted in more death and devastation than in many other situations ,¹⁰⁹ and it has been reported that COVID-19 has killed more people than severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) combined.¹¹⁵

Figure 1.1. Conceptual framework for COVID-19, Mental Health, and Chronic Diseases Syndemic



The COVID-19 pandemic has evolved into an extreme kind of syndemic, a pan-syndemic¹¹⁶, which has exposed inequities by increased disease burden and death compressed within a short time span globally.⁷¹ Higher mortality rates have been reported in underserved populations throughout the world in both developed and developing countries.¹¹⁷⁻¹¹⁹ The worldwide excess deaths in 2020 has surpassed the already shocking number of deaths directly attributed to COVID-19 but syndemic interactions are likely to be blamed.¹²⁰ Pre-existing patterns of uneven distribution of NCDs reflect well-known societal trends, especially along social class and ethnic lines. COVID-19's status is changed from pandemic to

syndemic within this nexus.¹²¹ An increase in the incidence and prevalence of anxiety and depression is as a result of the COVID-19 pandemic, and experts are already warning of a "echo pandemic";¹²² a new term that describes the possibility of widespread mental health issues that resemble COVID-19 in scale.¹²³

Since the coronavirus pandemic is an epidemiological and psychological crisis, there is some understanding of its effect on populations, and more research is underway, but the syndemic impact of COVID-19 and mental health on underlying chronic illnesses among the general population is not completely understood. Originally, syndemic theory was comprised of disease clustering, interaction between diseases, and the wide range of social factors giving rise to them, but it is a complex, multilevel phenomenon (Fig.2.1). The significance of this approach lies in its ability to predict how the interplay between different epidemics can magnify overall disease burden, which differs if each disease would have been examined individually. The collective factors between multiple epidemics can be interpreted with a syndemic approach. There is a gap to explore and investigate how epidemics interact both at the level of populations and individuals during this COVID-19 pandemic. The application of syndemic theory in the COVID-19 pandemic may guide public health planners to design effective interventions to mitigate disease burden. There is a need to generate evidence to support appropriate and effective interventions to improve the health and psychosocial wellbeing of vulnerable populations for future pandemics.¹⁰⁸ In order to protect the health of our communities, the syndemic and complex nature of the COVID-19 pandemic calls for a unique and sophisticated approach. The syndemic framework is an important and robust model with abilities to investigate and examine the potential benefits and impact of

codesigning COVID/NCDs/Mental Health programming services, which can tackle these pandemics concurrently.

1.10. Project Rationale

Population-level factors, such as the effect of social distancing measures and other necessary public health measures, affect overall health within a syndemic approach. A syndemic is at the intersection of demographics and health conditions and these interacting health effects and societal forces combine to form a syndemic and add complex knots of health determinants. Many of the available studies have highlighted the impact of COVID-19 on mental health only, by internally comparing characteristics among patients with comorbidities and COVID-19. The syndemic effects of COVID-19 have not been studied systematically yet, but it is expected to have significant effects.^{13,14} Research priorities around COVID-19 require us to embrace complexity by deploying multidimensional perspectives. The administrative data can be utilized as a system to investigate syndemic and to identify health effects at scale. Syndemic- informed approaches can lead to impactful multilevel prevention strategies and support informed decision making, resource management and cost-effective healthcare services.

1.11. Research Questions and Objectives

This dissertation aimed to assess the syndemic impact of COVID-19 and mental health on morbidity and mortality among the general population in Ontario, Canada with the following research questions:

- 1) What is the impact of the COVID-19 pandemic and mental health consequences among the adult Ontario population?
- 2) Has morbidity and mortality changed over time (before and after COVID-19 pandemic) in adult Ontarians, due to the COVID-19 pandemic?
- 3) What is the syndemic impact of COVID-19 and mental health on morbidity in the adult Ontario population?

The specific **research objectives** are listed below:

- To examine the impact of COVID-19 on mental health through anxiety/depression related health services utilization in the adult Ontario population during COVID-19 pandemic.
- To compare morbidity and mortality before and during the COVID-19 pandemic in the Ontario population.
- To understand the contribution of COVID-19 to morbidity and mortality over time.
- To investigate the syndemic nature of COVID-19, with a specific focus on understanding how viral infection, mental health issues, and pre-existing comorbidities interact and influence each other.
- To identify important risk factors associated with this syndemic

1.12. Dissertation Structure

This dissertation aims to explore the syndemic nature of COVID-19, mental health, and chronic diseases by examining their complex interactions and implications. Considering the COVID-19 pandemic's dual nature as both an epidemiological and psychological crisis, it is crucial to understand its syndemic impact on the overall health of the general population. It

also investigates the intricate connections between COVID-19 and socioeconomic as well as environmental factors. The overarching objective is to gain a comprehensive understanding of the syndemic dynamics of COVID-19 while accounting for its impact on mental health and chronic diseases, thereby informing evidence-based strategies for improving health outcomes. Furthermore, the dissertation seeks to highlight the significance of a syndemic framework that is an important and robust model with abilities to investigate and examine the potential benefits and impact of co-designing health programming services.

This dissertation adopts a manuscript-based approach and is composed of five chapters. The introductory chapter (Chapter 1) outlines the problem context for the work, establishes its purpose and objectives. Chapter 1 (Published in a peer reviewed journal) also provides a review of the literature and explains how the manuscripts presented in the body address the purpose and objectives. The subsequent three chapters (Chapters 2 to 4) each feature three manuscripts prepared for peer-reviewed journals. These manuscripts are currently under preparation for submission or already submitted. Chapter 5 provides a discussion and concludes this dissertation by summarizing the major findings, comparing, and commenting on the findings across the three studies, as well as highlighting major contributions. The limitations of this dissertation and future research directions are also discussed in this chapter.

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Chapter 2 Preamble

Study I (Chapter 2) was conducted to explore the association of COVID-19 PCR testing on individuals' mental health, particularly in terms of depression and anxiety amongst the Ontario population. By examining how individuals utilized healthcare services for anxiety and depression during the pandemic, the study aims to provide meaningful insights into the intersection of COVID-19 testing, mental well-being, and healthcare-seeking patterns. The broader context highlights the growing concern regarding the mental health impact of COVID-19, which has disproportionately affected vulnerable populations. Furthermore, the study acknowledges that while COVID-19 testing is crucial for controlling the virus's spread, it can induce various forms of psychological distress, including anxiety, and depression. These insights will contribute to a more holistic understanding of the pandemic's indirect effect on the mental health of the general population.

Chapter 2: The Impact of COVID-19 on Anxiety and Depression related Health Services Utilization among the Adult Ontario Population during the COVID-19 Pandemic

Status: Submitted

2.1. Abstract

Background: The implications of COVID-19 on population mental health are a matter of enormous concern. The objective of this study is to understand the impact of COVID-19 on mental health in terms of depression and anxiety health services utilization after the onset of the COVID-19 pandemic (Jan 2020 to March 2021) in Ontario, the most populous province in Canada.

Methods: A population based retrospective cohort study was conducted utilizing patient-level linked population-based health administrative data housed at the Institute for Clinical Evaluative Sciences, Ontario. This study included 6,175,114 individuals who were living in Ontario, Canada, had a valid health card, and for whom information on sex and age was available between Jan 2020 to March 2021. Exposure in this study was COVID-19 testing by standard lab-based tests in Ontario between Jan 2020 and Mar 2021, irrespective of COVID-19 disease status. The event of interest was the time in months until health services utilization related to anxiety and depression.

Results: Of 6,175,114 individuals, there were 4,274,037 (69.21%) without a standard lab-based test for COVID-19 and 1,755,519 (28.43%) with negative test results, while 145,558 (2.36%) tested positive for COVID-19 during the study period. In the adjusted Cox proportional hazards model for a propensity score matched sample, the individuals who had PCR tests had a higher risk of utilizing health services for anxiety and depression during the pandemic, (aHR, 6.37; 95% CI, 6.25-6.50 and aHR, 5.91; 95% CI, 5.87-5.95) for COVID-19

positive and COVID-19 negative respectively, as compared to those who had no PCR testing done for COVID-19. Also, a higher risk of utilizing health services for anxiety and depression was noted among young individuals, females and those residing in rural areas.

Conclusion: Individuals who had COVID-19 testing done, regardless of their disease status, demonstrated higher utilization of health services for anxiety and depression compared to those without any testing. To address psychological impacts and enhance preparedness for future pandemics, it is vital to investigate the reasons behind the mental stress related to COVID-19, particularly among individuals undergoing testing.

2.2. Background

Mental illness is a leading cause of disability worldwide, affecting over 450 million people.¹ Depression and anxiety are the most debilitating mental illnesses, which rank among the top 25 leading sources of disease burden globally.^{2,3} The COVID-19 pandemic and the restrictive measures implemented have led to a surge in mental health issues globally,⁴ including anxiety, depression, stress, sleep disorders, and fear, leading to increased substance abuse and, in some cases, suicidal ideation.⁵⁻⁷ According to a World Health Organization (WHO) research brief, anxiety and depression increased by 25% in the first year of the pandemic.⁸ A global study reported almost 76 million cases of anxiety and 53 million cases of major depressive disorder due to the pandemic, resulting in a 26% and 28% increase, respectively.⁹

Previous studies have noted that gender and age are significant risk factors for mental health issues, with women and young adults at elevated risk.^{10,11} Other risk factors for psychological disturbances, depression, post-traumatic stress disorder (PTSD), mood, and anxiety disorders include pre-existing psychiatric disorders, trauma exposure at an early age, remote work, unemployment, low income, immigrant status, and social isolation.^{12,13} Suicidal ideation is also related to pre-existing mental disorders and prior exposure to trauma.¹⁴ Moreover, unemployment, a solitary lifestyle, and having minimal communication with family and friends all elevate the probability of higher levels of depression.¹⁵ Quarantined individuals may experience irritability, anger, sleeplessness, anxiety, and depression due to physical separation and social isolation.¹⁶

The implications of COVID-19 on population mental health are a matter of enormous concern.¹⁷ Economic measures and social mitigation strategies were implemented in Canada and other developed countries, but problems arising from these strategies exposed vulnerable populations to poverty and its negative effects on their mental health, such as anxiety and depression.^{18,19} Mental health has long been recognized to be impacted by epidemics and pandemics; the mental issues caused by viral outbreaks have been dubbed a "parallel epidemic."²⁰ Concerns surrounding mental health during COVID-19 should also be viewed as a parallel epidemic instead of just a delayed outcome of the pandemic.²¹ The rise in the incidence and prevalence of anxiety and depression is an outcome of the COVID-19 pandemic, and mental health professionals have already issued a warning of an "echo pandemic"²² of mental health issues.²³

Testing for COVID-19 has played a crucial role in identifying and managing the spread of the virus. It is crucial to recognize and address the associated psychological distress that testing can induce. Anxiety, fear of the unknown, stigma, discomfort, information overload, and post-traumatic stress symptoms are among the psychological distress factors associated with COVID-19 testing.²⁴⁻²⁷ The objective of this study is to understand the impact of COVID-19 PCR testing on mental health in terms of depression and anxiety related health services utilization, after the onset of the COVID-19 pandemic (Jan 2020 to March 2021) in Ontario, the most populous province in Canada.

2.3. Methodology

Data Source: This study utilized secondary data from administrative health databases accessed through the Ontario Health Database Platform (OHDP). The platform permitted

access to patient-level linked population-based health administrative data held at the ICES. The ICES data repository consists of record-level, coded, and linkable health data sets that integrate health services data, registries, and surveys. ICES is an independent, non-profit research institute that houses routinely collected health data from Ontario's publicly funded health care system.

All residents of Ontario covered by the province's universal health coverage were identified, and their age and sex information were determined at the time of cohort extraction using the Registered Persons Database (RPDB), the central population registry file that enables linking across population-based health administrative data sets. Information on all psychiatric admissions to Ontario facilities with designated adult mental health beds is included in the Ontario Mental Health Reporting System (OMHRS). All inpatient acute bed discharges are documented in the Discharge Abstract Database (DAD). Almost the entire population of Ontario is covered by the Ontario Health Insurance Plan (OHIP), and billing claims for physician services and outpatient visits are recorded in the OHIP claims database. Information about visits to emergency departments (EDs) is included in the National Ambulatory Care Reporting System (NACRS). For demographic data, we used the RPDB, which includes all residents of Ontario who are eligible for OHIP, and the vital statistics-death (ORGD) database for death records. For identification of COVID-19 status, C19INTGR was used, which is an ICES-derived comprehensive dataset of all available standard lab-based PCR COVID-19 diagnostic laboratory results in Ontario. To identify individuals with chronic conditions included in this study, all relevant ICES-derived cohorts²⁸ were used i.e., asthma, hypertension, diabetes, chronic obstructive pulmonary disorder, and congestive heart failure. These datasets were linked using unique encoded identifiers and analyzed at

ICES (Appendix B). This study followed the Reporting of Studies Conducted Using Strengthening the Reporting of Observational studies in Epidemiology. (STROBE) reporting guidelines.²⁹

Study Design, Settings, and Cohort Eligibility

We constructed a retrospective cohort of people who were living in Ontario, Canada, had a valid health card, and for whom information on sex and age was available between the period of January 2020 to March 2021 (Figure 2.1). All cases who were not Ontario residents and were less than 18 years of age, and those who had a standard COVID-19 lab-based PCR test result after the study end period, i.e., beyond March 31, 2021, were excluded. We utilized the National Ambulatory Care Reporting System (NACRS) and the Ontario Health Insurance Plan (OHIP) to identify physician, outpatient visits, and emergency department visits for mental health, and we used the Canadian Institute for Health Information's Discharge Abstract Database (DAD) and Ontario Mental Health Reporting System (OMHRS) to capture psychiatric hospitalizations. The National Ambulatory Care Reporting System (NACRS) and the Discharge Abstract Database (DAD) use the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, with Canadian enhancements (ICD-10-CA) and the Ontario Mental Health Reporting System (OMHRS) uses the multiaxial *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). The codes used in this study to identify mental health visits have been used for mental health system performance measurement in Ontario and elsewhere in Canada.³⁰⁻³⁴ (Appendix B)

The exposure in this study was COVID-19 testing by standard lab-based PCR tests in Ontario between Jan 2020 and Mar 2021, irrespective of COVID-19 disease status, leading to three

groups for comparison: (i) those PCR tested with a positive COVID result; (ii) those PCR tested with a negative COVID result, and (iii) those who were not PCR tested. The event of interest was the time in months until health services utilization related to anxiety and depression, using DSM-V criteria, ICD-10 codes, and OHIP diagnostic codes during the study period. The participants were censored if there was no utilization of anxiety/depression-related health services by the end of the study follow-up period on March 31, 2021. Also, those who died during the study period were censored at the date of death.

Variables

Clinical variables: COVID-19 status was based on a standard lab-based PCR test, while the prevalence of chronic conditions was identified using ICES-derived cohorts. We aimed to use COVID-19 testing as a proxy to investigate the indirect effects of the pandemic, recognizing that while PCR testing is pivotal for assessing the spread of the virus and informing public health decisions, it may not capture all facets of the pandemic. Despite having multiple test records for each individual, we only considered the most recent and definitive available result for inclusion in the analysis. Details of each chronic condition and algorithm used are described in the supplementary information (Appendix B).

Service utilization variables: We utilized an algorithm^{35,36} to identify cases of health service utilization among the Ontario population aged ≥ 18 years within the ICES data holdings, defined as: (i) one hospitalization in OMHRS or DAD with a primary discharge diagnosis of either anxiety, depression, and anxiety or depressive episode otherwise not specified (NOS) based on DSM-V criteria and ICD-10 codes. (ii) at least one physician billing and/or emergency department visits in the OHIP claims database or NACRS with a diagnostic code

for anxiety, depression, and anxiety or depressive episode otherwise not specified (NOS) based on DSM-IV criteria and ICD-10 codes. A complete list of the codes used to define the study cohort and the study variables is available in the supplemental information (Appendix B).

Sociodemographic variables: We examined sociodemographic variables potentially associated with health service utilization including age, gender, place of residence, and neighborhood-level income quintile using the Ontario Marginalization Index (ON-Marg).³⁷ ON-Marg is an index that aims to measure marginalization and disparities in health and social well-being between different geographic areas or population groups in Ontario. It is based on four dimensions, namely, residential instability, material deprivation, dependency, and ethnic diversity. Each dimension is divided into five quintiles, with higher quintiles indicating higher levels of marginalization.³⁸ ON-Marg allows for a comprehensive exploration of multiple dimensions of marginalization in urban and rural areas of Ontario.

Statistical Analysis

Descriptive statistics (e.g., mean, median, range, standard deviation) were calculated for the study sample (N= 6,175,114) (Figure 2.1). Frequencies for demographic and health service use variables were examined with cross-tabulations across both COVID-19 test-based groups using t-tests and chi-squared statistics (Table 2.1). Criteria for statistical significance were set at $p < 0.05$. We followed people with and without COVID-19 standard lab-based PCR tests from January 01, 2020, to March 31, 2021, to estimate survival time. Time was defined as the interval between the COVID-19 PCR test date and an event (i.e., contact with health services for anxiety and depression). The Kaplan-Meier product limit method was utilized to

graphically examine the relation between COVID-19 standard lab-based PCR testing and time to health services utilization for anxiety and depression, and the log-rank test was used to compare the differences in survival experience between the three groups in this study.

Observational studies often suffer from treatment-indication bias or confounding by indication because the characteristics of individuals who receive interventions are typically different from those who do not. To correct for treatment-indication bias, we applied a binary logistic regression model, using age and sex as covariates. Propensity scores were computed by a 'replacement matching' algorithm, which resulted in an adjusted sample (n= 664,233) after matching. The process of matching with replacement involves reducing the distance between propensity scores of treatment and comparison units. This is done by matching each treatment unit to the nearest comparison unit, even if that comparison unit has already been matched to another treatment unit.³⁹

For our outcome analysis, Cox proportional-hazards regression analysis was conducted to assess the association of factors with time to anxiety and depression-related health services utilization, and results were summarized using hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for both the overall and propensity scores-matched adjusted sample. All analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC).

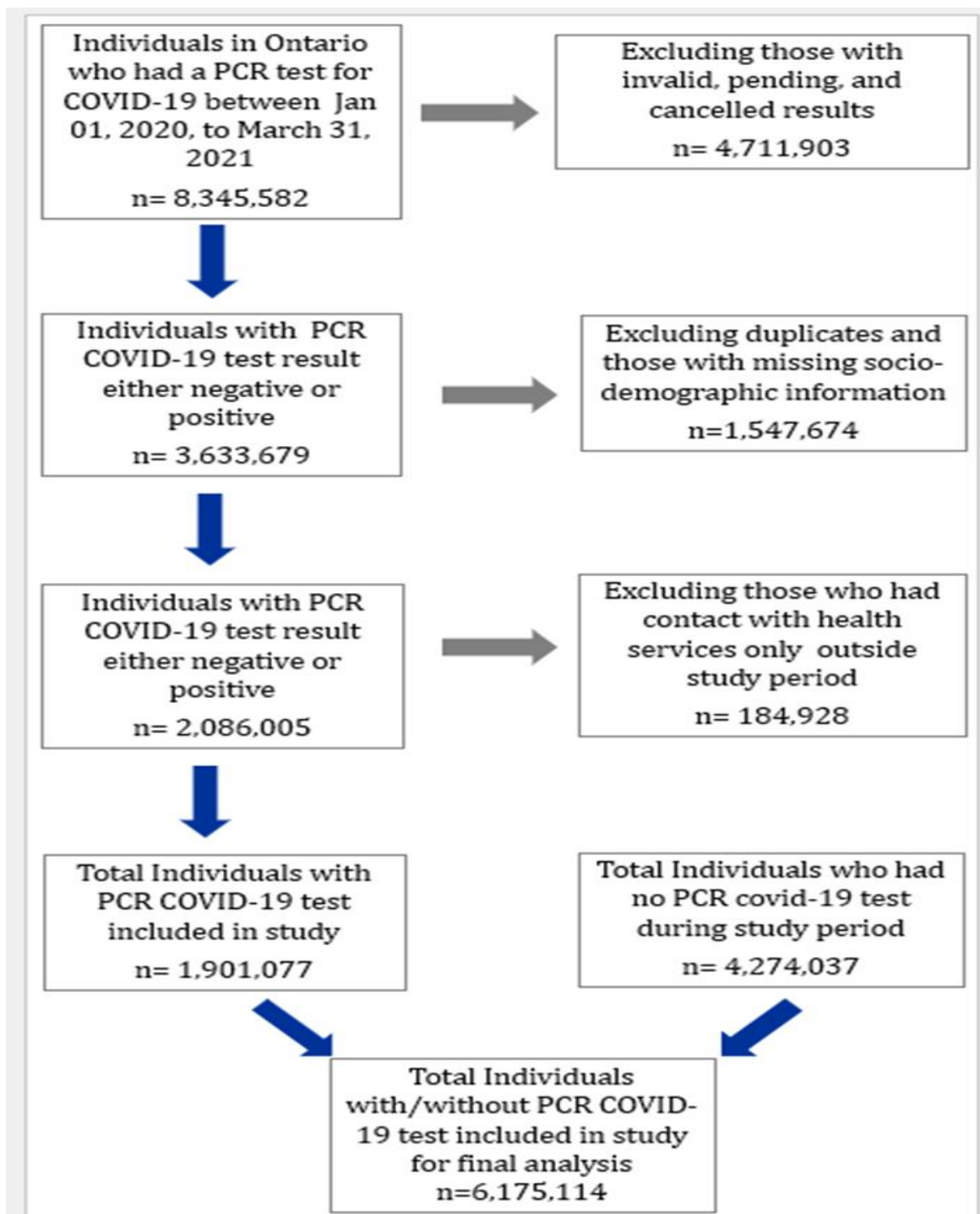
Ethics Approval

This study was approved by the University of Waterloo research ethics board (protocol reference no. 43910), and data use was authorized under section 45 of Ontario's *Personal*

Health Information Protection Act. ICES is a prescribed entity under section 45 of *Ontario's Personal Health Information Protection Act*

, which authorizes ICES to collect personal health information, without consent, for the purpose of health system evaluation and improvement.

