# PATTERNS AND PREDICTORS OF OPIOID USE IN OLDER ADULTS WITH CHRONIC NON-CANCER PAIN

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# ABSTRACT

## Background

Opioid use has increased globally which resulted in a dramatic rise in opioid overdose, abuse and mortality. Limited research is available on the patterns and predictors of opioid use in older adults in New Zealand and internationally.

## Aim

To investigate the incidence and prevalence of opioid use in general older adults. Additionally, the rate and predictors of persistent opioid use in older adults without cancer diagnosis were examined.

## Methods

This was a population-based retrospective cohort study. This was a population-based retrospective cohort study conducted using national administrative healthcare databases. The annual opioid use incidence (2008-2018) and prevalence (2007-2018) in older adults were determined and stratified by sex and opioid type. The rate and predictors of persistent opioid use among older adults without cancer diagnosis from 2013-2018 were also determined. Persistent opioid use is defined as having filled ≥1 opioid prescription in the 91 to 180 days after index opioid prescription. Multivariable logistic regression models were used to identify predictors of persistent opioid use. SQL and SPSS software were used to link and analyse data, respectively.

## Results

A total of 820,349 older adults were initiated on opioids during the study period. The overall incidence of opioid use in older adults showed a steady increase from 2008-2015, similarly, the prevalence has steadily increased from 2007-2015, and then both rates fluctuated thereafter. A slight decrease was observed in 2018. Codeine and tramadol were the most commonly dispensed opioids during the study period. Females had higher incidence and prevalence for all opioids. Among 268,857 non-cancer older patients with ≥1 opioid dispensing between 2013-2018, 2.2% became persistent opioid users. The use of fentanyl, strong opioids, slow-release preparations, presence of ≥3 co-morbidities, and the use of anti-epileptics and non-opioid analgesics were the strongest predictors of persistent opioid use.

## Conclusions

The study findings showed an increase in opioid incidence and prevalence in older adults over time. A considerable number of older adults became persistent opioid users and a number of factors were found to contribute to persistent opioid use. Understanding predictors of persistent opioid use will enable prescribers and policy-makers to target early interventions to prevent future opioid-related adverse events.

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# GLOSSARY

| | |
|---|---|
| **CIHI** | Canadian Institute for Health Information |
| **CCI** | Charlson Co-morbidity Index |
| **CI** | Confidence Interval |
| **CDC** | The U.S. Center for Disease Control and Prevention |
| **CNCP** | Chronic non-cancer pain |
| **CNS** | Central Nervous System |
| **COPD** | Chronic Obstructive Pulmonary Disorder |
| **COX-2** | Cyclooxygenase-2 |
| **ED** | Emergency Department |
| **FDA** | Food and Drug administration |
| **GBTM** | Group-based trajectory model |
| **GI** | Gastro-intestinal |
| **HQSC** | Health Quality and Safety Commission |
| **LA** | Long-acting |
| **MAOIs** | Monoamine oxidase inhibitors |
| **MORT** | The Mortality Collection |
| **MME** | Morphine Milligram Equivalents |
| **NHI** | National Health Index |
| **NMDA** | N-methyl-D-aspartate receptor |
| **NMDS** | National Minimum Datasets |
| **NNPAC** | The National Non-Admitted Patients |
| **NSAIDs** | Non-steroidal anti-inflammatory drugs |
| **NZ** | New Zealand |
| **OME** | Oral morphine equivalents |
| **PHARMS** | Pharmaceutical Collection |
| **PHO** | Primary Health Organisation |
| **RCT** | Randomised Control trial |
| **SPSS** | Statistical Package for the Social Sciences |
| **UK** | United Kingdom |
| **US** | United States |
| **WHO** | The World Health Organization |

# 1. INTRODUCTION

## 1.1 Background

The utilisation of opioids in Oceania, North America, and Western Europe is high. These three regions account for 17% of the world's population, but 92% of overall global opioid use (1). According to the 2017 Health Quality and Safety Commission (HQSC) report, 12% of adults in New Zealand (NZ) receiving strong opioids were prescribed opioid therapy for longer than six weeks, and older adults were three times more likely to be dispensed a strong opioid for longer than six weeks compared to younger adults. According to this report, rates of opioid dispensing are particularly high in adults aged ≥80 years (2).

Long-term opioid use for chronic non-cancer pain (CNCP) has increased dramatically in high income countries and regions including North America, Oceania, and Europe (3,4). This has been accompanied by increased rates of opioid-related adverse events (5-7). However, evidence for the effectiveness of long-term opioids use in CNCP is lacking (8) due to the absence of a consistent positive risk-benefit ratio (9).

In order to reduce harm from long-term opioid use in older adults, it is necessary to determine the patterns (incidence rate and prevalence) and trends of opioid use in NZ. It is also necessary to investigate the risk factors or predictors which can lead to long-term (persistent) opioid use amongst older adults. The predictors of persistent opioid use in older adults have not been previously studied in NZ, which makes the present study novel and unique. This study is particularly important to examine the characteristics of older adults who are likely to become persistent opioid users. Such information could enable prescribers to reduce future harms and risks associated with persistent opioid use.