Figure 2.1.: Flow chart of study inclusion and exclusion for population in Ontario



2.4. Results

The final study cohort was extracted as shown in Figure 2.1, while overall cohort characteristics at baseline are shown in Table 2.1. The demographic characteristics of propensity score matched sample are provided in the supplement. (Table S1.2).

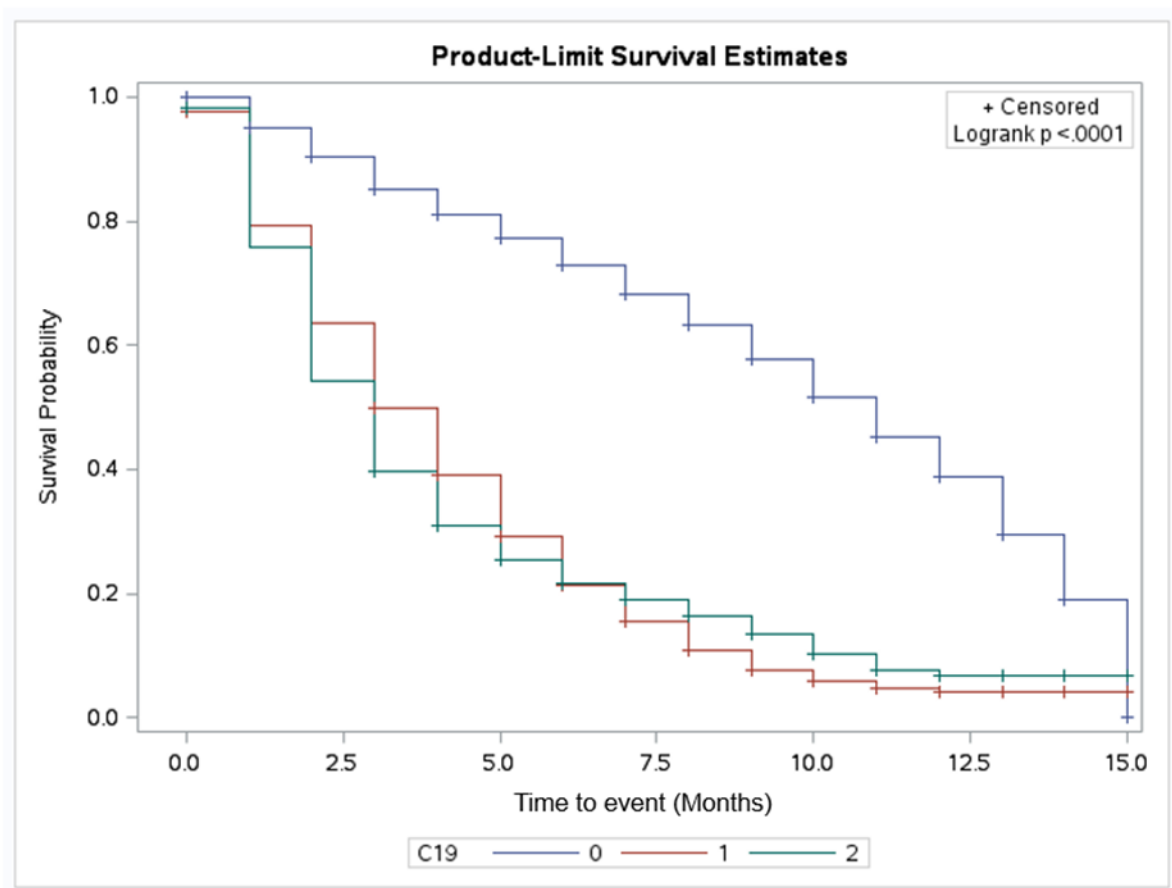
Out of 6,175,114 individuals, there were 4,274,037 (69.21%) without a standard lab-based PCR test for COVID-19. Out of those who were tested for COVID-19 infection, there were 1,755,519 (28.43%) with negative results while 145,558 (2.36%) tested positive for COVID-19 during the study period. The mean age of the overall sample was 42.9 years with a standard deviation of 15.5. The number of females in the overall sample was higher (n= 3,189,737; 51.65%), as compared to males (n=2,985,377; 48.35%). A higher proportion of individuals (n = 5,511,050; 89.25%) did not utilize health services for anxiety or depression-related issues as compared to those who contacted health services (n=664,064; 10.75%) for these medical reasons. Out of those who contacted health services, the highest proportion of the individuals was 18–45 years of age (57.80%), followed by those between 46–65 years (32.62%) and 66–104 years (9.58%), respectively. In terms of sociodemographic status, the sample included 29.19% vs. 16.21% (Q1 vs Q5) in dependency quintile, 24.61% vs. 17.29% (Q1 vs Q5) in deprivation quintile, 22.56% vs. 22.63% (Q1 vs Q5) in instability quintile, and 14.91% vs. 29.03% in ethnic diversity quintile (Table 2.1).

Table 2.1: Demographic characteristics and morbidity information of the study population cohort in Ontario (Jan 2020- Mar 2021)

Demographics & Morbidity information	Total sample	Individuals without PCR COVID-19 tests	PCR test with COVID negative result	PCR test with COVID positive result
Total n (Col %)	6175114	4274037	1755519	145558
Mean Age Yrs. (±SD)	42.95 (15.49)	43.84 (15.60)	41.07 (15.12)	39.39 (14.47)
Anxiety/depression related health service utilization				
No	5511050 (89.25)	3788384 (88.64)	1587938 (90.45)	134728(92.56)
Yes	664064 (10.75)	485653 (11.36)	167581 (9.55)	10830 (7.44)
Age groups n (%)				
18-45 yrs.	3569070 (57.80)	2363642 (55.30)	1108188 (63.13)	97240 (66.80)
46-65 yrs.	2014498 (32.62)	1454906 (34.04)	518139 (29.51)	41453 (28.48)
66+ yrs.	591546 (9.58)	455489 (10.66)	129192 (7.36)	6865 (4.72)
Sex n (%)				
Male	2985377 (48.35)	2136749 (49.99)	778344 (44.34)	70884 (48.29)
Female	3189737 (51.65)	2137288 (50.01)	977175 (55.66)	75274 (51.71)
Rural n (%)				
No	5580516 (90.37)	3845375 (89.97)	1594901 (90.85)	140240(96.35)
Yes	594598 (9.63)	428662 (10.03)	160618 (9.15)	5318 (3.65)
Ontario Marginalization Index (%)				
Dependency quintile				
1	1802531 (29.19)	1230040 (28.78)	519994 (29.62)	52497 (36.07)
2	1281491 (20.75)	882985 (20.66)	365722 (20.83)	32784 (22.52)
3	1078592 (17.47)	749393 (17.53)	305374 (17.40)	23825 (16.37)
4	1011615 (16.38)	708060 (16.57)	283600 (16.15)	19955 (13.71)
5	1000885 (16.21)	703559 (16.46)	280829 (16.00)	16497 (11.33)
Deprivation quintile				
1	1519683 (24.61)	1042701 (24.40)	451348 (25.71)	25634 (17.61)
2	1331132 (21.56)	922903 (21.59)	381542 (21.73)	26687 (18.33)

3	1169663 (18.94)	810983 (18.97)	330316 (18.82)	28364 (19.49)
4	1086791 (17.60)	755009 (17.67)	302288 (17.22)	29494 (20.26)
5	1067845 (17.29)	742441 (17.37)	290025 (16.52)	35379 (24.31)
Instability quintile				
1	1393327 (22.56)	970766 (22.71)	382819 (21.81)	39742 (27.30)
2	1186825 (19.22)	828652 (19.39)	333674 (19.01)	24499 (16.83)
3	1121085 (18.15)	781645 (18.29)	317085 (18.06)	22355 (15.36)
4	1076219 (17.43)	740661 (17.33)	312060 (17.78)	23498 (16.14)
5	1397658 (22.63)	952313 (22.28)	409881 (23.35)	35464 (24.36)
Ethnicity diversity quintile				
1	920772 (14.91)	654464 (15.31)	257398 (14.66)	8910 (6.12)
2	998212 (16.17)	691866 (16.19)	293106 (16.70)	13240 (9.10)
3	1114619 (18.05)	758660 (17.75)	336714 (19.18)	19245 (13.22)
4	1349162 (21.85)	919897 (21.52)	398032 (22.67)	31233 (21.46)
5	1792349 (29.03)	1249150 (29.23)	470269 (26.79)	72930 (50.10)
Asthma				
No	6118287 (99.08)	4240424 (99.21)	1734137 (98.78)	143726 (98.74)
Yes	56827 (0.92)	33613 (0.79)	21382 (1.22)	1832 (1.26)
COPD				
No	6115375 (99.03)	4232216 (99.02)	1738483 (99.03)	144676 (99.39)
Yes	59739 (0.97)	41821 (0.98)	17036 (0.97)	882 (0.61)
Hypertension				
No	5841788 (94.60)	4042477 (94.58)	1662482 (94.70)	136829 (94.00)
Yes	333326 (5.40)	231560 (5.42)	93037 (5.30)	8729 (6.00)
Congestive heart failure				
No	6156440 (99.70)	4263386 (99.75)	1747958 (99.57)	145096 (99.68)
Yes	18674 (0.30)	10651 (0.25)	7561 (0.43)	462 (0.32)
Diabetes				
No	6028038 (97.62)	4172160 (97.62)	1715613 (97.73)	140265 (96.36)
Yes	147076 (2.38)	101877 (2.38)	39906 (2.27)	5293 (3.64)

Figure 2.2: Kaplan-Meier plot of impact of COVID-19 PCR testing on time to anxiety- and/or depression-related service utilization



___ No COVID-19 PCR test ___ COVID-19 PCR test with positive result ___ COVID-19 PCR Test with negative result

As seen in Fig. 3.2, the time until the event (i.e., mental health service utilization), in months, was fastest in the group with negative COVID-19 test results, followed by the group with positive COVID-19 test results, both noticeably trailing those who never had standard lab-based PCR testing done for COVID-19 (Figure 2.2). For the negative group, the survival curve showed a gradual decrease in survival over time, whereas, for those without the COVID-19 PCR test i.e., the control group, the curve followed the same pattern throughout. In the multivariable Cox proportional hazards model, COVID-19 testing, age, female sex, and

chronic conditions were significantly associated with anxiety and depression (Table 2.2), with COVID-19 testing being the most statistically significant variable.

In the adjusted Cox proportional hazards model for the overall sample, the individuals who had PCR tests had a higher risk of utilizing health services for anxiety and depression during the pandemic, as compared to those who had no PCR testing done for COVID-19. The hazard ratios were aHR, 4.14; CI, 4.39-4.44 and aHR, 4.41; CI, 4.06-4.22; for COVID-19 test positive and COVID-19 test negative, respectively. (Table 2.2). A higher risk of anxiety and depression was observed among females (aHR,1.05; CI, 1.04-1.05), individuals in the 18–45 years age group (aHR 1.38; CI, 1.36-1.39), as well as individuals in the 46-65 years age group (aHR, 1.31; CI,1.30-1.33).

In the Cox proportional hazards model in the propensity score matched sample, the individuals who tested positive for COVID-19 (aHR, 6.37; CI, 6.25-6.50) had the highest risk of utilizing health services for anxiety and depression during the pandemic, followed by those who tested negative for COVID-19 (aHR, 5.91; CI, 5.87-5.95) (Table 2.3). Also, a higher risk of anxiety and depression was noted among young individuals, females, and those residing in rural areas. Moreover, a higher risk was observed for socioeconomic status, with material deprivation quintile significantly associated with anxiety and depression. For the neighborhood-level income quintile, similar risks of anxiety and depression were found among those in Q3-Q5 of the material deprivation quintile (Table 2.3).

In the Cox proportional hazards model stratified by age groups, the risk of anxiety and depression was highest among younger adults (aHR, 5.56; CI, 5.51-5.61), as compared to the middle-age group (aHR, 4.05; CI, 4.00-4.09) and older adults (aHR,1.59; CI, 1.55-1.62), who

tested negative with COVID-19 (Table S1.1). Females were at higher risk as compared to males across all age groups. (Table 2.3). Rural residence was only statistically significant among younger adults (aHR, 1.02; CI, 1.01-1.03) as compared to other age groups, though the effect is small. Among chronic conditions, asthma and hypertension were observed to be associated with anxiety and depression-related visits and hospitalization, across young and middle age groups. (Table S1.1).

Table 2.2: Multivariable Cox regression analysis of factors associated with anxiety/depression related health services utilization among Ontario population (Jan 2020-Mar 2021) for overall sample

Variables	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
COVID-19 test status				
COVID-19 Positive	3.83 (3.76-3.91)	<0.0001	4.14 (4.39-4.44)	<0.0001
COVID-19 Negative	4.21 (4.18-4.24)	<0.0001	4.41 (4.06-4.22)	<0.0001
No PCR test	Ref		Ref	
Age groups				
18-45 yrs.	1.21 (1.20-1.22)	<0.0001	1.38 (1.36-1.39)	<0.0001
46-65 yrs.	1.14 (1.13-1.15)	<0.0001	1.31 (1.30-1.33)	<0.0001
66+ yrs.	Ref		Ref	
Sex				
Female	1.05 (1.05-1.06)	<0.0001	1.05 (1.04-1.05)	<0.0001
Male	Ref	Ref	Ref	Ref
Rural				
Yes	1.00 (0.99-1.00)	<0.0001	0.99 (0.98-1.00)	0.2682
No	Ref		Ref	
Asthma				
Yes	1.07 (1.05-1.10)	<0.0001	1.00 (0.98-1.02)	0.7479
No	Ref		Ref	
COPD				
Yes	0.94 (0.92-0.96)	<0.0001	0.91 (0.89-0.93)	<0.0001
No	Ref		Ref	
Congestive heart failure				
Yes	0.69 (0.65-0.70)	<0.0001	0.43 (0.41-0.45)	<0.0001
No	Ref		Ref	
Hypertension				
Yes	0.97 (0.96-0.98)	<0.0001	0.99 (0.98-1.00)	0.2763
No	Ref		Ref	
Diabetes				

Yes	0.95 (0.94-0.97)	<0.0001	0.92 (0.91-0.94)	<0.0001
No	Ref		Ref	
Ontario Marginalization Index				
Dependency quintile				
1	Ref		Ref	
2	0.99 (0.98-1.00)	0.1920	1.00 (0.99-1.00)	0.9588
3	0.99 (0.98-1.00)	0.3700	1.00 (0.99-1.00)	0.7363
4	0.98 (0.98-0.99)	0.0023	0.99 (0.99-1.00)	0.7545
5	0.97 (0.97-0.98)	<0.0001	0.98 (0.97-0.99)	0.0002
Deprivation quintile				
1	Ref		Ref	
2	0.99 (0.98-1.00)	0.0761	0.99 (0.99-1.00)	0.8050
3	0.99 (0.98-1.00)	0.7505	1.00 (0.99-1.01)	0.2907
4	0.98 (0.97-0.99)	0.0002	1.00 (0.99-1.00)	0.9674
5	0.97 (0.97-0.98)	<0.0001	1.00 (0.99-1.00)	0.9923
Instability quintile				
1	Ref		Ref	
2	1.00 (0.99-1.00)	0.9996	0.99 (0.98-0.99)	0.0285
3	1.00 (0.99-1.00)	0.7777	0.99 (0.98-1.00)	0.0379
4	0.99 (0.99-1.00)	0.7811	0.97 (0.97-0.98)	<0.0001
5	0.98 (0.97-0.99)	<0.0001	0.96 (0.955-0.97)	<0.0001
Ethnic diversity quintile				
1	Ref		Ref	
2	1.01 (1.00-1.02)	0.0060	1.00 (0.99-1.00)	0.9285
3	1.01 (1.00-1.01)	0.0151	0.99 (0.98-1.00)	0.1295
4	1.00 (0.99-1.01)	0.5133	0.98 (0.97-0.99)	0.0095
5	0.978 (0.97-0.98)	<0.0001	0.97 (0.96-0.98)	<0.0001

Table 2.3: Multivariable Cox regression analysis of factors associated with anxiety/depression related health services utilization among Ontario population (Jan 2020-Mar 2021) after propensity scores computation

Variables	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
COVID-19 test status				
COVID-19 Positive	6.34 (6.21-6.46)	<0.0001	6.37 (6.25-6.50)	<0.0001
COVID-19 Negative	5.88 (5.84-5.92)	<0.0001	5.91 (5.87-5.95)	<0.0001
No PCR test	Ref		Ref	
Age groups				
18-45 yrs.	1.04 (1.03-1.05)	<0.0001	1.000 (0.977-0.996)	<0.0001
46-65 yrs.	1.00 (0.991-1.01)	0.7066	0.980 (0.971-0.989)	<0.0001
66+ yrs.	Ref		Ref	
Sex				
Female	1.00 (0.99-1.00)	0.0080	1.039 (1.034-1.044)	<0.0001
Male	Ref	Ref	Ref	Ref
Rural				
Yes	1.02 (1.02-1.03)	<0.0001	1.02 (1.01-1.03)	<0.0001
No	Ref		Ref	
Asthma				
Yes	1.04 (1.02-1.06)	<0.0001	0.94 (0.92-0.96)	<0.0001
No	Ref		Ref	
COPD				
Yes	1.00 (0.98-1.03)	0.3877	0.99 (0.97-1.01)	0.4776
No	Ref		Ref	
Congestive heart failure				
Yes	1.21 (1.16-1.27)	<0.0001	1.09 (1.05-1.14)	<0.0001
No	Ref		Ref	
Hypertension				
Yes	1.01 (1.00-1.02)	0.0014	1.00 (0.99-1.01)	0.2208
No	Ref		Ref	
Diabetes				

Yes	1.00 (0.98-1.01)	0.6820	0.99 (0.97-1.00)	0.4915
No	Ref		Ref	
Ontario Marginalization Index				
Dependency quintile				
1	Ref		Ref	
2	0.99 (0.99-1.00)	0.6058	0.99 (0.99-1.00)	0.3154
3	1.00 (0.99-1.00)	0.7809	0.99 (0.99-1.00)	0.5263
4	0.99 (0.99-1.00)	0.6277	1.00 (0.99-1.00)	0.8722
5	1.00 (0.99-1.00)	0.9174	0.99 (0.99-1.00)	0.8452
Deprivation quintile				
1	Ref		Ref	
2	0.99 (0.98-1.00)	0.3369	1.00 (0.99-1.01)	0.1062
3	1.00 (0.99-1.00)	0.6515	1.01 (1.00-1.02)	<.0001
4	0.99 (0.98-1.00)	0.0557	1.02 (1.01-1.03)	<.0001
5	0.98 (0.97-0.99)	<0.0001	1.03 (1.02-1.04)	<.0001
Instability quintile				
1	Ref		Ref	
2	1.00 (0.99-1.01)	0.5453	0.98 (0.98-0.99)	0.0044
3	1.00 (0.99-1.01)	0.4752	0.98 (0.97-0.99)	0.0001
4	1.00 (0.99-1.00)	0.7743	0.97 (0.96-0.97)	<.0001
5	0.98 (0.97-0.99)	<0.0001	0.95 (0.94-0.95)	<.0001
Ethnic diversity quintile				
1	Ref		Ref	
2	1.00 (0.99-1.00)	0.9959	0.99 (0.98-1.00)	0.1657
3	0.99 (0.98-0.99)	0.0127	0.97 (0.96-0.98)	<.0001
4	0.98 (0.97-0.98)	<0.0001	0.97 (0.96-0.98)	<.0001
5	0.96 (0.96-0.97)	<0.0001	0.97 (0.96-0.98)	<.0001

2.5. Discussion

The current study aimed to investigate the potential association between COVID-19 PCR testing and mental health issues, such as anxiety and depression, in a large population sample. Our findings suggest that there is a significant association between COVID-19 PCR testing and psychological distress, with a substantial proportion of participants reporting increased levels of anxiety and depression after being tested for COVID-19. Our study noted that anxiety and depression related health services utilization was higher among the individuals who had tested positive for COVID-19 as compared those who had tested negative for COVID-19. The mental health impacts of COVID-19 testing have been significant, with multiple factors responsible for increased levels of anxiety and depression, including fear of infection, uncertainty, stigma, quarantine, and social isolation in the general population.⁴⁰⁻⁴² Our study demonstrates an increased risk of anxiety and depression in the young age group (18-45 years), particularly in the female population. There is significant concern about a growing “mental health crisis” among young people and how COVID-19 is causing a disaster in terms of mental health, particularly in children and youth.⁴³⁻⁴⁶ Our findings are consistent with a study investigating changes in anxiety and depression symptoms during the pandemic which reported a deterioration in mental health among young adults with low levels of symptoms before the pandemic.⁴⁷

We observed that the risk of both anxiety and depression was high among residents of rural areas as compared to those residing in urban Ontario. The results are consistent with other studies that suggest that rural residents may have been at increased risk for anxiety and depression during the COVID-19 pandemic due to factors such as limited access to mental

health services, social isolation, and financial stress.^{48,49} Where people live, work, and play has an impact on their health, and social determinants of health (SDoH) can lead to barriers that worsen inequalities.⁵⁰⁻⁵² Our study observed that those from the low-income quintile were affected more in terms of mental health compared to those from the higher income quintile. This is similar to other studies reporting that people living at-risk-of-poverty were more likely to experience negative changes in their income and work situation, as indicated by significantly higher scores of psychosocial stress, depression, anxiety, and loneliness during COVID-19.^{53,54}

The COVID-19 pandemic has had a significant impact on the economic well-being of individuals and communities around the world. Mental illness episodes often follow the loss of jobs and declining income.^{55,56} There is evidence that in a community, those with the lowest income level are 1.5-3 times more likely to experience depression, anxiety, and other prevalent mental diseases, than those with the highest income.⁵⁷⁻⁵⁹ Poverty can lead to mental health problems, and the COVID-19 pandemic has disproportionately affected people living in poverty.⁶⁰ The stress and anxiety that come with financial insecurity and uncertainty can lead to a feeling of helplessness and hopelessness, and these feelings can exacerbate anxiety and depression and make it difficult for people to seek help.⁵⁹ Overall, the interaction between COVID-19, poverty, and mental health is complex and multi-faceted.

In our study, we also examined the relationship between chronic diseases and anxiety and depression during the COVID-19 pandemic. It was noted that asthma, hypertension, and congestive heart failure were risk factors for anxiety and depression. The Centers for Disease Control and Prevention (CDC) lists these conditions as high-risk factors for severe COVID-19

illness ⁶¹ and there has been previous research linking COVID-19 to chronic diseases and mental health.⁶²⁻⁶⁵ Furthermore, the pandemic has also led to disruptions in routine medical care and medication management for individuals with chronic diseases, leading to potential exacerbations of these conditions. This can further contribute to anxiety and depression, as individuals worry about their health and access to necessary medical care.⁶²

The COVID-19 outbreak has worsened already existing health disparities. Chronic health conditions, COVID-19 disease, hospitalization, and death have an adverse effect on some vulnerable populations, including those who belong to racial and ethnic groups,⁶⁶ as well as immigrants, due to limited resources and social support as they struggle to adjust to a new life in a new country.⁶⁷ The grim state of affairs of Canadians' mental health during the pandemic calls for action.⁶⁸ However, there is a scarcity of empirical evidence on who is most affected by the pandemic and how it interacts with the existing inequalities.⁶⁹

The COVID-19 pandemic has had far-reaching consequences that extend well beyond the realm of COVID-19 testing. The fear of contracting the virus, social isolation, loss of loved ones, and the uncertainty surrounding the future have contributed to increased levels of stress, anxiety, and depression. The need for mental health support has become more urgent than ever. Instead of only being the pandemic's psychological effect, concerns about mental health during COVID-19 could be seen as a parallel epidemic.⁷⁰⁻⁷²

Strengths and limitations

To our knowledge, this study is the largest and most comprehensive to date, assessing the impact of COVID-19 on anxiety and depression in Ontario. It examined various healthcare visits, including physician, emergency visits and psychiatric hospitalization, providing a

population-based approach. By utilizing outpatient data, all incident cases of anxiety and depression were identified for complete case ascertainment. Also, the use of administrative health data from a universal health care system captures virtually all health care visits, thereby increasing the generalizability of this study. Observational studies frequently encounter treatment-indication bias or confounding by indication, as individuals receiving interventions often differ in characteristics from those who do not. To address confounding bias, analyses were conducted on both the overall sample and on propensity scores adjusted sample based with age and sex as covariates.

Our study was limited by the variables available in the databases, preventing exploration of important factors such as employment, financial status, and income. Exclusion of individuals with missing demographic information may have introduced bias. Administrative data only captures individuals who use health services, excluding those with anxiety/depression disorders who do not seek help. Additionally, we lacked specific data to identify immigrants and indigenous populations, precluding examination of their mental health impact. Severity levels of anxiety and depression conditions could not be identified due to unavailable information. The analysis did not account for multiple testing, and it remains uncertain whether individuals with pre-existing anxiety were more inclined to undergo COVID-19 testing. A limitation of our study is the absence of individual-level information in the data, preventing us from accounting for individuals in occupations mandating mandatory COVID-19 testing. Disparities in testing rates may have introduced a bias, as higher testing rates in certain populations may lead to an overestimation of the prevalence of the conditions being studied in those groups, while lower testing rates in others could result in underestimation.

It is essential to consider and account for these testing rate variations to ensure the generalizability of our findings.

2.6. Conclusion

In conclusion, the findings of this study suggest that COVID-19 PCR testing is associated with the utilization of mental health care, specifically for anxiety and depression. The uncertainty surrounding the pandemic and the fear of contracting the virus have been found to contribute to the psychological distress experienced by individuals during this time. It is crucial to acknowledge the psychological impact of COVID-19 and develop interventions to support the mental health of individuals affected by this pandemic. The impact of the pandemic has been disproportionate, with the poor being more affected, and there is a possibility of lasting negative consequences on their economic and mental well-being. Investments in mental health were long overdue even before the pandemic and have become critically urgent now. It is essential to address the social and economic determinants of mental health to mitigate the negative impact of the pandemic on mental health outcomes. This includes providing access to financial support and resources, promoting social connections and support, and increasing access to mental health services.

The mental health impact of COVID-19 has also highlighted the need for comprehensive pandemic preparedness plans that address not only the physical health consequences but also the psychological implications of a pandemic. By incorporating mental health considerations into pandemic preparedness plans, we can better support the well-being and resilience of individuals and communities during times of crisis. There is also a need for co-designing and monitoring mental health services trends, which is critical for health system

planning and service delivery as the pandemic and its expected long-term effects on population mental health continue.

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Data Availability Statement: The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at <https://www.ices.on.ca/DAS>. The full data set creation plan and

underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Chapter 3 Preamble

Study II (Chapter 3) of this dissertation was conducted to assess the impact of the COVID-19 pandemic on morbidity and mortality among the adult Ontario population. Specifically, we aimed to compare healthcare utilization before and during the pandemic, focusing on physician or emergency department visits, hospitalizations related to mental health issues (anxiety and depression), and chronic diseases. The pandemic-induced changes in healthcare utilization have substantial clinical and public health implications. Missed diagnoses and delayed treatments during this period can lead to heightened morbidity and mortality rates, underscoring the importance of healthcare system adaptation and pandemic preparedness. The complex interplay of COVID-19, mental health issues, and chronic diseases portrays a syndemic nature where these health factors interact synergistically, amplifying the overall disease burden. By comparing the change in healthcare utilization, this study contributes to a deeper understanding of the COVID-19 syndemic, highlighting the importance of effective interventions and preparedness strategies for current and future pandemics.

Chapter 3: Changes in Health Services Utilization and Mortality during the COVID-19 Pandemic in Ontario, Canada: An Interrupted Time Series Analysis

3.1. Abstract

Objective: Our aim was to compare morbidity and mortality before and during the COVID-19 pandemic in the Ontario population, in terms of physician or ED visits as well as hospitalization related to mental health issues of anxiety and depression and chronic diseases.

Methods: We constructed a cohort of 1,880,882 adult (18+ years), using administrative health databases, who had utilized health services during the period between Jan 2017-Mar 2021, either due to chronic diseases or mental health problems of anxiety and depression and recorded the number of visits each individual had in the follow up period related to chronic conditions. The data were then analyzed using an interrupted time-series design, to observe changes in; (1) monthly physician or emergency visits and hospitalizations and (2) monthly all-cause deaths before and during the pandemic. The exposure in this study was the onset of the COVID-19 pandemic in Ontario, Canada.

Results: Initially, there was a decline in physician visits and hospitalizations for individuals with chronic diseases during the COVID-19 pandemic's first wave in Ontario, likely due to fear of virus transmission and healthcare system adjustments. However, as the pandemic progressed, there were subsequent periods of notable increases in physician visits and hospitalizations. We also observed increased mortality following the onset of COVID-19.

Conclusions: The changes in healthcare utilization during the pandemic have clinical and public health implications, including missed diagnoses and delayed treatment, increased morbidity and mortality, and the need for healthcare system adaptation and pandemic preparedness. Addressing barriers to care is crucial to ensure individuals receive necessary medical attention, especially for those with chronic diseases, during a pandemic when resources may be limited. Measuring excess mortality is crucial for gaining deeper insights into both the direct and indirect impacts of the COVID-19 pandemic.

3.2. Background

Canada was one of the countries that was affected early by the COVID-19 pandemic, with Ontario recording the first confirmed case on January 25, 2020, in Toronto. To prevent the spread of the virus, public health measures such as hand hygiene, self-isolation, social distancing, and lockdowns were implemented, along with a testing strategy to identify positive cases and their close contacts. On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic.¹ Among the four Canadian provinces that account for 93% of all confirmed COVID-19 cases in Canada, Ontario had the highest contribution, making up 28% of the total confirmed cases.²

To prevent healthcare infrastructure from being overwhelmed with new cases, Canadians were asked to avoid social contact from mid-March 2020. The aim was to "flatten the curve" by slowing down the number of infected people, ensuring that health care facilities didn't run out of space and equipment. A directive to ramp down elective surgeries and non-emergent health services was issued on March 15, 2020, in Ontario. Health care providers and organizations were also directed to stop or reduce all non-essential or elective services until further notice.³

The Ontario government introduced an online self-assessment tool and implemented drive-through centers for COVID-19 testing in March 2020.⁴ Telehealth and virtual medicine were also used to assess patients remotely. In early April 2020, the Public Health Agency of Canada released initial interim guidelines for the clinical management of individuals diagnosed with COVID-19.⁵ Various alternatives were put into place to ensure that individuals could receive care while staying at home.

The public health measures implemented to limit the spread of COVID-19 affected all segments of the population with an impact on the processes of normal comprehensive care for chronic patients, due to disruption in delivery care.⁶ The government restrictions, increased fear of infection, and a shift in emphasis on COVID treatment, led to the discontinuation of many in-person physical face-to-face consultations. Moreover, community based care and supports were also reduced.^{6,7} The pandemic restricted laboratory testing and physical examinations, which had a negative impact on healthcare decision-making globally.^{8,9}

The impact of coronavirus disease 2019 (COVID-19) in Canada has been significant, with a substantial cumulative burden. The Public Health Agency of Canada has received reports of nearly 4.6 million confirmed infections through polymerase chain reaction testing.¹⁰ This is an underestimate as many cases were diagnosed through rapid testing or were not tested at all. While a minority of cases required hospitalization, it is crucial to thoroughly examine the characteristics and outcomes of these cases due to their substantial morbidity, significant cost, and the strain they put on healthcare systems.^{11,12} In this study, we aim to compare the morbidity and mortality before and during the COVID-19 pandemic in the Ontario population, in terms of physician or ED visits as well as hospitalization related to mental health issues of anxiety or depression and chronic diseases, and mortality in terms of all cause deaths.

3.3. Methodology

Data Source

This study utilized secondary data from administrative health databases accessed through the Ontario Health Database Platform (OHDP). The platform permitted access to patient-level linked population-based health administrative data held at Institute for Clinical Evaluation Sciences (ICES). The ICES data repository consists of record-level, coded, and linkable health data sets that integrate health services data, registries, and surveys. ICES is an independent, non-profit research institute that houses routinely collected health data from Ontario's publicly funded health care system. We constructed a cohort of 1,880,882 adults (18+ years), using health administrative databases who were living in Ontario, Canada, between the period of Jan 2017 to March 2021 and recorded the number of visits each patient had in the follow up period (Fig 4.1). These datasets were linked using unique encoded identifiers and analyzed at ICES. The details about data dictionaries utilized and study cohort derivation have been described in Appendix B. All those who had utilized health care services, either physician or emergency visits as well as hospitalization for chronic conditions of interest in this study and had a PCR test done during the COVID-19 pandemic period, were included.

Study design, settings, and cohort derivation

We used an algorithm to identify all adult Ontario population aged 18 and above, alive on January 01, 2017, and who had utilized health services during the period between Jan 2017-Mar 2021, either due to chronic diseases or mental health problems of anxiety and depression. The chronic diseases in this study included asthma, chronic obstructive

pulmonary disease, diabetes, congestive heart failure and hypertension. The study period was January 01, 2017, to March 31, 2021. The period between January 2017 to December 2019 was considered as ‘pre-pandemic period’ while the period between January 2020 to March 2021 was considered as the ‘pandemic period’.

We excluded the cases who were not Ontario residents and were less than 18 years of age, as well as those who had visits outside the study period.

Primary Outcome: The primary outcome of interest in this study was “morbidity” which was defined as “either a physician visit or emergency visit or hospitalization to a medical hospital bed for reasons related to either chronic diseases or mental health issues of anxiety and depression” during the study period. We utilized ICD-9, ICD-10 codes and OHIP diagnostic codes to identify physician visits, emergency visits, ambulatory care visits and hospitalization, either elective or through emergency, related to either chronic diseases or mental health issues, during the study period. The secondary outcome of this study was all-cause mortality, during the study period.

Variables

Clinical variables: COVID status was based on standard lab-based PCR test while the prevalence of chronic conditions was identified using ICES derived cohorts. Details of each chronic condition and algorithm used are described elsewhere. (Appendix B)

Service utilization variables: We utilized an algorithm ^{13,14} to identify cases of health service utilization among Ontario population aged ≥ 18 years within the ICES data holdings, defined as: (i) one hospitalization in (Ontario Mental Health Reporting System) OMHRS or Discharge Abstract Database (DAD) with a primary discharge diagnosis of either ‘chronic illnesses of

interest, anxiety, depression, and ‘anxiety or depressive episode’ otherwise not specified (NOS) based on DSM-V criteria and ICD-10 codes. (ii) at least one physician billing and/or emergency department visits in the Ontario Health Insurance Plan (OHIP) claims database or National Ambulatory Care Reporting System (NACRS) with a diagnostic code for either ‘chronic illnesses of interest, anxiety, depression and anxiety or depressive episode’ otherwise not specified (NOS) based on DSM-V criteria and ICD-10 codes. A complete list of the codes used to define the study cohort and the study variables is available in the supplemental information. (Appendix B)

Statistical analysis: Descriptive statistics (e.g., mean, median, range, standard deviation) were calculated for the study sample. Frequencies for demographic, and service-use variables were examined with cross-tabulations across both pre-COVID-19 period and post-COVID onset period. An interrupted time series study design was adopted, using segmented regression models^{15,16} to assess the monthly impact of COVID-19 on overall morbidity defined as “monthly healthcare services utilization” and mortality in Ontario population. For every assessment period (defined as month), we determined the total number of morbidity episodes and mortalities per month for each year. The time period from January 2017 to December 2019 was considered the ‘control’ period and the time period from January 2020 to March 2021 was the ‘intervention’ period. The single point intervention was the month corresponding to the time of the first case diagnosis of COVID-19 in Ontario (Jan 2020). The primary outcome of ‘morbidity’ was assessed based on physician or ED visits or hospitalization. Autoregressive error segmented regression models were run to assess the change in mean monthly count (slope) pre-COVID-19, the change in the level of mean

monthly counts when COVID-19 hit, and the difference between slopes (change in mean monthly number) post-vs pre-COVID-19, correcting for autocorrelation.

The general model equations ¹⁵⁻¹⁷ used were:

$$Y_t = \beta_0 + \beta_1 * t + \beta_2 * X_t + \beta_3 * Z_t + \varepsilon$$

where 'Y_t' represents the outcome of interest i.e., change in the number of visits per month t; β_0 , the baseline monthly outcome count before COVID-19 ; β_1 , the monthly change in outcome (slope) before COVID-19; 't', the time in calendar months beginning on January 1, 2017; β_2 , the change in the level of outcome during COVID-19; X_t , the dummy variable marking the period before (0) and after (1) COVID-19 onset ; β_3 , the difference in slope (change in monthly visits numbers) after COVID-19 onset vs before COVID-19; Z_t , the time (in months) post start of COVID-19 ; and ε , model error term adjusted for autocorrelation. Estimated monthly count and estimated mean monthly count (trend) values from the maximum likelihood fitted autocorrelation-corrected regression models were also generated with the AUTOREG procedure using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC).^{17,18} Autocorrelation was assessed with Durbin-Watson tests. Statistical significance was defined as $P(p\text{-value}) < 0.05$.

Ethics Approval

This study was approved by the University of Waterloo research ethics board (protocol reference no. 43910), and data use was authorized under section 45 of Ontario's *Personal Health Information Protection Act*. ICES is a prescribed entity under section 45 of Ontario's

Personal Health Information Protection Act, which authorizes ICES to collect personal health information, without consent, for the purpose of health system evaluation and improvement.

Figure 3.1: Flow Chart of Study Inclusion and Exclusion for study cohort

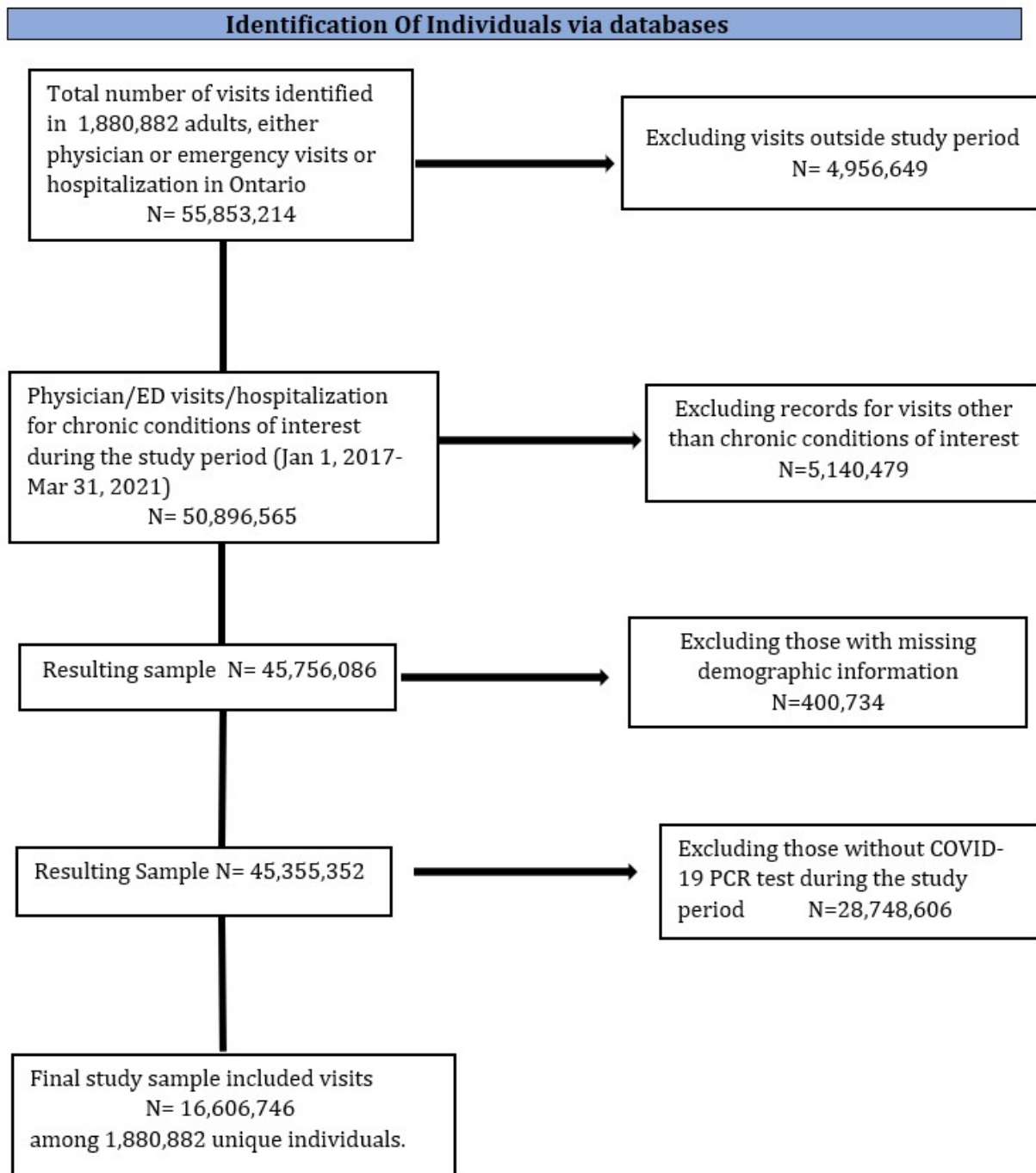
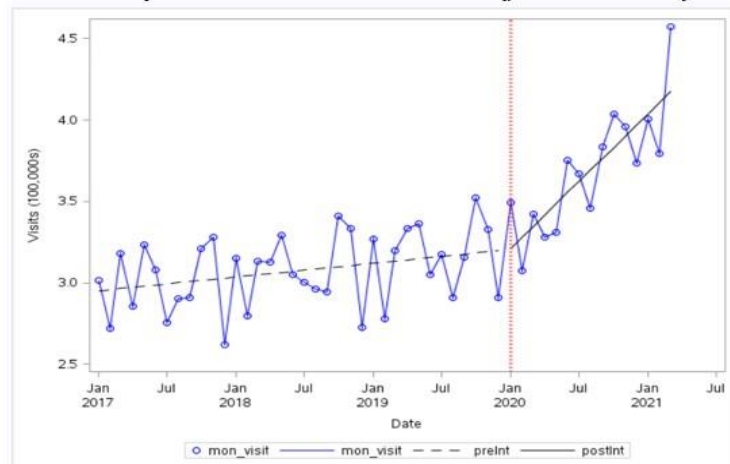
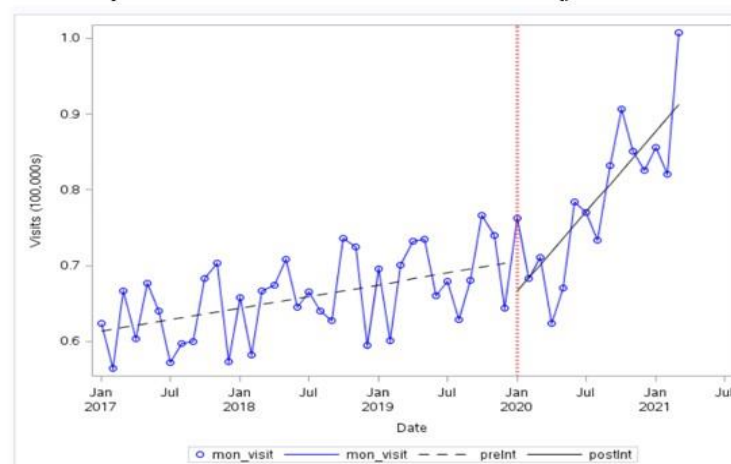


Figure 3.2: Monthly Health Services Utilization and All-cause Deaths in Ontario Population (Jan 2017- Mar 2021)