Definition and epidemiology of chronic pain

Chronic pain is highly prevalent in both developed and developing countries (10) and poses significant socioeconomic and public health challenges globally. Although no universally accepted definition exists for chronic pain, it is often defined as pain that persists beyond three months (10-17). Chronic pain is associated with substantial disability from reduced mobility, sleep impairment, avoidance of activity, depression and anxiety and isolation (18). The

negative effects of chronic pain often extend beyond the person, disrupting both family functioning and social relationships (18).

The prevalence of CNCP ranges from 8% to 50% in adults, depending on the definitions and methods used and populations studied (11). Older adults are reported to be more likely to suffer from chronic pain than younger individuals (19). In a US study, the prevalence of chronic pain in older adults was between 45% and 85% (20). In NZ, chronic pain prevalence was reported to be 16.9% in adults >15 years (21). As the population of older adults (≥65 years) continues to rise, the prevalence of chronic pain in this age group will likely increase (22). The most common causes of CNCP in older adults include arthritis, diabetes mellitus, cardiovascular diseases, and neurological conditions (23). The risk factors for chronic pain reported in the literature include being female, lower socioeconomic status, obesity, those with history of depression or anxiety, injury, or have a physically strenuous job (24).

Management of chronic non-cancer pain

The World Health Organization (WHO) has developed an analgesic ladder in 1986, which is a framework used to guide pharmacological treatment for chronic cancer pain and has undergone several amendments over the years. Although this strategy was proposed for the treatment of chronic cancer pain, it is also applied for the management of acute and CNCP (25). The WHO pain ladder consists of three steps:

- Step 1: Mild pain: non-opioid analgesics (e.g., paracetamol or non-steroidal anti-inflammatory drugs [NSAIDs]) with or without adjuvants (e.g., tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, corticosteroids, cannabinoids, bisphosphonates and topical anaesthetics).

- Step 2: Moderate pain: weak opioids with or without non-opioid analgesics (e.g., paracetamol or NSAIDs) and with or without adjuvants.

- Step 3: Severe or chronic pain: strong opioids with or without non-opioid analgesics (e.g., paracetamol or NSAIDs) and with or without adjuvants.

A recent study analysed the current relevance and usage of the WHO analgesic ladder in CNCP through evaluating studies published from 1980 to 2019 (17). A revised 4-step ladder has been generated, where integrative therapies (non-pharmacological) were adopted in each step. Minimal invasive interventions (e.g., radiofrequency, spinal cord stimulation, nerve block,

surgical intervention and spinal administration of local anaesthetics) have been added as the new Step 3 if weak opioids and non-opioids analgesics are not effective. This step was introduced to delay the use of strong opioids (17). In both suggested ladder models, opioids are introduced in Step 2, when non-opioid and adjuvant analgesics are not sufficient for achieving pain control. A study has found that two thirds of adults with CNCP have not used non-opioid analgesics before trialling opioids, which denotes suboptimal treatment with non-opioid analgesics (26). In CNCP, opioids should be reserved for adults who are unresponsive to optimised non-opioid analgesics (26).

Although pharmacological interventions are often required for CNCP, a combined pharmacological and non-pharmacological (such as psychological and social interventions) is favoured and recommended (27). Non-pharmacological treatment options include cognitive behavioural therapy, exercise therapy, yoga, nerve stimulation techniques, acupuncture, massage and pilates (27). Psychological and social interventions include communicating with the patient to empower them to take a role in leading their medical condition, ensuring the patient has achievable expectations in regard to their treatment and encouraging patients to have a positive attitude, as this can alter their perception of pain (27).

Pharmacology of opioids

Opioids are classified into three categories based on their synthetic process: naturally occurring compounds (e.g., codeine and morphine), semi-synthetic compounds (e.g., oxycodone and buprenorphine) and synthetic compounds (e.g., fentanyl and methadone) (28). Opioids can also be classified based on their chemical structures into four categories: benzomorphans, phenylpiperidines, diphenylheptanes and phenanthrenes. The benzomorphans class includes pentazocine, while fentanyl, sufentanil, meperidine, alfentanil and remifentanil belong to the phenylpiperidines class. Methadone and propoxyphene are classified into the diphenylheptanes class, while oxycodone, hydrocodone, morphine, codeine, hydromorphone, levorphanol, butorphanol, buprenorphine and nalbuphine are classified into the phenanthrenes class (29). A third classification of opioids is based on their pharmacodynamic profiles, where morphine, fentanyl or remifentanil are full agonists, and buprenorphine, pentazocine and nalbuphine are agonists-antagonists (29). Lastly, opioids can be classified as either strong or weak opioids, based on their potency. Strong opioids include buprenorphine, methadone, diamorphine, fentanyl, hydromorphone, morphine,

oxycodone, hydrocodone, and pethidine, while weak opioids include codeine, dihydrocodeine and tramadol (30).