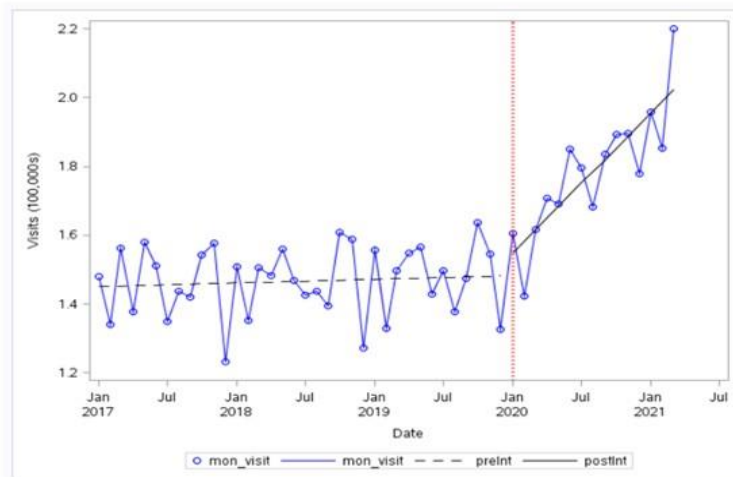
(a) Overall monthly health services utilization in Ontario (Jan2017-Mar 2021)



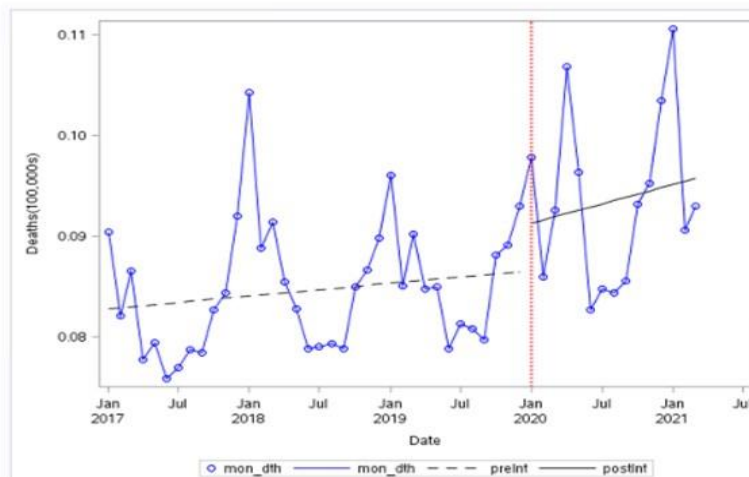
(b) Overall monthly health services utilization for chronic diseases (Jan 2017-Mar 2021)



(c) Overall monthly health services utilization for mental health (Jan 2017-Mar 2021)



(d) All cause monthly deaths in Ontario (Jan 2017-Mar 2021)



*The overall monthly services utilization depicts the overall monthly visits all inclusive (Physician/ED visits/Hospitalization), in **all** those who had PCR tests done either with positive OR negative results and comprise of all the various types of conditions considered (i.e., chronic diseases as well as mental health issues)

** visits (100,000) mean the total count of monthly visits expressed as 100,000

Table 3.1: Segmented regression analysis of change in Health Service Utilization & Mortality following the onset of COVID-19 pandemic in Ontario

Baseline monthly visits Pre COVID (Intercept)		Change in monthly visits (Slope) Pre- COVID		Level change of monthly visits post-COVID 19 onset		Change in monthly visits (slope difference) post COVID-19 onset vs pre- COVID	
Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)
Overall Healthcare Services Utilization (per 100,000)							
2.9441	<0.0001 (2.7948-3.0934)	0.0070	0.0474 (-0.0000-0.0140)	-0.0560	0.6835 (-0.3339-0.2220)	0.0619	<0.0001 (0.0347-0.0890)
Monthly Visits due to Chronic Diseases (per 100,000)							
0.6104	<0.0001 (0.5745-0.6462)	0.0025	0.0033 (0.0008-0.0042)	-0.0544	0.1033 (-0.1211-0.0123)	0.0150	<0.0001 (0.0085-0.0215)
Monthly Visits due to Mental Health Issues (per 100,000)							
1.4501	<0.0001 (1.3796-1.5205)	0.0008	0.5953 (-0.0024-0.0041)	0.0337	0.6030 (-0.0974-0.1648)	0.0330	<0.0001 (0.0201-0.0457)
All-cause Monthly Deaths (per 100,000)							
0.0827	< 0.0001 (0.0778-0.0875)	0.0001	0.3499 (-0.0001-0.0003)	0.0045	0.3112 (-0.0044-0.0135)	0.0002	0.6246 (-0.0006-0.0010)

*The overall monthly services utilization depicts the overall monthly visits all inclusive (Physician/ED visits/Hospitalization), in **all** those who had PCR tests done either with positive OR negative results and comprise of all the various types of conditions considered (i.e., chronic diseases as well as mental health issues)

3.4. Results

Overall Healthcare Services Utilization

The entire adult Ontario population that had utilized health care services at least once during the study period including either physician or emergency visits as well as hospitalization and had a PCR test done during the COVID-19 pandemic period were included in the analysis (Fig. 4.1).

For the overall PCR-tested population at baseline in 2017, the mean monthly visit number was 2.9441 hundred thousand (294,410). This number increased by an average 0.0070, or 700 visits per month during the pre-COVID months ($P < 0.05$). After the onset of COVID-19 in Ontario, a statistically significant decline in mean monthly visits, with the introduction of COVID-19-related public health measures was observed across the overall population. The estimated mean monthly visit number increased in the months afterwards, reaching the highest level by the end of the study period in March 2021. The difference in rate of change in mean monthly visit counts (slope of the curve) post COVID-19 onset vs pre-COVID-19 was 0.0619 visits (6,190) per month and was statistically significant when compared with the pre pandemic period (Fig. 4.2a & Table 3.1).

To estimate the change in monthly visits in the COVID-19 negative and COVID-19 positive population, the data were stratified based on COVID-19 PCR test result, i.e., COVID-19 negative and COVID-19 positive population (Table S2.1). The stratified results were similar to the overall sample. The baseline monthly visits were estimated to be 2.7333 (273,330) and 0.2108 (21,080) for the respective COVID-19 negative and positive individuals. The monthly change in visits pre-COVID was statistically significant for both the COVID-19

positive as well as the COVID-19 negative group, being 0.0005 (50) and 0.0065 (6,500) respectively. A statistically significant decline in mean monthly visits with the introduction of COVID-19- related public health measures was observed across both groups. The difference in the rate of change in mean monthly visit number (slope of the curve) post-vs pre-COVID-19 was 0.0562 (5,620) and 0.0057 (570) with $P < 0.05$, for the COVID-19 negative and COVID-19 positive population respectively, as compared to pre-pandemic period.

Health Services Utilization for Chronic Diseases

A separate analysis was conducted to analyze the change in monthly visits related to the five chronic conditions included in this study (Fig. 4.2b). For the overall PCR tested population, the baseline mean monthly visit number was 0.6104 hundred thousand (61,040). This number increased by an average 0.0025, or 250 visits per month during the pre-COVID months ($P < 0.05$). A non-statistically significant drop was seen at the onset of COVID-19, followed by a statistically significant monthly increase above pre-COVID levels, 0.0150 or 1500 visits per month. The estimated mean monthly visit number increased in the months afterwards, reaching the highest level by the end of the study period in March 2021. The difference in rate of change in mean monthly visits counts (slope of the curve) post COVID-19 onset vs pre-COVID-19 was 0.0150 hundred thousand (1500) per month and was statistically significant ($P < 0.05$), when compared with the pre pandemic period (Table 3.1).

After stratification based on COVID-19 PCR result, the estimated baseline monthly number of healthcare visits was 0.5577 (55,770) and 0.0527 (5,270), for the COVID- 19 negative and COVID-19 positive groups. The difference in rate of change in mean monthly visit number

(slope of the curve) post COVID-19 onset vs pre-COVID-19 was 0.0139 (1,390) and 0.0010 (100) with $P < 0.05$, for the COVID-19 negative and COVID-19 positive population respectively, as compared to pre-pandemic period. The groups exhibited statistically significantly increased monthly visits pre-COVID. However, at COVID-19 onset, only COVID positive exhibited a statistically significant drop at the onset of COVID-19 pandemic (Table S2.1).

Health Services Utilization for Mental Health Issues

Another analysis was conducted to analyze the change in monthly visits number related to mental health issues of anxiety and depression (Fig. 4.2c). For the overall PCR tested population, the baseline mean monthly visit number was 1.4501 hundred thousand (145,010). Each month there was an insignificant increase in patients over the time period. Likewise, there was an insignificant drop in visits at the onset of COVID-19. The difference in rate of change in mean monthly visits (slope of the curve) post COVID-19 onset vs pre-COVID-19 was 0.0330 hundred thousand (3300) per month and was statistically significant ($P < 0.05$), when compared with the pre-pandemic period (Table 3.1). Analyzing the data based on COVID negative and COVID positive PCR tests results, the estimated baseline monthly visits were 1.3709 (137,090) and 0.0792 (7,920), respectively. Both groups showed statistically significant monthly visits increases post COVID-19 onset vs pre-COVID, 0.0307 (3,070) and 0.0023 (230), respectively (Table S2.1).

All-cause Deaths

We also examined the monthly all-cause deaths as presented in Figure 3.2d. The estimated baseline monthly mortality was 0.0827, or 8,270 deaths per month. The pre-COVID monthly

change as well as the baseline change due to COVID-19 was found to be insignificant. Moreover, the monthly changes for all cause deaths were 0.0002 (20) and did not significantly change pre- and post-COVID onset (Table 3.1). We also considered the models after stratification into three broad age groups: 18 – 45 years (young adults), 46 – 65 years (middle-aged adults), and 66 years and above (older adults). The monthly all-cause deaths increased with age, leading to baseline month estimates of 0.0026, 0.0117, and 0.0683 for the three groups, respectively. All three groups had a drop in the number of deaths reported at the start of COVID-19. Only the youngest group, 18 – 45 years, was found to report higher monthly all-cause deaths post-COVID (Table S2.2).

3.5. Discussion

Our study investigated morbidity and mortality through healthcare utilization and death records in Ontario during the period from January 2020 to March 2021 related to chronic diseases and mental health issues of anxiety and depression. The outbreak of the COVID-19 pandemic has had a significant impact on healthcare utilization, leading to changes in healthcare-seeking behavior globally.^{19,20} In Ontario, Canada, the pandemic led to fluctuations in healthcare utilization since January 2020, as healthcare systems have had to adapt to the demands of the pandemic while continuing to provide necessary care for other medical issues.^{21,22}

Our study noted that there were drops in physician visits and hospitalizations initially in Ontario during the COVID-19 pandemic's first wave, likely due to the factors such as mitigation strategies, fear of exposure to the virus and healthcare system adjustments to the pandemic's demands. Furthermore, during the initial four months of the COVID-19

pandemic, primary care in Ontario witnessed significant transitions from in-person office visits to virtual care. This transition disrupted many patients' visits, a pattern observed in locations beyond Ontario. For example, physician services experienced a significant decline in three Canadian provinces during March and April, followed by subsequent increases in May and June of 2020 while a similar partial recovery was observed in the US after a period of decline.^{23,24} Over time, there was a partial recovery in healthcare visits following the initial sharp decline during the start of the COVID-19 pandemic. However, we did not observe drops for mental health utilization. This difference aligns with other studies, which showed individuals with mental healthcare needs experienced the smallest decrease in total visits.²⁵ Nonetheless, generally across the population, primary care visits decreased by 35% from March to May 2020 compared to the same period in 2019 and hospitalization rates for non-COVID-19 related issues decreased by 24% in April 2020 compared to April 2019.²⁵

Our observations also revealed a cyclic pattern to healthcare utilization, during the COVID-19 pandemic. Other studies show primary care visits in Ontario increased by 18% from May to August 2020 but decreased by 6% from September to November 2020 compared to the same period in 2019. It is also important to note that the period during the COVID-19 pandemic spanning from mid-March to the end of July 2020 was characterized by varying degrees of restrictions being gradually lifted in different regions during the period from early May to mid-July.²⁶ Trends showed increasing visits over this time period, with greater increases in June and July, along with decreases in virtual care.^{27,28} Despite the cyclic pattern, the results exhibited a clear upward trend.

However, as the pandemic progressed, there were periods when the number of physician visits and hospitalizations sharply rose, likely due to the virus's continued spread, emergence of new variants and increasing severity of cases. Other studies have shown one year after the pandemic, physician visits and hospitalizations increased exponentially by 60% and 40%, respectively, compared to 2019.²⁵ Moreover, in December 2020, hospitalizations for COVID-19 reached their highest levels in Ontario, which put pressure on the healthcare system and may have led to a decrease in non-COVID-19 related hospitalizations.¹² We also observed a drop in healthcare utilization in January 2021. After a continuous rise in COVID-19 cases throughout the fall and winter of 2020, reported cases and hospitalizations reached their peak in early January 2021. Subsequently, there was a decline in COVID-19 cases until the end of January 2021, which can be attributed to the implementation of lockdown measures initiated shortly after the December holiday season.²⁹ Following the issuance of stay-at-home orders in January 2021, different regions gradually phased them out between February and early March 2021.

The highest healthcare utilization was seen at the end of the study period in March 2021. This aligns with the emergence of the B.1.1.7 (Alpha) variant of concern in Ontario. The first cases were detected in December 2020, and its rapid spread led to a significant increase in COVID-19 cases and hospitalizations starting in late February 2021.³⁰ Moreover, the exponential rise in healthcare utilization we observed one-year post-pandemic onset may be attributed to the relaxation of public health measures and the emergence of new virus variants. For example, the Delta variant was associated with increased hospitalization rates compared to the Alpha variant.³¹ During the third wave of the pandemic in Ontario, which started in March 2021, hospitalization rates for COVID-19 reached their highest levels at that

point. According to data from the Ontario government, hospitalizations for COVID-19 peaked at over 2,000 in April 2021. This surge in hospitalizations likely impacted the availability of healthcare resources and may have led to a decrease in non-COVID-19 related hospitalizations with an impact on chronic illnesses.

Our study observed a pre-existing stable trend in mental health visits, which sharply escalated during the pandemic. This indicates that the pandemic intensified mental health challenges, leading to a significant surge in demand for mental health services. The Canadian population's mental health and coping abilities have deteriorated against the backdrop of the pandemic.³² The situation is even more grim for those already suffering from mental illnesses, given that 1.6 million Canadians each year had unmet mental healthcare needs in the pre-pandemic period.³³ Prior to the pandemic, Canada was already in the grip of a mental health crisis with anxiety and depression being the two most common mental illnesses affecting more than 6.7 million Canadians,³⁴ and it has been reported that by the time they reach the age of 40, one in every two Canadians will experience a mental disorder.³⁵ Furthermore, several polls have examined the mental health consequences of COVID-19, revealing an increase in mental health disorders among Canadians.³⁶ Due to COVID-19 and related measures, people in Canada experienced higher levels of stress, worry, anxiety, and depression.^{32,36} Moreover, during the COVID-19 pandemic, over half of a large sample of Canadians with no prior history of mental illness tested positive for depression using standard clinical tests, and about a third tested positive for generalized anxiety disorder.³⁷ The findings underscore the critical need for expanded support and resources to address the escalating mental health needs during and after crises like the COVID-19 pandemic.

Visits due to chronic diseases also showed large increases post-COVID onset. Approximately 73% of Canadians over 65 years of age live with at least one chronic disease, which often requires frequent use of healthcare services, including visits with specialists. However, the COVID-19 pandemic made managing chronic diseases more difficult due to health service closures, diversion of resources to COVID-19 care, and patients' fear of exposure to the virus. This can lead to severe health complications and even death. In-person specialist visits for chronic disease management had significantly decreased during the pandemic, with up to 94% fewer visits in April 2020 compared to April 2019. Another study found that there was a 40.6% reduction in non-COVID-19-related hospital admissions compared to the same period in 2019.²⁰ Virtual care services increased to offset this, with over 42 million specialist consultations provided in Ontario alone through telephone, text, or video-conferencing;. However, virtual visits are not always a good substitute for in-person care, and many patients still struggled to access chronic disease care during the pandemic.³⁸ Although virtual care was implemented for a range of chronic health conditions, its acceptance and integration differed across various conditions, including mental health. ³⁹The limitations on accessing healthcare services resulted in a rise in medical complications and emergencies, particularly for elective procedures, and care delays. However, it is not clear whether the delays were due to patients delaying seeking medical attention or due to the barriers to accessing services.

We also observed increased mortality, particularly among younger groups following the onset of COVID-19. Likewise, some studies have found higher mortality rates and increased burden of disease.²⁰ And in Canada, the number of deaths remained higher than expected from spring 2020 to winter 2021, with excess deaths peaking alongside pandemic waves.⁴⁰

We observed similar patterns for mortality during the study period. Studies have shown, at times, that the volume of excess deaths persisted above the volume of COVID-19 deaths, indicating that indirect pandemic-related or alternative causes contributed to a spike in deaths.^{41,42} Excess deaths include both direct and indirect pandemic-related causes, such as delayed or missed care, hesitancy to seek care, mental health disorders, substance use, and other health determinants affected by the pandemic.^{43,44} During the COVID-19 peak in September 2020, deaths not related to COVID-19 were 5% higher than the expected mortality rate for a normal year. This pattern is similar to excess mortality seen in other countries during the pandemic.^{45,46} The provinces of Quebec, Ontario, and British Columbia all had varying levels of excess deaths during the first wave, with a higher share of excess deaths reported for those aged 85 years and older.^{47,48}

Strengths and Limitations

This study utilized a large population-based longitudinal administrative database, resulting in increased statistical power and generalizability, the ability to analyze longitudinal trends, and the use of real-world data reflecting actual healthcare practices. There are several limitations to consider when interpreting our findings. Firstly, it is important to note that our study period ended in March 2021, before a significant portion of the population had received COVID-19 vaccinations. The generalizability of our results may be limited to populations without significant barriers to testing. Another limitation is the potential for selection bias, as the data may only include individuals who sought healthcare services or had specific insurance coverage. The data may not capture the experiences and health outcomes of individuals who do not access healthcare or are underrepresented in the

database. Despite these limitations, our findings can provide valuable insights, particularly in the context of emerging variants and the removal of public health interventions.

3.6. Conclusion

In conclusion, this study sheds light on the profound impact of the COVID-19 pandemic on physician visits and hospitalizations. The findings clearly demonstrate a significant rise in healthcare utilization for mental health and chronic diseases during this unprecedented crisis. The disruptions caused by the pandemic, coupled with the surge in COVID-19 cases, led to a substantial increase in both the demand for medical care and the strain on healthcare systems worldwide. As a result, physician visits and hospitalizations experienced a notable and unprecedented rise, highlighting the immense challenges faced by healthcare providers. These findings emphasize the need for robust and adaptive healthcare systems that can effectively respond to public health emergencies while maintaining access to essential medical services. Furthermore, this study underscores the importance of ongoing research to comprehend the full scope of the pandemic's impact on healthcare utilization and to guide future efforts aimed at mitigating the adverse effects of similar crises. The changes in physician visits and hospitalizations during the COVID-19 pandemic also have clinical and public health implications. The reduction in healthcare utilization during the pandemic's first wave may have led to missed or delayed diagnoses and treatment of non-COVID-19-related medical issues, which can worsen medical conditions and lead to higher morbidity and mortality. The surge in emergency department visits and hospitalizations during the pandemic's second wave highlights the need for healthcare systems to adapt to the pandemic's demands and significance of pandemic preparedness plans. This includes

ensuring that healthcare providers have the necessary resources to meet the demand for care. From a public health perspective, addressing barriers to care is critical to ensure that individuals receive necessary medical care during a pandemic as the limited availability of healthcare resources may have led to poor outcomes and increased mortality, particularly for those with chronic diseases.

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Data Availability Statement: The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at <https://www.ices.on.ca/DAS>. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Chapter 4 Preamble

The significance of Study III (Chapter 4) of this dissertation lies in its examination of the syndemic relationship among COVID-19 and mental health, in terms of their combined impact on health outcomes. The COVID-19 pandemic has disproportionately affected marginalized communities due to factors like socioeconomic conditions and limited healthcare access. In the context of a syndemic, these determinants contribute to the complex interplay between various health challenges. Through an exploration of the syndemic nature of COVID-19, where viral infection, mental health, and pre-existing conditions converge, the study provides insights into the complex interactions among these elements. Recognizing how social determinants of health shape the syndemic dynamics of COVID-19, holds paramount importance for shaping policies, healthcare delivery, and resource allocation. By identifying the syndemic nature of the COVID-19 pandemic, this study highlights the significance of strategies to foster equitable health outcomes and overall well-being of diverse populations.

Chapter 4: The syndemic impact of COVID-19 and mental health on health services utilization related to chronic diseases among adult Ontario population

Status: Submitted

4.1. Abstract

Background: A syndemic is characterized by the interaction of two or more diseases or health conditions, interacting with, and exacerbating each other within a specific population or environment. There is a need to consider COVID-19 a syndemic; which calls for a comprehensive approach to tackle the associated interconnected challenges. The objective of this study is to investigate the syndemic of COVID-19 and mental health, with a specific focus on understanding how viral infection and pre-existing comorbidities interact and influence each other.

Methods: This retrospective cohort study included 2,863,423 individual adults (18+ years) in Ontario, Canada, between Jan 2020 to March 2021. The cohort was created based on criteria of PCR-based lab-confirmed COVID-19 disease status followed by the diagnosis of either anxiety or depression, leading to four comparison groups: COVID-19 negative without anxiety or depression, COVID-19 negative with anxiety or depression, COVID-19 positive without anxiety or depression, and COVID-19 positive with anxiety or depression. All of these groups were followed until the end of the study period for at least one physician visit, emergency department visit, or hospitalization related to the five chronic conditions.

Results: In the final adjusted regression model for the sample, the individuals who were COVID-19 positive and had either anxiety or depression were more likely to utilize health

services for chronic conditions of interest during the pandemic (ORs, 1.33; 95% CI, 1.12-1.58), as compared to those who were COVID-19 negative with mental health issues. A higher risk of morbidity was observed among males (ORs 1.28; CI,1.16-1.41), as well as in individuals with diverse ethnic backgrounds and low socioeconomic status.

Conclusions: COVID-19 and the effects it has on mental health could be viewed as a "syndemic" where the effects on vulnerable populations with chronic diseases are deteriorated by their complex interactions. This relationship highlights the importance of integrated public health strategies. By recognizing this as a syndemic, policymakers can design targeted approaches to alleviate poor health impacts in higher risk populations when future pandemics arise.

4.2. Introduction

The emergence of the COVID-19 pandemic in late 2019 has led to an unprecedented global crisis, burdening healthcare systems, disrupting economies, and causing significant social disruptions.¹ It has become more evident that COVID-19 should not be seen solely as a pandemic but rather a syndemic; as researchers and public health professionals continue to explore the complex nature of this disease.² A syndemic is characterized by the interaction of two or more diseases or health conditions, interacting with and exacerbating each other within a specific population or environment.³ In the case of COVID-19, the interactions between the viral infection, its impact on pre-existing health conditions, and the socioeconomic determinants of health have amplified the severity and complexity of the pandemic's consequences.^{4,5} The syndemic paradigm offers a thorough perspective to investigate the complex connections between these health issues and the synergistic influences they have on the overall health of the population.⁶ The syndemic perspective acknowledges that while COVID-19 itself may primarily be a biological phenomenon, the challenges arising from mitigation strategies and the adverse impacts of the virus often result from underlying social, economic, and political factors.⁷ These factors encompass the interplay between COVID-19 and other diseases, such as non-communicable diseases (NCDs), mental health disorders, and health disparities.⁸

Non-communicable diseases (NCDs) have been identified as a significant risk factor for COVID-19 patients.⁹ One key aspect of COVID-19 as a syndemic is the association between the virus and pre-existing NCDs. Individuals with underlying health conditions such as cardiovascular diseases, diabetes, obesity, and respiratory disorders are at a higher risk of

severe illness or mortality when infected with COVID-19.¹⁰ Furthermore, the syndemic nature of COVID-19 extends beyond the physical health realm to impact mental health and well-being. The pandemic has triggered an upsurge in mental health disorders, including anxiety, depression,¹¹ and post-traumatic stress disorder, affecting individuals of all ages and backgrounds.¹² The bidirectional relationship between mental health and COVID-19 adds another layer of complexity, as the stressors associated with the pandemic can exacerbate preexisting health conditions, while the mental health burden can compromise individuals' ability to adopt preventive measures or seek appropriate healthcare.^{13,14} The combination of these comorbidities, COVID-19, and stress creates a unique set of challenges for healthcare systems worldwide, as they must simultaneously address the treatment and management of chronic diseases while combating the immediate threat of the viral infection.

Inequalities in the social determinants of health play a crucial role in shaping various aspects of life, including health, well-being, and financial status.¹⁵ These inequalities stem from factors like poor social and economic conditions, environmental factors, social marginalization, and government policies that either support or hinder healthcare access.⁸ Health inequities have been clearly highlighted by the COVID-19 epidemic. The effects of the COVID-19 pandemic have disproportionately affected marginalized communities, which include racial and ethnic minorities, socioeconomically disadvantaged populations, and people with inadequate access to healthcare resources.¹⁶ Social determinants of health, such as income inequality, poor housing conditions, and limited access to healthcare services, have an impact on this disparity in health outcomes in terms of disease severity, and mortality rates among different populations, contributing to the syndemic aspect of COVID-19.^{17,18}

There is a need to consider COVID-19 a syndemic; which calls for a comprehensive approach to tackle the associated interconnected challenges. This involves recognizing the complex interactions between the viral infection, pre-existing health conditions, mental health, and social determinants of health. Policymakers, healthcare providers, and researchers can utilize this understanding to develop holistic strategies that address the multifaceted impact of COVID-19 and promote the overall well-being of the population. The objective of this study is to investigate the syndemic of COVID-19 and mental health, with a specific focus on understanding how viral infection and pre-existing comorbidities interact and influence each other.

4.3. Methodology

This study utilized secondary data from administrative health databases accessed through the Ontario Health Data Platform (OHDP). The platform permitted access to patient-level linked population-based health administrative data held at ICES, known as the Institute of Clinical Evaluative Sciences. The ICES data repository consists of record-level, coded, and linkable health data sets that integrate health services data, registries, and surveys in Ontario, Canada. These datasets were linked using encoded identifiers and analyzed at ICES

Study Design and Cohort Eligibility

We constructed a retrospective cohort of people who are living in Ontario, Canada, have a valid health card, and for whom information on sex and age was available, between the period of January 2020 to March 2021. Another eligibility criteria for the cohort were that these individuals had a COVID-19 PCR test done, either with negative or positive COVID-19 disease status. Detailed characteristics of the cohort and related data are presented

elsewhere. (Appendix B). All those cases who were less than 18 years of age, as well as those who had a first standard COVID-19 lab-based PCR test result beyond March 31, 2021, were excluded.

Definitions

COVID-19 status was based on a standard lab-based PCR test, while the prevalence of chronic conditions was identified using ICES derived cohorts. We utilized an algorithm to identify cases of health service utilization among the Ontario population aged ≥ 18 years within the ICES data holdings, defined as: 1. One primary diagnosis of either chronic diseases or anxiety or depression using the Ontario Mental Health Reporting System (OMHRS) or medical bed using the Discharge Abstract Database (DAD) between January 01, 2017, and March 31, 2021, OR 2. At least one emergency department identified through National Ambulatory Care Reporting System (NACRS) or physician visit identified through the Ontario Health Insurance Plan Claims Database (OHIP) during the study period for anxiety or depression or chronic diseases from January 01, 2017, and March 31, 2021. The chronic diseases in this study included asthma, chronic obstructive pulmonary disease, diabetes, congestive heart failure and hypertension. The primary outcome of interest in this study was “morbidity” which was defined as at least one physician visit or emergency department visit or hospitalization to a medical bed for reasons related to chronic diseases of interest included in this study. We used DSM-V criteria and ICD-10 codes to classify physician visits, emergency department visits, ambulatory care visits, and hospitalization as either elective or urgent, related to chronic illnesses and mental health issues.

The sociodemographic variables utilized in this study that are potentially associated with health service utilization include age, gender, place of residence (urban/rural residence), and area-level measures from the Ontario Marginalization Index (ON-Marg).¹⁹ ON-Marg is an index that aims to measure marginalization and disparities in health and social well-being between different geographic areas or population groups in Ontario. It is based on four dimensions, namely, residential instability, material deprivation, dependency, and ethnic diversity. Each dimension is divided into five quintiles, with higher quintiles indicating higher levels of marginalization. Residential instability reflects high rates of family or housing instability within an area, while material deprivation refers to the inability of individuals and groups to access basic material needs due to poverty. Dependency captures the concentration of people without employment-based income, such as seniors, children, and those with unpaid employment. Ethnic diversity measures the concentration of recent immigrants and visible minorities in an area (defined by Statistics Canada as “persons, other than aboriginal peoples, who are non-Caucasian in race or non-white in color”).²⁰ ON-Marg allows for a comprehensive exploration of multiple dimensions of marginalization in urban and rural areas of Ontario.

The cohort was created based on criteria of PCR-based lab-confirmed COVID-19 disease status followed by the diagnosis of either anxiety or depression based on DSM-V criteria and ICD-10 codes, leading to four comparison groups: COVID-19 negative without anxiety or depression, COVID-19 negative with anxiety or depression, COVID-19 positive without anxiety or depression, and COVID-19 positive with anxiety or depression. All of these groups were followed until the end of the study period for at least one physician visit, emergency department visit, or hospitalization related to the five chronic conditions. (Table 4.1)

Table 4.1: Details of comparison groups in the study

Group No.	Group Name	COVID-19 Disease Status	Mental Health Diagnosis
0	COVID-19 -VE/MH-VE	COVID-19 Negative	MH Negative
1	COVID-19 -VE/MH+VE	COVID-19 Negative	MH Positive
2	COVID-19 +VE/MH+VE	COVID-19 Positive	MH Negative
3	COVID-19 +VE/MH+VE	COVID-19 Positive	MH Positive

MH = Mental Health in terms of anxiety and Depression

Statistical Analysis

Descriptive statistics (e.g., mean, median, range, standard deviation) were calculated for the study sample. Frequencies for demographic and service-use variables were examined with cross-tabulations across comparison groups using chi-squared statistics. Criteria for statistical significance was set at p-value (p) < 0.05. Multiple logistic regression analysis was utilized to identify important risk factors associated with the syndemic impact of COVID-19 and anxiety or depression on morbidity, among comparison groups. Characteristics of participants that were evaluated in various models included age, sex, socioeconomic status based on ON-Marg quintiles, and health care utilization for the five chronic conditions in this study.

First, to explore the potential interaction between COVID-19 and mental health, a multiple logistic regression model was utilized (Table S3.1). Based on the statistically significant interaction between COVID-19 and mental health issues, a joint variable was created for both COVID-19 disease status and mental status, leading to four comparison groups.(Table 4.1). Different multiple logistic models were generated to examine the risk factors across all comparison groups with morbidity as outcome. The final model was based on comparison of outcome among two groups only i.e., COVID-19 positive with either anxiety or depression

and COVID-19 negative with either anxiety or depression. We performed an additional stratified analysis based on the number of times a COVID-19 PCR test was done, to account for changes in being diagnosed with anxiety or depression status over time. Two separate multiple models were generated based on the first time tested and multiple time-tested cohorts, to examine the outcome of morbidity. For interpretation, adjusted odds ratios and their respective 95% confidence intervals (CIs) were estimated. A separate multiple logistic regression model was generated to examine the relationship between characteristics of participants with COVID-19 disease status and mental health status.

All analyses were performed using SAS Enterprise Guide 8.3 (SAS Institute, Cary, NC). This study was approved by the University of Waterloo research ethics board (protocol reference no. 43910), and data use was authorized under section 45 of Ontario's *Personal Health Information Protection Act*. ICES is a prescribed entity under section 45 of *Ontario's Personal Health Information Protection Act*, which authorizes ICES to collect personal health information, without consent, for the purpose of health system evaluation and improvement.

4.4. Result

The overall cohort included 2,863,423 individuals. Of these, 2,659,880 (92.89%) were tested COVID-19 negative, while 203,543 (7.11%) were tested COVID-19 positive. The mean age of the overall sample was 45.57 years with a standard deviation of 17.49. The number of females in the overall sample was higher (n= 1,571,101; 54.87%), as compared to males (n=1,292,322; 45.13%). The majority of individuals (2,559,812, or 89.40%) were not diagnosed with either anxiety or depression, while a proportion of individuals (303,611, or 10.60%) were diagnosed with either of these conditions. Out of those who had utilized health

services for any of the five chronic conditions in this study, the highest proportion of individuals was 45-65 years of age (302,161;10.55%), followed by those older than 65 years (220,623; 7.70%). (Table 4.2)

A separate multiple logistic regression model was generated to examine the relationship between characteristics of participants with COVID-19 disease status and mental health status. Being COVID-19 positive as well as diagnosed with anxiety or depression was associated with material deprivation, ethnicity, dependency, and chronic conditions. (Table 4.3).

Table 4.2: Demographic characteristics of the study sample

Demographics	Overall Sample	Morbidity	
		No	Yes
Total N (Col %)	2863423	2195320	668103
Mean Age (Yrs.) ($\pm$ SD)	45.57 (17.49)	42.05 (16.49)	57.12 (15.58)
COVID-19 Status			
COVID-19 Negative	2659880 (92.89)	2046026 (93.20)	613854 (91.88)
COVID-19 Positive	203543 (7.11)	149294 (6.80)	54249 (8.12)
Anxiety/Depression			
No	2559812 (89.40)	1893376 (86.25)	666436 (99.75)
Yes	303611 (10.60)	301944 (13.75)	1667 (0.25)
COVID-19 & Mental Health			
COVID-19 -VE/ MH-VE	2374525 (82.93)	1762186 (80.27)	612339 (91.65)
COVID-19 -VE/ MH+VE	285355 (9.97)	283840 (12.93)	1515 (0.23)
COVID-19 +VE/ MH-VE	185287 (6.47)	131190 (5.98)	54097 (8.10)
COVID-19 +VE/ MH+VE	18256 (0.64)	18104 (0.82)	152 (0.02)
Age groups			
18-45 yrs.	1465893 (51.19)	1320574 (60.15)	145319 (21.75)
46-65 yrs.	954774 (33.34)	652613 (29.73)	302161 (45.23)
66+ yrs.	442756 (15.46)	222133 (10.12)	220623 (33.02)
Sex			
Female	1571101 (54.87)	1229828 (56.02)	341273 (51.08)
Male	1292322 (45.13)	965492 (43.98)	326830 (48.92)
Rural			
No	2596174 (90.67)	1987013 (90.51)	609161 (91.18)
Yes	267249 (9.33)	208307 (9.49)	58942 (8.82)
Ontario Marginalization Index			
Deprivation Quintile			

1	663673 (23.18)	530961 (24.19)	132712 (19.86)
2	603519 (21.08)	469309 (21.38)	134210 (20.09)
3	550906 (19.24)	419484 (19.11)	131422 (19.67)
4	525450 (18.35)	392566 (17.88)	132884 (19.89)
5	519875 (18.16)	383000 (17.45)	136875 (20.49)
Dependency Quintile			
1	768196 (26.83)	605531 (27.58)	162665 (24.35)
2	587947 (20.53)	454821 (20.72)	133126 (19.93)
3	506243 (17.68)	389120 (17.72)	117123 (17.53)
4	481256 (16.81)	364874 (16.62)	116382 (17.42)
5	519781 (18.15)	380974 (17.35)	138807 (20.78)
Instability Quintile			
1	618545 (21.60)	474715 (21.62)	143830 (21.53)
2	541505 (18.91)	418052 (19.04)	123453 (18.48)
3	519694 (18.15)	398944 (18.17)	120750 (18.07)
4	523900 (18.30)	399884 (18.22)	124016 (18.56)
5	659779 (23.04)	503725 (22.95)	156054 (23.36)
Ethnicity Quintile			
1	447589 (15.63)	341199 (15.54)	106390 (15.92)
2	485380 (16.95)	376477 (17.15)	108903 (16.30)
3	534956 (18.68)	421425 (19.20)	113531 (16.99)
4	620385 (21.67)	486371 (22.15)	134014 (20.06)
5	775113 (27.07)	569848 (25.96)	205265 (30.72)

*Group '0' = COVID-19 -VE/MH-VE, Group '1' = COVID-19 -VE/MH+VE, Group '2' = COVID-19 +VE/MH-VE, Group '3' = COVID-19 +VE/MH+VE

Table 4.3: Multiple multinomial logistic regression model to identify characteristics of study population associated with COVID-19 disease and Mental Health status

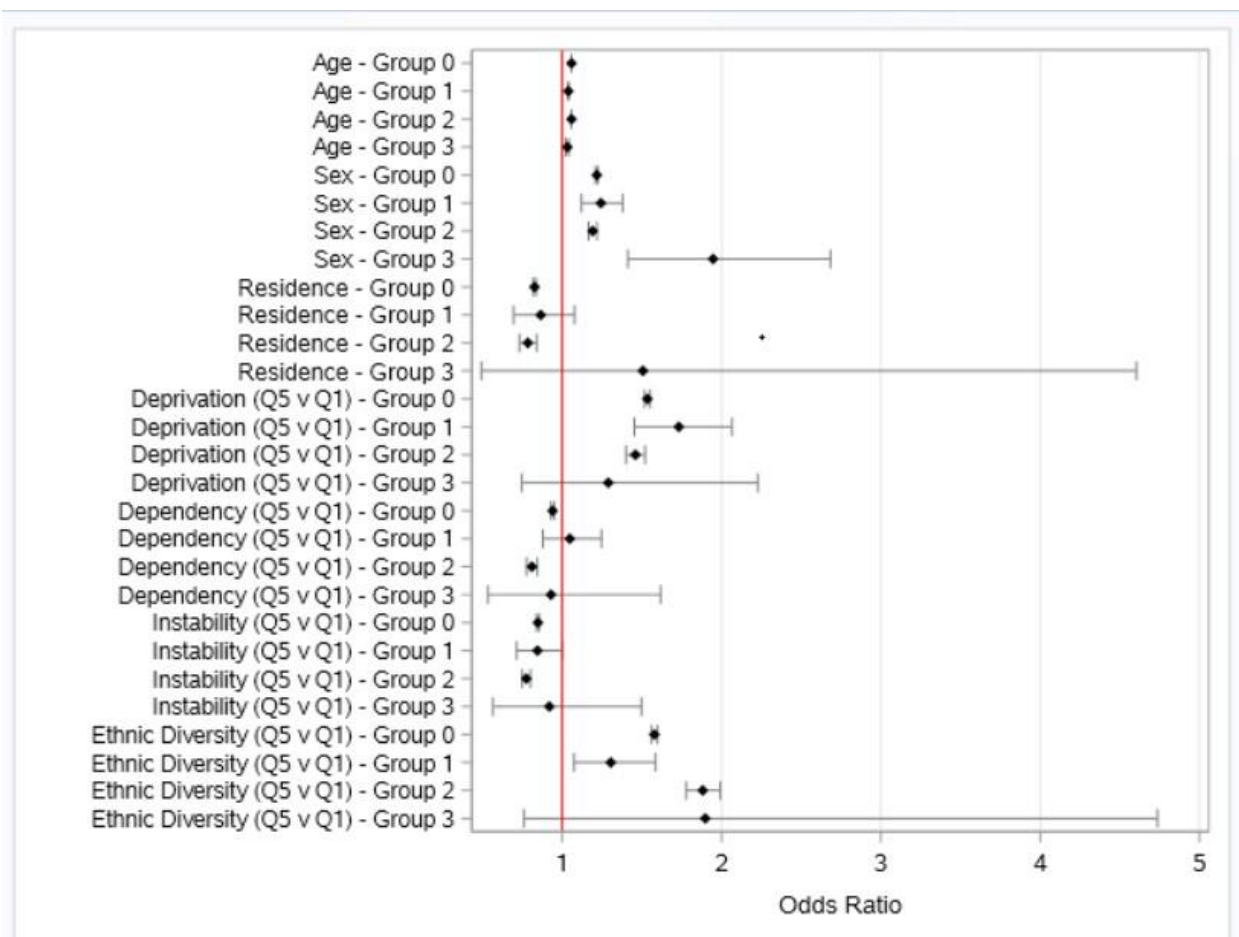
Variables	C19-VE/MH+VE	C19+VE/MH-VE	C19+VE/MH+VE
Age			
18-45 yrs.	Ref	Ref	Ref
46-65 yrs.	0.73 (0.73-0.74)	0.96 (0.95-0.97)	0.86 (0.83-0.90)
66+ yrs.	0.56 (0.55-0.57)	0.80 (0.78-0.81)	0.72 (0.68-0.76)
Sex			
Female	Ref	Ref	Ref
Male	0.58 (0.58-0.59)	1.11 (1.10-1.12)	0.62 (0.60-0.64)
Rural			
No	Ref	Ref	Ref
Yes	0.84 (0.82-0.85)	0.69 (0.67-0.71)	0.58 (0.53-0.64)
Deprivation Quintile			
1	Ref	Ref	Ref
2	1.00 (0.99-1.01)	1.22 (1.20-1.24)	1.14 (1.08-1.20)
3	0.95 (0.94-0.96)	1.54 (1.51-1.56)	1.37 (1.30-1.44)
4	0.99 (0.97-1.00)	1.74 (1.71-1.77)	1.47 (1.40-1.54)
5	1.07 (1.06-1.08)	1.90 (1.96-1.83)	1.82 (1.74-1.90)
Dependency Quintile			
1	Ref	Ref	Ref
2	1.00 (0.98-1.01)	1.02 (1.01-1.04)	1.04 (1.00-1.08)
3	1.00 (0.99-1.01)	1.03 (1.01-1.05)	1.06 (1.02-1.11)
4	0.98 (0.97-0.99)	1.01 (1.00-1.03)	1.07 (1.02-1.13)
5	0.97 (0.96-0.99)	1.13 (1.11-1.15)	1.18 (1.11-1.24)
Instability Quintile			
1	Ref	Ref	Ref
2	1.04 (1.02-1.05)	0.86 (0.85-0.87)	0.90 (0.86-0.95)
3	1.07 (1.05-1.08)	0.82 (0.81-0.83)	0.68 (0.65-0.71)
4	1.17 (1.15-1.18)	0.76 (0.75-0.77)	0.87 (0.83-0.92)
5	1.34 (1.33-1.36)	0.82 (0.81-0.83)	1.01 (0.97-1.05)
Ethnic Diversity Quintile			
1	Ref	Ref	Ref
2	1.10 (1.08-1.11)	1.26 (1.23-1.29)	1.41 (1.31-1.52)
3	1.21 (1.19 -1.22)	1.65 (1.62-1.69)	1.98 (1.85-2.12)
4	1.23 (1.21-1.24)	2.38 (2.33-2.43)	2.69 (2.52-2.86)
5	1.01 (1.00-1.02)	4.77 (4.68-4.87)	4.32 (4.07-4.59)

*The table shows the regression parameter estimates for each variable with corresponding 95% CI for model outcome= 'COVID-19 & Mental health status'

*Group '0'= COVID-19 -VE/MH-VE, Group '1'= COVID-19 -VE/MH+VE, Group '2'= COVID-19 +VE/MH-VE, Group '3'= COVID-19 +VE/MH+VE

We also observed important risk factors significantly associated with health services utilization across all comparison groups based on COVID-19 disease and mental health Status (Figure 4.1). A higher risk for health services utilization was observed for males and socioeconomic status with material deprivation quintile in Q5 vs Q1 AND ethnic diversity quintile Q2-Q5 among those who were COVID-19 positive and were diagnosed with anxiety or depression.

Figure 4.1: Comparison of risk factors associated with health services utilization across all comparison groups



Group '0'= COVID-19 -VE/MH-VE, Group '1'= COVID-19 -VE/MH+VE, Group '2'= COVID-19 +VE/MH-VE, Group '3'= COVID-19 +VE/MH+VE

Table 4.4: Multiple logistic regression model for factors associated with morbidity for all four comparison groups

Variables	Crude ORs (95% CI)	Adjusted ORs (95% CI)
Group Variable		
COVID-19 -VE/MH-VE	Ref	Ref
COVID-19-VE/MH+VE	0.015 (0.015-0.016)	0.015 (0.014-0.016)
COVID-19 +VE/ MH-VE	1.18 (1.17-1.19)	1.13 (1.11-1.14)
COVID-19+VE /MH +VE	0.024 (0.021-0.028)	0.020 (0.017-0.023)
Age Groups		
18-45 yrs.	Ref	Ref
46-65 yrs.	4.20 (4.17-4.23)	4.41 (4.38-4.45)
66+yrs.	9.02 (8.95-9.09)	10.23 (10.14-10.32)
Sex		
Female	Ref	Ref
Male	1.22 (1.21-1.22)	1.18 (1.17-1.19)
Rural		
No	Ref	Ref
Yes	0.92 (0.91-0.93)	0.82 (0.81-0.83)
Deprivation Quintile		
1	Ref	Ref
2	1.14 (1.13-1.15)	1.13 (1.12-1.14)
3	1.25 (1.24-1.26)	1.26 (1.25-1.27)
4	1.35 (1.34-1.36)	1.36 (1.35-1.37)
5	1.43 (1.41-1.44)	1.47 (1.46-1.49)
Dependency Quintile		
1	Ref	Ref
2	1.09 (.108-1.09)	0.98 (0.97-0.99)
3	1.12 (1.11-1.13)	0.98 (0.97-0.99)
4	1.18 (1.17-1.19)	0.98 (0.97-0.99)
5	1.35 (1.34-1.36)	1.00(0.99-1.01)
Instability Quintile		
1	Ref	Ref
2	0.97 (0.96-0.98)	0.96 (0.95-0.97)
3	0.99 (0.99-1.00)	0.94 (0.93-0.94)
4	1.02 (1.01-1.03)	0.89 (0.88-0.90)
5	1.02 (1.01-1.03)	0.84 (0.84-0.85)
Ethnic Diversity Quintile		
1	Ref	Ref
2	0.92 (0.91-0.93)	1.03 (1.01-1.04)
3	0.86 (0.85-0.87)	1.06 (1.05-1.07)
4	0.88 (0.87-0.89)	1.18 (1.16-1.19)
5	1.15 (1.14-1.16)	1.57 (1.55-1.59)

Group '0'= COVID-19 -VE/MH-VE, Group '1'= COVID-19 -VE/MH+VE, Group '2'= COVID-19 +VE/MH-VE, Group '3'= COVID-19 +VE/MH+VE
The table shows the regression parameter estimates for each variable along with corresponding 95% CI for model outcome= 'morbidity'

In our sample, we observed variations in the morbidity and co-occurrence of COVID-19 and mental health issues of anxiety or depression among different groups. The mental health issues were notably higher among younger individuals, while those with chronic conditions were predominantly from the middle-aged and older age groups. This observed pattern introduced a potential negative confounding, as depicted in Table 4.4. Additionally, the odds ratios for other groups in Table 4.4 indicate the existence of residual confounding, a factor beyond the study's control. (Table 4.2). The multiple logistic regression model for the four comparison groups showed that COVID-19 positive status was associated with higher risk of utilization of health services. (Table 4.4).

In the final adjusted regression model, the individuals who were COVID-19 positive and had either anxiety or depression were more likely to utilize health services during the pandemic, as compared to those who were COVID-19 negative with mental health issues (Table 4.5). The adjusted odds ratios were (ORs, 1.33; CI, 1.12-1.58) for COVID-19 positive individuals with anxiety or depression compared to COVID-19 negative individuals with anxiety or depression. A higher risk of morbidity was observed among males compared to females (ORs 1.28; CI, 1.16-1.41); and individuals in the 65+ years age group (ORs 4.87; CI, 4.27-5.56) as well as individuals in the 46-65 years age group (ORs 3.00; CI, 2.68-3.37), each compared to the 18-45 years age group. Moreover, a higher risk was observed for socioeconomic status, with material deprivation quintile in Q4-Q5, as well as in Q5 of ethnic diversity quintile significantly associated with health services utilization in COVID-19 positive individuals as compared to COVID-19 negative individuals. (Table 4.5)

Table 4.5: Multiple logistic regression model for factors associated with morbidity in COVID-19 positive and COVID-19 negative individuals with co-occurring anxiety or depression

Variables	Crude ORs (95% CI)	Adjusted ORs (95% CI)
COVID-19 Disease Status		
COVID-19-Negative/MH-Positive	Ref	
COVID-19-Positive /MH-Positive	1.57 (1.33-1.86)	1.33 (1.12-1.58)
Age		
18-45 yrs.	Ref	
46-65 yrs.	2.99 (2.67-3.35)	3.00 (2.68-3.37)
66+ yrs.	4.81 (4.23-5.47)	4.87 (4.27-5.56)
Sex		
Female	Ref	
Male	1.29 (1.17-1.43)	1.28 (1.16-1.41)
Rural		
No	Ref	
Yes	0.85 (0.70-1.04)	0.88 (0.71-1.09)
Deprivation Quintile		
1	Ref	
2	1.19 (1.02-1.39)	1.17 (1.00-1.37)
3	1.16 (0.99-1.37)	1.04 (0.96-1.34)
4	1.41 (1.20 -1.64)	1.37 (1.16-1.62)
5	1.67 (1.44-1.93)	1.63 (1.38-1.93)
Dependency Quintile		
1	Ref	
2	0.94 (0.81-1.08)	0.89 (0.77-1.04)
3	0.97 (0.83-1.12)	0.93 (0.80-1.09)
4	1.03 (0.88-1.20)	0.96 (0.82-1.13)
5	1.27 (1.10-1.46)	1.10 (0.93-1.30)
Instability Quintile		
1	Ref	
2	0.93 (0.79-1.10)	0.96 (0.81-1.13)
3	0.94 (0.80-1.11)	0.91 (0.76-1.08)
4	1.02 (0.87-1.19)	0.90 (0.76-1.07)
5	1.12 (0.97-1.29)	0.89 (0.75-1.04)
Ethnic Diversity Quintile		
1	Ref	
2	0.79 (0.66-0.95)	0.85 (0.70-1.03)
3	0.82 (0.69-0.97)	0.92 (0.76-1.12)
4	0.96 (0.81-1.12)	1.09 (0.90-1.31)
5	1.28 (1.09-1.49)	1.33 (1.10-1.61)

Group '1'= COVID-19 -VE/MH+VE, Group '3'= COVID-19 +VE/MH+VE

The table shows the regression parameter estimates for each variable along with corresponding 95% CI for model outcome= 'morbidity'

In additional multiple regression models stratified by the number of times COVID-19 PCR testing was done, the risk of health services utilization was higher among those who were tested multiple times (ORs 1.43; CI, 1.15-1.78) (Table S3.3) as compared to those who were tested once only (Table S3.2). A higher risk of morbidity was observed among males (ORs 1.49; CI, 1.28-1.74), individuals in the 65+ years age group (ORs 4.07; CI, 3.33-4.99) as well as individuals in the 46-65 years age group (ORs 2.79; CI, 2.34-3.34). Moreover, a higher risk was observed for socioeconomic status, with material deprivation quintile in Q4-Q5, significantly associated with health services utilization. (Table S3.3)

4.5. Discussion

Our study aimed to assess the syndemic impact of COVID-19 and related stress in terms of anxiety and depression on health services utilization for pre-existing chronic conditions in the general Ontario population. The COVID-19 pandemic can be considered as a syndemic, as it encompasses critical dimensions that illustrate the complex and multifaceted nature of its impact.^{5,7} Our study found that there was an increase in health services utilization, due to chronic conditions among those individuals who were diagnosed with COVID-19 as well as anxiety and depression. In our sample, there were variations in the morbidity and co-occurrence of anxiety or depression among different groups. It might be due to the reason that those dealing with chronic conditions were mainly in the middle-aged and older groups (Table S3.5). This observed discrepancy introduced a potential negative or residual confounding, which was beyond the study's control. This complexity might be attributed to the multifactorial nature of mental stress during the pandemic, where numerous contributing factors couldn't be singled out due to data limitations. These factors encompass

pandemic mitigation strategies such as lockdowns, isolation, quarantine, job loss, and uncertainties surrounding employment etc.

The unique and widespread nature of the pandemic has raised concerns about its potential long-term psychological and biological impacts.²¹⁻²³ Research studies have demonstrated a direct link between chronic diseases and mental health issues like anxiety and depression in the general population.²⁴⁻²⁷ Our study found that there was an increase in health services utilization, due to chronic conditions among those individuals who were diagnosed with COVID-19 as well as anxiety and depression. These findings highlight the importance of considering both physical and mental health aspects in the overall well-being of individuals, especially during the COVID-19 pandemic.

The COVID-19 pandemic has led to a significant increase in anxiety and depression cases worldwide, primarily as a result of both direct and indirect consequences of the virus. These consequences include factors such as social isolation, fear of infection and economic instability. Notably, these mental health challenges have been more prevalent among individuals with lower socioeconomic status, primarily due to the pandemic's adverse economic effects, such as job loss and financial strain. There are complex interactions among different diseases and health conditions as well as socioeconomic factors, resulting in an escalated overall illness burden across all levels of society. Our study provides evidence that these social, physical, and mental health interactions have contributed to elevated risks in individuals with poor socioeconomic conditions among vulnerable population groups, leading to the clustering of COVID-19 and mental health and higher health services utilization. Our results are similar to previous research which has highlighted specific groups

that may be more vulnerable to the pandemic's psychological as well as biological consequences in terms of severe outcomes or even fatality. These include in particular, individuals facing economic instability or lower income, people living with chronic conditions, and those perceiving a higher risk of COVID-19 infection.²⁸⁻³⁰

The COVID-19 pandemic's impact on chronic patients is expected to be more severe among those with low socioeconomic status. The individuals in socio-economically disadvantaged neighborhoods and minority ethnic groups have elevated rates of various clinical risk factors that worsen the severity and mortality of COVID-19. These risk factors include hypertension, diabetes, asthma, chronic obstructive pulmonary disease (COPD), heart disease, liver disease, renal disease, cancer, cardiovascular disease, obesity, and smoking.³¹ For socially vulnerable groups, the pandemic acts as a syndemic, exacerbating existing non-communicable diseases (NCDs) and inequalities in social determinants of health.³¹ Although initially considered socially neutral, epidemiological data show clear differences, reflecting pre-existing health disparities. Socially vulnerable groups, ethnic minorities, and marginalized populations face additional challenges in confronting the pandemic.³²⁻³⁴ Additionally, the vulnerable populations face a higher likelihood of engaging in unhealthy habits, such as smoking and alcohol consumption and tend to have more underlying chronic diseases that manifest at a younger age, making them more susceptible to severe COVID-19 outcomes. Limited access to chronic care services, coupled with lower health literacy levels, further exacerbates their vulnerability to the pandemic's adverse effects.³⁵⁻³⁹ The relationship between physical and mental health is intricate and can exacerbate the progression of both conditions.⁴⁰ Socially, the disruption of routines, limited access to healthcare, and reduced social support networks can hinder the management of chronic

conditions, exacerbating their effects.⁴¹ This biopsychosocial synergy amplifies the overall burden on individuals' health.⁴²

Based on the findings, it can be argued that COVID-19, in conjunction with mental health, could be regarded as a syndemic, a situation where multiple health issues interact and exacerbate each other, leading to a more complex and severe impact on affected populations. In this case, the combination of COVID-19 and mental health issues seem to produce a mutually reinforcing effect causing an increased health service utilization among individuals with chronic conditions, thus emphasizing the importance of considering both aspects when addressing public health strategies and interventions. By recognizing this syndemic nature, policymakers and healthcare professionals can better comprehend the interconnected challenges and design more comprehensive and targeted approaches to mitigate the health consequences within vulnerable communities.

Limitations

Our study leveraged a large administrative database, offering significant strengths, including a large sample size that enhanced the statistical power and generalizability of our findings. By analyzing longitudinal trends and utilizing real-world data, we gained valuable insights into actual healthcare practices. However, it is crucial to acknowledge certain limitations when interpreting our results. Additionally, our study did not account for the impact of pandemic-related social restrictions, lockdowns, and their subsequent effects on mental health or healthcare-seeking behaviors. Despite these limitations, our research provides essential insights into considering COVID-19 and mental health; a syndemic due to the

complex interplay between various chronic conditions, mental health, and their implications for public health during the COVID-19 pandemic.

4.6. Conclusion

The ongoing COVID-19 syndemic/pandemic has brought to the forefront the long-standing disparities in healthcare systems. Throughout history, the most vulnerable and socially disadvantaged communities worldwide have experienced the highest rates of infection and mortality, and COVID-19 is no exception. The pandemic has laid bare the pre-existing social, economic, and political inequities in accessing healthcare, especially for individuals affected by non-communicable diseases.⁴³ COVID-19 along with associated stress has disproportionately affected individuals with low socioeconomic status and socially vulnerable groups, acting as a syndemic, worsening existing non-communicable diseases and health inequalities. This has led to adverse health outcomes leading to increased healthcare utilization. Our study highlights the urgent need to address and rectify these disparities to ensure equitable healthcare for all. Health systems need to balance the response to COVID-19 while ensuring that adequate resources are allocated to manage chronic diseases effectively.

Without a comprehensive preparedness plan and a new anthropological syndemic approach to future pandemics, a growing number of people worldwide will needlessly suffer and health inequities will widen.⁴⁴ It is crucial that we learn from this experience and work together to build a more resilient and just health system for the future. By addressing these health challenges simultaneously, the syndemic approach supports efforts to improve the overall well-being of populations. Embracing this perspective can lead to co-designed and

integrated programming that enhances public health outcomes and supports better health for all.

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Data Availability Statement: The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at <https://www.ices.on.ca/DAS>. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Chapter 5: Discussion & Conclusion

5.1. Summary of key findings

In conclusion, the COVID-19 pandemic has unveiled itself as a syndemic, characterized by complex interactions among various diseases and health conditions, leading to an increased overall burden of illness. This syndemic nature of the pandemic encompasses not only the direct consequences of the virus but also its far-reaching indirect effects on mental health and chronic diseases.

Study 1 (Chapter 2) has shed light on the intricate relationship between COVID-19 testing and mental health issues, with a significant association found between PCR testing and psychological distress, notably anxiety and depression. The mental health repercussions of COVID-19 extend beyond the fear of infection and encompass factors such as uncertainty, stigma, quarantine, and social isolation, predominantly affecting the younger population. This worrisome trend highlights the emergence of a concerning mental health crisis, featuring the pandemic's devastating indirect effects on mental well-being. Study 2 (Chapter 3) depicted the complex trajectory of healthcare utilization during the pandemic's waves. It offered valuable insights into the shifts in healthcare usage patterns before and after the onset of COVID-19. While the initial decline in physician visits and hospitalizations could be attributed to fear and healthcare system adjustments, subsequent periods witnessed increases in healthcare utilization and mortality rates, highlighting the evolving dynamics of the pandemic's impact. Study 3 (Chapter 4) investigated the syndemic impact of COVID-19 and related stress on individuals with preexisting chronic conditions. Notably, individuals diagnosed with COVID-19 and co-occurring mental health issues of anxiety and depression

exhibited increased healthcare service utilization. Furthermore, individuals with lower socioeconomic status and diverse ethnic backgrounds were identified as having an elevated risk of morbidity, highlighting the syndemic nature of the COVID-19 pandemic. This points towards the interconnectedness of physical and mental health and emphasizes the importance of addressing both aspects for individuals' overall well-being, especially within the context of the COVID-19 pandemic.

Collectively, this dissertation underscores the need for a holistic approach to understanding and managing the multifaceted challenges posed by the COVID-19 syndemic. It is imperative that healthcare systems and policymakers consider the complex interplay between infectious disease, mental health, and chronic conditions in their strategies to mitigate the pandemic's long-term effects. As we navigate the ongoing crisis and prepare for future challenges, recognizing the syndemic nature of COVID-19 is essential for promoting the health and resilience of individuals and communities.

5.2. Limitations and Strengths

This dissertation possesses notable strengths due to its comprehensive and extensive approach in assessing the impact of COVID-19 and mental health as a syndemic in the province of Ontario. One significant strength is its utilization of administrative health data from a universal healthcare system, which captures nearly all related healthcare visits and hospitalization. This aspect enhances the applicability of its findings to the broader population. The use of a longitudinal database enables the examination of trends over time, providing valuable insights into the evolving impact of COVID-19 on mental health and chronic conditions. Ultimately, these strengths highlight the study's valuable contributions

to our comprehension of the complex relationship among chronic conditions, mental health, and public health during the COVID-19 pandemic, framing it as a syndemic.

However, it is vital to acknowledge the limitations of our study. The variation in testing rates during the pandemic could have had an impact on the results and analysis. Fluctuations in testing rates may introduce biases in the data, influencing the identification and confirmation of COVID-19 cases. Differing testing rates across time or demographic groups can affect the reliability and generalizability of findings. It is crucial for researchers to consider and account for variations in testing rates when interpreting results to ensure a more accurate and comprehensive understanding of the pandemic's impact.

The available variables in the databases restricted our ability to explore individual level crucial factors such as employment, financial status, and income, which could have influenced health outcomes. This limitation constrained our exploration of syndemic data using alternative analytical methods, such as structural equation modeling or agent-based modeling, which could offer valuable insights into the interactions among various conditions.

Due to the constraints of relying solely on demographic information from OMI, we were unable to factor in certain occupations, such as healthcare workers and others mandated to undergo testing. It is important to acknowledge that our study concluded in March 2021, prior to a significant portion of the population receiving COVID-19 vaccinations, which may limit the generalizability of our findings to populations. Furthermore, potential selection bias may exist, as the data may primarily represent individuals accessing healthcare services or those with specific insurance coverage during the initial year of the pandemic. Therefore, our study may not fully capture the experiences and health outcomes of individuals who do not

access healthcare or are underrepresented in the database. Also, severity levels of anxiety and depression conditions could not be identified due to unavailable information. A limitation of our research study was the restricted access to data concerning the immigrant and indigenous populations. This limited access was primarily due to challenges in obtaining comprehensive and representative datasets that specifically capture the healthcare experiences and characteristics of these specific population groups. Factors contributing to this limitation include potential underrepresentation in available databases, privacy concerns, and the complexities associated with collecting and categorizing data on immigrant and indigenous communities.

We incorporated data from individuals who utilized virtual care services during the initial phase of the pandemic, identified through OHIP dictionary. However, relying on administrative billing codes meant that we were unable to ascertain the specific virtual platform used by physicians who billed the temporary codes as well as the requisite detail to assess the content or quality of care of the visits.

Despite the acknowledged limitations, our study effectively delved into the benefits of utilizing a sizable population-based longitudinal administrative database. This approach provided increased statistical power and greater applicability, allowing us to analyze trends over time and extract meaningful insights from valid healthcare data reflecting real-world practices.

5.3. Implications for Public Health

The research findings in this study hold significant implications for public health planning and action. It highlights the need to explore and understand how epidemics interact at both

population and individual levels. This research emphasizes the need for a unique and sophisticated approach to the COVID-19 pandemic, given its syndemic and complex nature. The syndemic framework offers a robust model for investigating and examining the potential benefits of co-designing services for COVID-19, non-communicable diseases (NCDs), and mental health concurrently. This holistic perspective can guide health policymakers and program implementers in their efforts to improve the overall health of populations by addressing these pandemics comprehensively.

Moreover, this dissertation emphasizes the importance of incorporating mental health considerations into pandemic preparedness plans. Beyond addressing physical health consequences, these plans should acknowledge the psychological implications of a pandemic. This includes the provision of accessible mental health services, targeted interventions to address stressors associated with the pandemic, and the establishment of robust community support systems. Building resilient healthcare systems that can adapt to sudden surges in demand, such as during a pandemic, is essential. Adequate resource allocation, healthcare workforce preparedness, and infrastructure planning should be integral components of public health strategies.

Furthermore, the dissertation underscores the importance of generating evidence to support appropriate and effective interventions aimed at improving the health and psychosocial well-being of vulnerable populations. The pandemic has disproportionately affected the most vulnerable and socially disadvantaged communities, revealing long-standing disparities in healthcare access and outcomes. Addressing these disparities is an urgent public health

priority, requiring a multifaceted approach that balances the response to COVID-19 with the allocation of resources to effectively manage chronic diseases.

Intersectionality and syndemic are two distinct but interconnected concepts that can be relevant in studies, especially when examining health disparities and complex interactions among various factors. There can be overlap between intersectionality and syndemic perspectives, especially when examining health disparities. For instance, certain social determinants identified through an intersectional lens may contribute to the clustering of health conditions observed in a syndemic. In summary, intersectionality focuses on the interconnectedness of social identities, while syndemic perspectives explore the interaction of multiple health conditions. Both concepts are valuable in health data studies to address health disparities and gain insights into the complex interplay between social and health factors. Researchers may employ these frameworks to design studies that account for the multifaceted nature of health experiences and outcomes in diverse populations.

In conclusion, the research findings presented in this dissertation provide valuable insights into the multifaceted challenges posed by the COVID-19 syndemic. These insights have significant implications for public health planning and action, emphasizing the need for a holistic approach that addresses COVID-19, chronic diseases, and mental health simultaneously. Such an approach is essential to reduce health disparities, improve overall population health, and build a more resilient and just health system for the future.

5.4. Directions for future Research

To comprehensively address the nuances of mental health disparities, future research endeavors should consider augmenting existing ICES data dictionaries with targeted surveys to capture the experiences of individuals who may not have utilized the healthcare system for mental health concerns. While ICES data provides valuable insights into diagnosed cases within the healthcare system, supplementary surveys can shed light on those who remain outside this purview. Surveys have the potential to uncover barriers to healthcare access, stigma-related issues, and the prevalence of subclinical symptoms that might not have triggered formal diagnoses but still significantly impact individuals' well-being. Additionally, these surveys can explore cultural factors, community perceptions, and personal coping mechanisms, providing a more holistic understanding of mental health in diverse populations. Despite potential biases in survey responses, the combination of ICES data and survey results can yield a more nuanced and comprehensive depiction of mental health disparities, allowing researchers to develop targeted interventions that address the full spectrum of mental health needs within communities. This integrated approach ensures a more inclusive analysis that goes beyond the confines of healthcare utilization data, ultimately enhancing the capacity to design effective strategies for promoting mental health equity.

Future research should prioritize long-term, longitudinal studies to comprehensively track the evolving impact of the COVID-19 pandemic on mental health, chronic diseases, and healthcare utilization over time. These studies should encompass diverse demographic

groups, including immigrants and indigenous communities, to identify unique challenges and disparities in health outcomes.

Enhancing the data dictionaries to include more comprehensive information on mental health visits is imperative for future studies. A refined mental health data dictionary would enable researchers to capture nuanced details about mental health interactions, including the type and frequency of visits, specific interventions, and outcomes. This level of granularity is crucial for a more nuanced understanding of mental health dynamics, facilitating the identification of patterns, disparities, and the effectiveness of interventions. Improving the data dictionary ensures that future studies can draw more accurate and meaningful conclusions, contributing to the advancement of mental health research and the development of targeted interventions and policies.

Additionally, research efforts should investigate the broader social determinants of health, such as employment status and financial stability, to understand how these factors influence mental health outcomes and healthcare access during pandemics. This calls for an improvement of data dictionaries in terms of providing individual level information on occupation, employment, and socioeconomic status.

Health disparities persist as a pressing issue in contemporary healthcare, with a growing body of evidence emphasizing the disproportionate burden borne by minority and vulnerable populations. In order to effectively design and implement targeted interventions, it is imperative to enhance our understanding of the intricate factors contributing to these disparities. This suggestion advocates for the expansion of ICES dictionaries, particularly

those encompassing information on ethnic origin and immigration status, to facilitate a more nuanced examination of health outcomes within these communities.

Evaluating the effectiveness and impact of remote healthcare services, such as telehealth and virtual medicine, is crucial, especially in managing chronic diseases and providing mental health support. As vaccination campaigns progress, research should explore how COVID-19 vaccination influences mental health, chronic disease management, and healthcare utilization. Healthcare system resilience during pandemics, including adaptability, resource availability, and the maintenance of essential services, warrants further investigation to enhance preparedness for future pandemics. Understanding the influence of public health mitigation strategies on behavior and mental health during pandemics is essential for optimizing crisis communication strategies.

The syndemic approach, which examines the interconnectedness of COVID-19, chronic diseases, and mental health, should be explored for its potential benefits in integrated programming. Incorporating an intersectional perspective into syndemic research has the potential to tackle factors frequently neglected in traditional public health or syndemic investigations. This approach not only serves to illuminate the complexities inherent in syndemic but also provides a crucial lens for understanding how specific subgroups may be uniquely affected, thus, highlighting the necessity for multi-level interventions. Drawing on this insight, future studies are encouraged to explore the interplay between syndemic conditions and intersectionality, acknowledging the unique impact on specific subgroups and advocating for interventions that address the broader socio-structural determinants contributing to health disparities.

Comparative international studies can provide insights into the impact of different healthcare systems and responses on outcomes. Investigating barriers to accessing healthcare during pandemics, especially for individuals with chronic conditions, is critical for ensuring equitable access to care. Lastly, research should examine the enduring health and economic consequences of the COVID-19 pandemic, particularly on vulnerable populations, to inform policies aimed at addressing the aftermath of the crisis and building resilience for the future.

Appendix A

Study I Supplement (Chapter 2)

Table S1.1: Multivariable Cox regression analysis of factors associated with anxiety/depression related health services utilization among Ontario population stratified by age groups.

Variables	Young Adults (18-45 yrs.)	Middle-aged adults (46-65 yrs.)	Older adults (65-104 yrs.)
COVID-19 Test Status			
No PCR	Ref	Ref	Ref
COVID-19 Negative	5.56 (5.51-5.61) **	4.05 (4.00- 4.09)**	1.59 (1.55-1.62)**
COVID-19 Positive	5.46 (5.33-5.60)**	4.24 (4.10- 4.38)**	0.95 (0.88-1.03)
Sex			
Female	1.05 (1.05- 1.06) **	1.05 (1.04-1.06) **	1.10 (1.08-1.12) **
Male	Ref	Ref	Ref
Rural			
Yes	1.02 (1.01-1.03) **	0.99 (0.97-1.00)	0.94 (0.91-0.97)
No	Ref	Ref	Ref
Asthma			
Yes	1.06 (1.04-1.09) **	1.08 (1.04-1.12) **	1.09 (1.01-1.17) *
No	Ref	Ref	Ref
COPD			
Yes	0.99 (0.95-1.03)	0.99 (0.96- 1.02)	0.92 (0.88-0.97)
No	Ref	Ref	Ref
Congestive Heart Failure			
Yes	1.00 (0.87-1.14)*	0.88 (0.83-0.94)	0.60 (0.56-0.64)
No	Ref	Ref	Ref
Hypertension			
Yes	1.02 (1.00-1.04)*	1.02 (1.00-1.03) *	1.00 (0.97-1.02)*

No	Ref	Ref	Ref
Diabetes			
Yes	1.01 (0.98-1.03)*	0.97 (0.95-1.00)	0.87 (0.84-0.91)
No	Ref	Ref	Ref
Ontario Marginalization Index			
Dependency quintile			
1	Ref	Ref	Ref
2	1.00 (0.99-1.01)	0.99 (0.98-1.00)	0.98 (0.95-1.01)
3	1.00 (0.99-1.01)	0.99 (0.98-1.01)	0.99 (0.97-1.02)
4	1.00 (0.99-1.01)	0.99 (0.97-1.00)	0.98 (0.96-1.01)
5	1.01 (1.00-1.02)	0.98 (0.97-0.99)	0.96 (0.94-0.99)
Deprivation quintile			
1	Ref	Ref	Ref
2	0.98 (0.97-0.99)	1.00 (0.98-1.01)	0.99 (0.96-1.01)
3	0.99 (0.98-1.00)	0.99 (0.98-1.00)	0.97 (0.95-1.00)
4	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.94 (0.91-0.96)
5	0.98 (0.97-0.99)	0.96 (0.95-0.97)	0.93 (0.91-0.96)
Instability quintile			
1	Ref	Ref	Ref
2	1.00 (0.99-1.01)	0.99 (0.98-1.00)	0.99 (0.96-1.02)
3	1.01 (1.00-1.02)	0.99 (0.97-1.00)	0.98 (0.95-1.01)
4	1.01 (1.00-1.02)	0.98 (0.97-0.99)	0.96 (0.93-0.98)
5	1.00 (0.99-1.01)	0.96 (0.94-0.97)	0.95 (0.93-0.98)
Ethnic diversity quintile			
1	Ref	Ref	Ref
2	1.00 (0.99-1.01)	1.01 (1.00-1.03)	1.02 (0.99-1.05)
3	1.00 (0.99-1.01)	1.00 (0.98-1.01)	1.02 (1.00-1.05)
4	0.98 (0.97-0.99)	0.99 (0.98-1.01)	1.01 (0.98-1.04)
5	0.95 (0.94-0.96)	0.98 (0.96-0.99)	0.98 (0.95-1.01)

** p-value < .0001 * p-value < .01

Table S1.2: Demographic characteristics and morbidity information of the study population cohort in Ontario (Jan 2020- Mar 2021) after propensity score matching

Demographics & Morbidity information	Total sample	Individuals without PCR COVID-19 tests	PCR test with COVID-19 negative result	PCR test with COVID-19 positive result
Total n (%)	664233 (100)	485780 (73.13)	167616 (25.23)	10837 (1.63)
Mean Age Yrs. (±SD)	42.82 (14.45)	43.43 (14.51)	41.09 (14.13)	41.96 (14.21)
Anxiety/depression related health service utilization				
No	169 (0.03)	127 (0.02)	35 (0.01)	7 (0.00)
Yes	664064 (99.97)	485653 (73.11)	167581 (25.23)	10837 (1.63)
Age groups n (%)				
18-45 yrs.	393466 (59.24)	278653 (41.95)	108199 (16.29)	6614 (1.00)
46-65 yrs.	217627 (32.76)	165319 (24.89)	48715 (7.33)	3593 (0.54)
66-104 yrs.	53140 (8.00)	41808 (6.29)	10702 (1.61)	630 (0.09)
Sex n (%)				
Female	419725 (63.19)	300302 (45.21)	112270 (16.90)	7153 (1.08)
Male	244508 (36.81)	185478 (27.92)	55346 (8.33)	3684 (0.55)
Rural n (%)				
No	608616 (91.63)	443770 (66.81)	154394 (23.24)	10452 (1.57)
Yes	55617 (8.37)	42010 (6.32)	13222 (1.99)	385 (0.06)
Ontario Marginalization Index (%)				
Dependency quintile				
1	18723 (28.19)	135382 (20.38)	48160 (7.25)	3690 (0.56)
2	138335 (20.83)	100526 (15.13)	35385 (5.33)	2424 (0.36)
3	118132 (17.78)	86546 (13.03)	29713 (4.47)	1873 (0.28)
4	108911 (16.40)	80507 (12.12)	26882 (4.05)	1522 (0.23)
5	111623 (16.80)	82819 (12.47)	27476 (4.14)	1328 (0.20)
Deprivation quintile				
1	161494 (24.31)	116409 (17.53)	42968 (6.47)	2117 (0.32)

2	139878 (21.06)	102343 (15.41)	35549 (5.35)	1986 (0.30)
3	123657 (18.62)	90467 (13.62)	31000 (4.67)	2190 (0.33)
4	116977 (17.61)	85995 (12.95)	28899 (4.35)	2083 (0.31)
5	122227 (18.40)	90566 (13.63)	29200 (4.40)	2461 (0.37)
Instability quintile				
1	135253 (20.36)	99928 (15.04)	32483 (4.89)	2842 (0.43)
2	120248 (18.10)	88675 (13.35)	29799 (4.49)	1774 (0.27)
3	118297 (17.81)	87188 (13.13)	29478 (4.44)	1631 (0.25)
4	123344 (18.57)	89990 (13.55)	31491 (4.74)	1863 (0.28)
5	167091 (25.16)	119999 (18.07)	44365 (6.68)	2727 (0.41)
Ethnicity diversity quintile				
1	97384 (14.66)	72816 (10.96)	23872 (3.59)	696 (0.10)
2	113164 (17.04)	82827 (12.47)	29246 (4.40)	1091 (0.16)
3	132414 (19.93)	95473 (14.37)	35266 (5.31)	1675 (0.25)
4	154578 (23.27)	111325 (16.76)	40691 (6.13)	2562 (0.39)
5	166693 (25.10)	123339 (18.57)	38541 (5.80)	4813 (0.72)
Asthma				
No	654826 (98.58)	497734 (72.22)	164498 (24.77)	10594 (1.59)
Yes	9407 (1.42)	6046 (0.91)	3118 (0.47)	243 (0.04)
COPD				
No	655047 (98.62)	479059 (72.12)	165263 (24.88)	10725 (1.61)
Yes	9186 (1.38)	6721 (1.01)	2353 (0.35)1	112 (0.02)
Hypertension				
No	623147 (93.81)	455802 (68.62)	157383 (23.69)	9962 (1.50)
Yes	41086 (6.19)	29978 (4.51)	10233 (1.54)	875 (0.13)
Congestive heart failure				
No	662106 (99.68)	484455 (72.93)	166869 (25.12)	10782 (1.62)
Yes	2127 (0.32)	1325 (0.20)	747 (0.11)	55 (0.01)
Diabetes				
No	647373 (97.46)	473590 (71.30)	163410 (24.60)	10373 (1.56)
Yes	16860 (2.54)	12190 (1.84)	4206 (0.63)	464 (0.07)

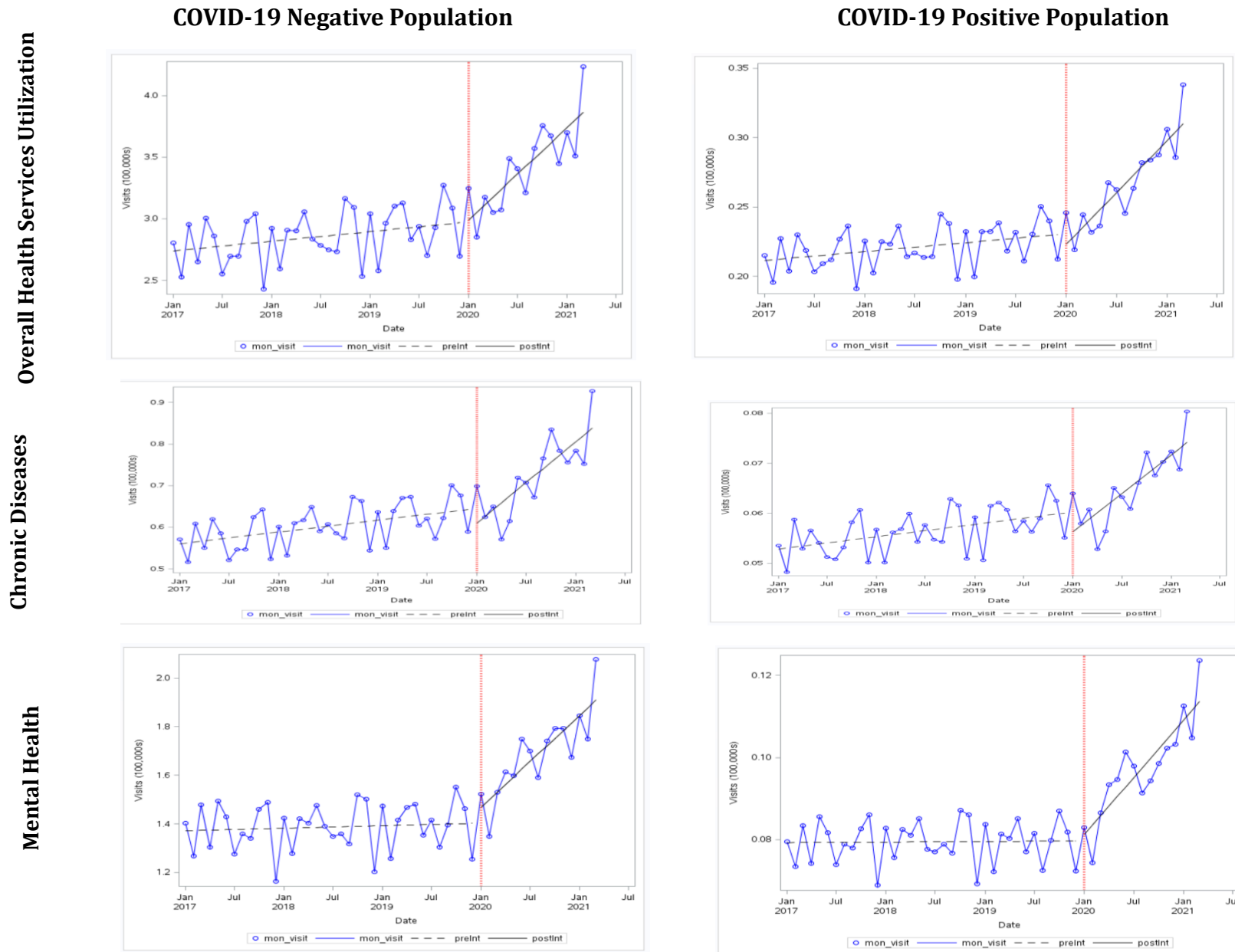
Study II Supplement (Chapter 3)

Table S 2.1: Segmented Regression analysis of change in Health Service Utilization following the COVID-19 pandemic onset in Ontario stratified by COVID-19 disease status

	Baseline monthly visits Pre COVID (Intercept)		Change in monthly visits (Slope) Pre-COVID		Level change of monthly visits post-COVID 19 onset		Change in monthly visits (slope difference) post-vs pre- COVID onset	
	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)
Overall Health Services Utilization (per 100,000)								
COVID Negative Population	2.7333	<0.0001 (2.5340-2.8731)	0.0065	0.050 (-0.0000-0.0130)	-0.0426	0.7403 (-0.3031-0.2178)	0.0562	<0.0001 (0.0307-0.0816)
COVID Positive Population	0.2108	<0.0001 (0.2009-0.2206)	0.0005	0.0237 (0.0000-0.0010)*	-0.0133	0.1456 (-0.0317-0.0050)	0.0057	<0.0001 (0.0039-0.0075)
Health Services Utilization for Chronic Diseases (per 100,000)								
COVID Negative Population	0.5577	<0.0001 (0.5244-0.5909)	0.0023	0.0035 (0.0008-0.0039)	-0.0494	0.1107 (-0.1113-0.0125)	0.0139	<0.0001 (0.0079-0.0199)
COVID Positive Population	0.0527	<0.0001 (0.0499-0.0553)	0.000205	0.002 (0.0000-0.0003)	-0.0050	0.0489 (-0.0101-0.0000)	0.0010	<0.0001 (0.0005-0.0015)
Health Services Utilization for Mental Health (per 100,000)								
COVID Negative Population	1.3709	<0.0001 (1.3039-1.4378)	0.0008	0.5813 (-0.0023-0.0040)	0.0345	0.5760 (-0.0902-0.1591)	0.0307	<0.0001 (0.0185-0.0428)
COVID Positive Population	0.0792	<0.0001 (0.0755-0.0829)	0.0000	0.8961 (-0.0001-0.0001)	-0.0007	0.8247 (-0.0076-0.0061)	0.0023	<0.0001 (0.0016-0.0029)

*The overall monthly services utilization depicts the overall monthly visits all inclusive (Physician/ED/Hospitalization), in **all** those who had PCR tests done either with positive OR negative results and comprise of ALL kinds of conditions (chronic diseases as well as mental health issues)

Figure S2.1: Monthly Health Services Utilization stratified by COVID-19 disease status (Jan 2017- Mar2021)



TableS2.2: Segmented Regression analysis of change in All Cause Deaths following the COVID-19 pandemic start in Ontario (Jan 2020-Mar 2021)

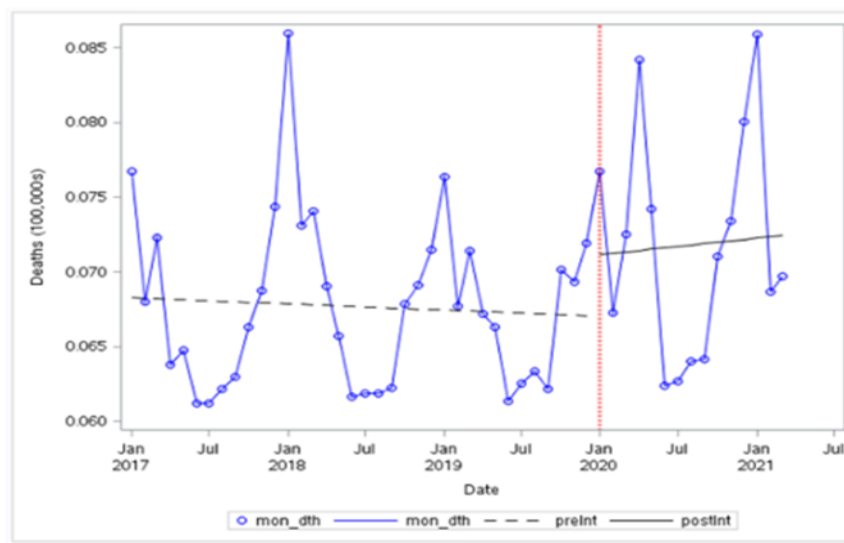
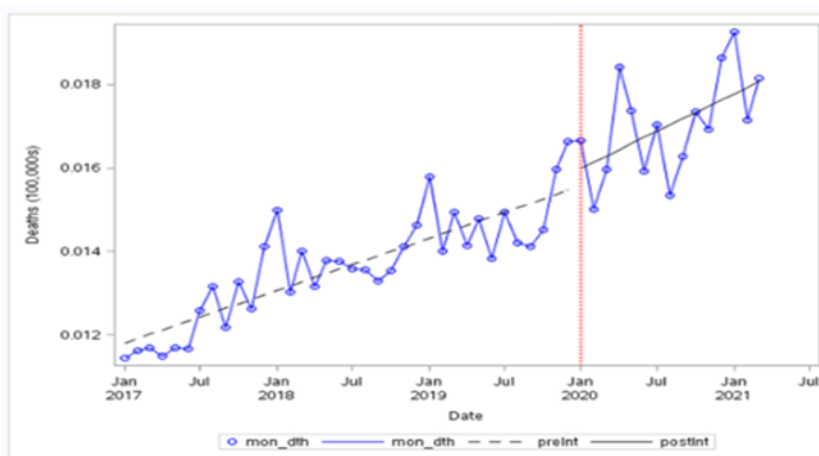
	Baseline monthly all cause deaths Pre-COVID (Intercept)		Change in monthly all cause deaths (slope) Pre COVID		Level change in monthly all cause deaths post-COVID onset		Change in monthly all cause deaths (slope difference) Post- vs Pre- COVID onset	
	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)	Estimate	P-Value (95% CI)
All-Cause Deaths (100,000 population)								
Deaths in 18-45 yrs.	0.002690	<0.0001 (0.0024-0.0028)	0.0000351	<0.0001 (0.00002-0.00004)	0.000147	0.4393 (-0.0002-0.0005)	0.0000418	0.0276 (0.0000-0.0000)*
Deaths in 46-65 yrs.	0.0117	<0.0001 (0.0111-0.0122)	0.000105	<0.0001 (0.0000-0.0001)	0.000379	0.4710 (-0.0006-0.0014)	0.0000440	0.3915 (-0.0000-0.0001)
Deaths in 66 yrs. & above	0.0683	<0.0001 (0.0639-0.0726)	-0.000034	0.7377 (-0.0002-0.0001)	0.003995	0.3240 (-0.0041-0.0121)	0.000126	0.7479 (-0.0006-0.0009)

Figure S2.2: Monthly All-cause Deaths in Ontario Population stratified by age groups (Jan 2017- Mar2021)

(a) Monthly deaths in Young adults (18-45 yrs.)



(b) Monthly deaths in middle aged adults (45-65 yrs.)



(c) Monthly deaths in older adults (66 & above yrs.)

Study III Supplement (Chapter 4)

Table S3.1: Multiple Logistic Regression model to identify interaction between COVID-19 and mental health with morbidity as outcome

Variables		Crude ORs (95% CI)	
COVID-19 disease Status			
COVID-19-Negative	Ref		
COVID-19-Positive	1.18 (1.17-1.19)		
Mental Health Status			
No	Ref		
Yes	0.015 (0.014-0.016)		
COVID-19*Mental Health			
COVID-19 Positive vs COVID-19 Negative			
Mental Health=No	1.18 (1.17-1.19)	1.13 (1.11-1.14)	
Mental Health =Yes	1.57 (1.32-1.85)	1.29 (1.09-1.52)	
Age			
18-45 yrs.	Ref		
46-65 yrs.	4.20 (4.17-4.23)	4.41 (4.38-4.45)	
66+ yrs.	9.02 (8.95-9.09)	10.23 (10.14-10.32)	
Sex			
Female	Ref		
Male	1.22 (1.21-1.22)	1.18 (1.17-1.19)	
Rural			
No	Ref		
Yes	0.92 (0.91-0.93)	0.82 (0.81-0.83)	
Deprivation Quintile			
1	Ref		
2	1.14 (1.13-1.15)	1.13 (1.12-1.14)	
3	1.25 (1.24-1.26)	1.26 (1.25-1.27)	
4	1.35 (1.34-1.36)	1.36 (1.35-1.37)	
5	1.43 (1.41-1.44)	1.47 (1.46-1.49)	
Dependency Quintile			
1	Ref		
2	1.09 (1.08-1.09)	0.98 (0.97-0.99)	
3	1.12 (1.11-1.13)	0.98 (0.97-0.99)	
4	1.18 (1.17-1.19)	0.98 (0.97-0.99)	
5	1.35 (1.34-1.36)	1.00 (0.99-1.01)	
Instability Quintile			
1	Ref		
2	0.97 (0.96-0.98)	0.96 (0.95-0.97)	
3	0.99 (0.99-1.00)	0.95 (0.94-0.96)	
4	1.02 (1.01-1.03)	0.91 (0.90-0.92)	
5	1.02 (1.01-1.03)	0.88 (0.87-0.89)	
Ethnic Diversity Quintile			
1	Ref		
2	0.92 (0.91-0.93)	1.03 (1.01-1.04)	
3	0.86 (0.85-0.87)	1.06 (1.05-1.07)	
4	0.88 (0.87-0.89)	1.18 (1.16-1.19)	
5	1.15 (1.14-1.16)	1.67 (1.55-1.59)	

Table S3.2: Multiple Logistic Regression model for factors associated with morbidity in individuals with Anxiety or Depression (“First time tested” Cohort)

Variables	Crude ORs (95% CI)	Adjusted ORs (95% CI)
COVID-19 Status		
COVID-19-Negative/MH-Positive	Ref	
COVID-19-Positive/MH-Positive	1.37 (1.03-1.82)	1.17 (0.88-1.55)
Age		
18-45 yrs.	Ref	
46-65 yrs.	3.12 (2.69-3.63)	3.16 (2.71-3.67)
66+ yrs.	5.29 (4.46-6.27)	5.50 (4.63-6.55)
Sex		
Female	Ref	
Male	1.14 (1.00-1.30)	1.15 (1.01-1.31)
Rural		
No	Ref	
Yes	0.87 (0.68-1.12)	0.91 (0.69-1.20)
Deprivation Quintile		
1	Ref	
2	1.32 (1.08-1.62)	1.28 (1.05-1.58)
3	1.22 (0.98-1.51)	1.20 (0.97-1.49)
4	1.42 (1.15-1.74)	1.41 (1.38-1.76)
5	1.74 (1.43-2.11)	1.75 (1.40-2.18)
Dependency Quintile		
1	Ref	
2	0.87 (0.72-1.06)	0.83 (0.68-1.00)
3	0.91 (0.75-1.11)	0.87 (0.71-1.07)
4	0.97 (0.80-1.18)	0.90 (0.72-1.11)
5	1.19 (0.99-1.43)	1.03 (0.83-1.28)
Instability Quintile		
1	Ref	
2	0.94 (0.76-1.16)	0.98 (0.79-1.21)
3	0.90 (0.72-1.11)	0.88 (0.70-1.10)
4	1.02 (0.83-1.25)	0.92 (0.74-1.15)
5	1.05 (0.87-1.26)	0.85 (0.69-1.05)
Ethnic Diversity Quintile		
1	Ref	
2	0.93 (0.73-1.17)	1.01 (0.79-1.29)
3	0.81 (0.64-1.03)	0.94 (0.72-1.21)
4	1.00 (0.80-1.24)	1.15 (0.90-1.48)
5	1.37 (1.11-1.67)	1.46 (1.14-1.88)

Group '1'= COVID-19 -VE/MH+VE, Group '3'= COVID-19 +VE/MH+VE

The table shows the regression parameter estimates for each variable along with corresponding 95% CI for model outcome= 'morbidity'

Table S3.3: Multiple Logistic Regression model for factors associated with morbidity in individuals with Anxiety or Depression (“Multiple time tested” Cohort)

Variables	Crude ORs (95% CI)	Adjusted ORs (95% CI)
COVID-19 Status		
COVID-19-Negative/ MH-Positive	Ref	
COVID-19-Positive/MH-Positive	1.68 (1.36-2.08)	1.43 (1.15-1.78)
Age		
18-45 yrs.	Ref	
46-65 yrs.	2.83 (2.37-3.37)	2.79 (2.34-3.34)
65-104 yrs.	4.21 (3.45-5.13)	4.07 (3.33-4.99)
Sex		
Female	Ref	
Male	1.56 (1.34-1.81)	1.49 (1.28-1.74)
Rural		
No	Ref	
Yes	0.83 (0.61-1.12)	0.84 (1.59-1.18)
Deprivation Quintile		
1	Ref	
2	1.02 (0.80-1.31)	1.01 (0.79-1.30)
3	1.09 (0.85-1.40)	1.06 (0.82-1.37)
4	1.39 (1.09-1.76)	1.32 (1.03-1.70)
5	1.57 (1.25-1.97)	1.48 (1.14-1.92)
Dependency Quintile		
1	Ref	
2	1.04 (0.82-1.30)	1.00 (0.79-1.26)
3	1.05 (0.83-1.34)	1.03 (0.81-1.32)
4	1.12 (0.88-1.43)	1.07 (0.83-1.38)
5	1.39 (1.12-1.73)	1.21 (0.93-1.56)
Instability Quintile		
1	Ref	
2	0.92 (0.71-1.20)	0.93 (0.71-1.22)
3	1.01 (0.78-1.30)	0.95 (0.75-1.25)
4	1.01 (0.79-1.30)	0.88 (0.67-1.15)
5	1.21 (0.97-1.51)	0.93 (0.73-1.20)
Ethnic Diversity Quintile		
1	Ref	
2	0.62 (0.46-0.82)	0.66 (0.48-0.88)
3	0.82 (0.63-1.06)	0.90 (0.68-1.20)
4	0.90(0.71-1.16)	1.00 (0.75-1.33)
5	1.16 (0.92-1.47)	1.17 (0.87-1.56)

Group ‘1’= COVID-19 -VE/MH+VE, , Group ‘3’= COVID-19 +VE/MH+VE

The table shows the regression parameter estimates for each variable along with corresponding 95% CI for model outcome= ‘morbidity’

Table S3.4: Multiple Logistic Regression model for factors associated with morbidity across all comparison groups

Variables	COVID-19-VE/MH-VE	COVID-19-VE/MH+VE	COVID-19+VE/MH-VE	COVID-19+VE/MH+VE
Age				
	1.05 (1.05-1.05)	1.03 (1.03-1.04)	1.05 (1.05-1.05)	1.03 (1.02-1.04)
Gender				
Female	Ref	Ref	Ref	Ref
Male	1.21 (1.20-1.22)	1.24 (1.12-1.38)	1.19 (1.16-1.21)	1.94 (1.41-2.68)
Rural				
No	Ref	Ref	Ref	Ref
Yes	0.82 (0.81-0.83)	0.86 (0.69-1.07)	0.78 (0.73-0.84)	1.50 (0.49-4.60)
Deprivation Quintile				
1	Ref	Ref	Ref	Ref
2	1.14 (1.13-1.15)	1.23 (1.03-1.45)	1.10 (1.05-1.14)	0.72 (0.40-1.30)
3	1.28 (1.26-1.29)	1.19 (1.00-1.42)	1.26 (1.21-1.31)	0.81 (0.46-1.41)
4	1.39 (1.37-1.40)	1.44 (1.21-1.72)	1.40 (1.35-1.46)	1.06 (0.62-1.83)
5	1.53 (1.51-1.55)	1.73 (1.45-2.06)	1.45 (1.40-1.52)	1.28 (0.74-2.22)
Dependency Quintile				
1	Ref	Ref	Ref	Ref
2	0.98 (0.98-0.99)	0.90 (0.70-1.05)	0.98 (0.95-1.01)	0.79 (0.50-1.26)
3	0.97 (0.96-0.98)	0.92 (0.78-1.09)	0.94 (0.91-0.97)	0.88 (0.53-1.46)
4	0.97 (0.96-0.98)	0.94 (0.79-1.12)	0.89 (0.85-0.92)	0.82 (0.48-1.42)
5	0.94 (0.93-0.95)	1.04 (0.87-1.24)	0.86 (0.83-0.90)	0.93 (0.53-1.61)
Instability Quintile				
1	Ref	Ref	Ref	Ref
2	0.96 (0.95-0.97)	0.95 (0.80-1.14)	0.94 (0.91-0.97)	0.88 (0.50-1.53)
3	0.94 (0.93-0.95)	0.88 (0.74-1.16)	0.89 (0.85-0.92)	0.98 (0.55-1.72)
4	0.88 (0.87-0.89)	0.87 (0.73-1.04)	0.86 (0.83-0.90)	0.89 (0.51-1.55)
5	0.84 (0.83-0.85)	0.84 (0.71-1.00)	0.77 (0.74-0.80)	0.91 (0.56-1.49)
Ethnicity Quintile				
1	Ref	Ref	Ref	Ref
2	1.03 (1.01-1.04)	0.86 (0.71-1.04)	1.05 (0.99-1.12)	0.80 (0.28-2.30)
3	1.07 (1.05-1.08)	0.90 (0.74-1.09)	1.10 (1.03-1.16)	1.65 (0.65-4.18)
4	1.18 (1.17-1.20)	1.08 (0.89-1.31)	1.34 (1.26-1.41)	1.44 (0.57-3.62)
5	1.57 (1.555-1.59)	1.30 (1.07-1.58)	1.88 (1.78-1.99)	1.89 (1.76-4.73)

*The table entries are the regression parameter estimates for each variable, along with the respective 95% CIs.I for model outcome= 'morbidity'

Table S3.5: : Demographic characteristics of the study sample stratified by age groups

Demographics	Overall Sample	Morbidity	
Age Group 18-45 years		No	Yes
Total N (Col %)	1465893	1320574	145319
Mean Age (Yrs.) (±SD)	31.22(8.02)	30.81(7.95)	34.97(7.70)
COVID-19 & Mental Health			
COVID-19 -VE/ MH-VE	1187025(80.98)	1055801(79.95)	131224(90.30)
COVID-19 -VE/ MH+VE	170625(11.64)	170176(12.89)	449(0.31)
COVID-19 +VE/ MH-VE	98027(6.69)	84429(6.39)	13598(9.36)
COVID-19 +VE/ MH+VE	10216(0.70)	10168 (0.77)	48(0.03)
Age Group 46-64 years		No	Yes
Total N (Col %)	954774	652613	302161
Mean Age (Yrs.) (±SD)	54.45(5.24)	53.98(5.17)	55.48(5.22)
COVID-19 & Mental Health			
COVID-19 -VE/ MH-VE	801883(83.99)	527836(80.88)	274047(90.70)
COVID-19 -VE/ MH+VE	83367(8.73)	82706(12.67)	661(0.22)
COVID-19 +VE/ MH-VE	63733(6.68)	36349(5.57)	27384(9.06)
COVID-19 +VE/ MH+VE	5791(0.61)	5722(0.88)	69(0.02)
Age Group 65+ years		No	Yes
Total N (Col %)	442756	222133	220623
Mean Age (Yrs.) (±SD)	73.91(7.19)	73.86(7.43)	73.97(6.95)
COVID-19 & Mental Health			
COVID-19 -VE/ MH-VE	385617(87.09)	178549(80.38)	207068(93.86)
COVID-19 -VE/ MH+VE	31363 (7.08)	30958(13.94)	405(0.18)
COVID-19 +VE/ MH-VE	23527 (5.31)	10412(4.69)	13115(5.94)
COVID-19 +VE/ MH+VE	2249 (0.51)	2214(1.00)	35(0.02)

Sample size and mean age (Mean Age (Yrs.) (±SD) in four comparison groups			
COVID-19 -VE/ MH-VE N= 2374525	COVID-19 -VE/ MH+VE N= 285355	COVID-19 +VE/ MH-VE N= 185287	COVID-19 +VE/ MH+VE N= 18256
Mean Age (46.06±17.56)	Mean Age (42.20±16.67)	Mean Age (44.60±17.17)	Mean Age (43.73±17.28)

Appendix B

Table 1: Details of ICES data dictionaries utilized in the study.

	Data Dictionaries (Jan 2020-Mar 2021)		Category
1.	C19INTGR	COVID19 Integrated Testing Data	Health Services
2.	RPDB	Registered Persons Database	Population& Demographic
3.	Asthma	Ontario Asthma Dataset	ICES-Derived Cohort
4.	COPD	Chronic Obstructive Pulmonary Disease	ICES-Derived Cohort
5.	HYPER	Ontario Hypertension dataset	ICES-Derived Cohort
6.	ODD	Ontario Diabetes Dataset	ICES-Derived Cohort
7.	CHF	Congestive Heart Failure	ICES-Derived Cohort
8.	OMHRS	Ontario Mental Health Reporting System	Health Services
9.	DAD	Discharge Abstract Database DAD	Health Services
10.	OHIP	Ontario Health Insurance Plan Claims Database	Health Services
11.	NACRS	National Ambulatory Care Reporting System	Health Services
12.	ORGD	Vital Statistics-Death	Population& Demographic
11.	ONMARG	Ontario Marginalization Index	Coding & Geography

Table 2. Description of cohort definition and variables within the study cohort (administrative database), and the codes used.

Variable name	Source of data	Description	Variable name in database	Database codes
exposure				
Covid result based on PCR test	C19INTGR	COVID19 Integrated Testing Data Covid standard lab-based PCR test Result between January 2020 and March 31, 2021.	COVIDRESULT	P= Positive N=Negative
Outcome/Event				
Health services utilization for a mental health reason	DAD OMHRS NACRS OHIP	- Primary diagnosis of either anxiety or depression from a psychiatric bed (OMHRS) or medical bed (DAD) between January 1, 2020, and March 31, 2021, * OR - At least one emergency department (NACRS) or physician visits (OHIP) during study period for Anxiety/Depression from January 1, 2020, and March 31, 2021*	DX10CODE1 (DAD) MHA_DXGROUP (OMHRS) DX10CODE (NACRS) DXCODE (OHIP)	ICD-10 Codes (DAD) and (NACRS) to identify Anxiety /Depression DSM-IV criteria (OMHRS) OHIP diagnostic codes
All-cause Mortality				
Vital Statistics-Death	ORGD	All cause mortality between January 1, 2020, and March 31, 2021	DTHDATE	1= died 0=Alive
Demographic Factors				
Age at index date	RPDB	Age at index date	BDATE	Variable calculated based on index date and birth date
Sex	RPDB	Recorded sex	SEX	1 = Male 2 = Female
Rural residence	RPDB	Rural place of residence, defined as residing in a community of $\leq 10,000$	RURAL	1 = Rural flag 0 = non-Rural

Variable name	Source of data	Description	Variable name in database	Database codes
Ontario Marginalization Index				
Residential Instability	ONMARG	Neighbourhood-level indicator of residential instability constructed based on census data	INSTABILITY_Q	1 = Least Marginalized 5 = Most Marginalized
Material Deprivation	ONMARG	Neighbourhood-level indicator of material deprivation constructed based on census data	DEPRIVATION_Q	1 = Least Marginalized 5 = Most Marginalized
Ethnic Diversity	ONMARG	Neighbourhood-level indicator of ethnic concentration constructed based on census data	ETHNICDIV_Q	1 = Least Marginalized 5 = Most Marginalized
Dependency	ONMARG	Neighbourhood-level indicator of social dependency constructed based on census data	DEPENDENCY_Q	1 = Least Marginalized 5 = Most Marginalized
Chronic Diseases				
Asthma	ASHTMA	Ontario Asthma dataset	ASTHMA	1= Diagnosed with Asthma 0 = No asthma
CHF	CHF	Congestive Heart Failure	CHF	1= Diagnosed with CHF 0 = No CHF
HTN	HTN	Hypertension	Hyper	1= Diagnosed with HTN 0 = No HTN
COPD	COPDC	Chronic Obstructive Pulmonary Disease	COPD	1= Diagnosed with COPD 0 = No COPD
Diabetes	ODD	Ontario Diabetes Dataset	ODD	1= Diagnosed with Diabetes 0 = No Diabetes
DAD Variables				

Variable name	Source of data	Description	Variable name in database	Database codes
Diagnosis of medical condition	DAD	To identify the individuals with chronic conditions of interest	DX10CODE1 (DAD)	All ICD-10 Codes for Anxiety and Depression
Hospital Admission Date	DAD	Date of Hospital Admission	DAD_ADMNDATE	
NACRS Variables				
Registration Date		NACRS Registration Date	REGDATE	
Diagnosis of medical condition	NACRS	To identify the individuals with chronic conditions of interest	DX10CODE1 (NACRS)	All ICD-10 Codes for chronic conditions of interest
OMHRS Variables				
Diagnosis of Mental Illnesses	OMHRS	General Mental Health and Addiction Hospitalization Episodes	MHA_DXGROUP	ANX = Anxiety MDIS_DEP = Mood Disorders - Depressive Based on DSM-IV criteria
Hospital Admission due to mental reason	OMHRS /DAD	Date of Episode Admission	EPI_ADNDATE	
OHIP Variables				
Diagnosis of medical condition	OHIP	OHIP Diagnosis Code	DXCODE	300 = Anxiety neurosis, hysteria, neurasthenia, obsessive compulsive neurosis, reactive depression 311 = Depressive or other non-psychotic disorders, not elsewhere classified

Variable name	Source of data	Description	Variable name in database	Database codes
Service date		Date on which service was provided	SERVDATE	

Table 3. List of definitions of comorbidities

Comorbidity	Case definition	Codes	Validation
Asthma ¹	At least one hospitalization admission with a diagnosis of asthma or two physician claims of asthma diagnosis in a two-year period preceding the index date	ICD-9/OHIPDX: 493 ICD-10: J45, J46	Sensitivity = 81% Specificity = 81%
COPD ²	At least 1 physician billing within 2 years or one hospitalization with a COPD diagnosis code prior to index date.	ICD-9/OHIPDX: 491, 492, 496 ICD-10: J41, J42, J43, J44	Sensitivity = 85% Specificity = 79%
Hypertension ³	At least one hospital admission with a diagnosis of hypertension or two physician claims for hypertension within two years prior to index date. Cases of gestational hypertension would be excluded.	ICD-9/OHIPDX: 401x, 402x, 403x, 404x, 405x ICD-10: I10, I11, I12, I13, I15	Sensitivity = 73% Specificity = 95%
Diabetes ⁴	Age = 18: At least four physician claims with a diabetes diagnosis code in a two-year period prior to index date OR at least one physician claims with a diabetes fee code. Age 19+: At least one hospital admission with a diagnosis of diabetes or two physician claims	ICD-9/OHIPDX: 250 ICD-10: E10, E11, E13, E14 OHIP Feecode: Q040, K029, K0303, K045, K046 ODB DINS: INSULIN or ORAL ANTI-GLYCEMICS	Age =18: Sensitivity: 83% Specificity: 99% Age 19+ Sensitivity = 90% Specificity = 98%

¹ Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Canadian respiratory journal* 2009; 16(6): 183-8.

² Gershon A, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2009; 6(5): 388-94

³ Tu K, Campbell NR, Chen Z-L, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open medicine* 2007; 1(1): e18

⁴ Lipscombe LL, Hwee J, Webster L, Shah BR, Booth GL, Tu K. Identifying diabetes cases from administrative data: a population-based validation study. *BMC health services research* 2018; 18(1): 1-8.

	for diabetes or one prescription claim for diabetes medications within 1 year. Cases of gestational diabetes would be excluded.		
Congestive heart failure ⁵	At least one hospital admission with a congestive heart failure diagnosis, one physician claim/emergency department visit with a congestive heart failure diagnosis followed within one year by a second record from either source or one hospital admission.	ICD-9/OHIPDX: 428 ICD-10: I500, I501, I509	Sensitivity = 85% Specificity = 97%
Anxiety & Depression	Primary diagnosis of either anxiety or depression from a psychiatric bed (OMHRS) or medical bed (DAD) between January 1, 2020, and March 31, 2021, * OR At least one emergency department (NACRS) or physician visits (OHIP) during study period for Anxiety/Depression from January 1, 2020, and March 31, 2021*	Anxiety disorders DSM-IV ICD-9: 300.0, 300.2, 300.3, 309.8, 308.3 ICD-10: F40, F41, F42, F93.0–F93.2 F43.0, 43.1, 43.8, 43.9 Depression DSM-IV ICD-9: 296.2, 296.3, 300.4, 311 ICD-10: F32, F33, F34.1, F38.1	Not validated

⁵ Schultz SE, Rothwell DM, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic diseases and injuries in Canada* 2013; 33(3).

Table 4: Details of Ontario Marginalization Index (OMI)³⁷

OMI Measures	Explanation
Material Deprivation	Closely connected to poverty and it refers to inability for individuals and communities to access and attain basic material needs Includes indicators of Income, quality of housing, educational attainment, and family structure characteristics
Dependency	Area-level concentrations of people who do not have income from employment. It includes seniors, children, and adults whose work is not compensated. Adults included under this measure may be taking care of households, taking care of people in the community and/or prevented from working due to disability
Residential Instability	Area-level concentrations of people who experience high rates of family or housing instability. The indicators included in this dimension measure the types and density of residential accommodations, as well as certain family structure characteristics.
Ethnic Diversity	Area-level concentrations of people who are recent immigrants and/or people belonging to a 'visible minority' group (defined by Statistics Canada as "persons, other than aboriginal peoples, who are non-Caucasian in race or non-white in color").