Opioids bind to three main receptors; mu (μ), delta (δ), and kappa (κ) receptors which mediate analgesia spinally and supra-spinally. Most opioids bind to the μ-receptors in the central and peripheral nervous system (28). The σ -receptor is no longer considered as an opioid receptor and is not part of opioid-induced analgesia, but rather a phencyclidine target site (29). The mechanism of action of opioids is complex. The analgesic effect is achieved due to opioids acting both pre-synaptically and post-synaptically. In the presynaptic terminal, calcium channels are blocked by opioids on nociceptive afferent nerves, leading to the inhibition of neurotransmitters release such as substance P and glutamate that contribute to nociception. In the postsynaptic terminal, potassium channels are opened by opioids, leading to hyperpolarisation of cell membranes, and increasing the action potential required to generate nociceptive transmission (31). Some opioids such as tramadol, oxycodone, fentanyl, methadone, dextromethorphan, meperidine, codeine, and buprenorphine may affect serotonin kinetics in the presence of agents with serotonergic activity. Therefore, these opioid agents should be co-prescribed cautiously with other serotonergic agents (e.g., selective serotonin reuptake inhibitors) as they have the potential to cause serotonin syndrome (31). Methadone is also an antagonist at the N-methyl-D-aspartate (NMDA) receptor, where it binds to it and antagonises the effect of glutamate. This explains why methadone is more efficacious in the treatment of neuropathic pain compared to other opioids (31).

Indications of opioids

Opioids are indicated for the management of moderate to severe pain (32) including acute pain, cancer pain, or CNCP (13), when an opioid analgesic is deemed appropriate (31). In clinical trials, opioid therapy has been associated with alleviation of pain in the short term (33,34). However, there is a lack of concrete evidence that they are effective when used long-term (5,35). This finding was supported by previous systematic reviews and meta-analyses which concluded that there is no strong evidence to support the effectiveness of long-term opioid use (34,36). The US Centre for Disease Control and Prevention's (CDC) 2016 guidelines state that for chronic pain management, prescribers should consider opioid therapy only if its benefits outweigh risks to the patient, and that it should be combined with non-pharmacological treatment and non-opioid medication if appropriate (31). Some opioids (such as methadone)

are also indicated for opioid dependency where treatment with persistent opioid substitutes is required (13).

Classification of opioids in NZ

In NZ, opioids are classified differently based on their risk of harm. Class A and B controlled drugs have more restrictions compared to Class C in terms of period of supply, requirements of the prescription form, and expiry of the prescription (37). Morphine is classified as a B1 controlled drug (38), while oxycodone, fentanyl, pethidine and methadone are classified as B3 controlled drugs (39-42). Codeine and dihydrocodeine are classified as C2 controlled drugs (43,44), while buprenorphine is classified as a C4 controlled drug (45). Lastly, tramadol is classified as a prescription-only medicine (46). All opioids available in NZ are subsidised except for buprenorphine (45). In NZ, a number of opioids are used with different formulations. Examples of opioids used in NZ and their available formulations are shown in Table 1 (32).

**Table 1:** Opioids available in NZ and their formulations

| Formulation | Name of opioid agent |
|---|---|
| Oral (e.g., tablet, capsule and oral liquid) | Codeine phosphate, dihydrocodeine tartrate, methadone hydrochloride, morphine sulphate, oxycodone hydrochloride, pethidine hydrochloride and tramadol hydrochloride |
| Injection | Buprenorphine, fentanyl, methadone hydrochloride, morphine hydrochloride, morphine sulphate, oxycodone hydrochloride, pethidine hydrochloride, and tramadol hydrochloride |
| Patch | Buprenorphine and fentanyl |
| Suppository | Morphine sulphate |

In NZ, weak opioids available include codeine, dihydrocodeine and tramadol; while strong opioids available include morphine, oxycodone, pethidine, buprenorphine, fentanyl and methadone.

Definition of persistent opioid use

Defining “persistent opioid use” has been inconsistent and definitions vary widely. “Persistent use” can also be referred to as “long-term”, “chronic”, or “prolonged” use in literature. Most

studies defined persistent use as >90 days of opioid use, which corresponds to the CDC definition (5,15,16,47-50). A recent systematic review examined the definitions for persistent opioid use across 34 studies. This systematic review identified 41 variations of persistent opioid use definitions, where definitions have differed by consistency of opioid use, follow-up time, cumulative duration of persistent opioid use, and time points used for defining persistent opioid therapy. Out of the 41 definitions, 46% defined persistent opioid use to be 3 months or over. (51). In addition, the definition of persistent opioid therapy in previous literature often lacks key information about prescription characteristics, including opioid types (short-acting versus long-acting), days of supply and dosages, which can differentiate between low and high-risk persistent opioid therapy. Since most studies refer to persistent opioid use as the use of opioids for >90 days, this definition was adopted for the current study.

Opioid-related adverse effects

The role of opioids in CNCP has been controversial. The main concerns regarding long-term opioid use include the risk of misuse, addiction, and the lack of evidence for safety and efficacy (32). Different types of opioid misuse were identified in literature, including underuse, overuse, disorganised or erratic use, inappropriate use for other indications (e.g., anxiety), and use in combination with recreational drugs or alcohol (52).

There is a growing body of evidence suggesting that patients with CNCP should not be managed by long-term opioids due to the unproven efficacy and well-established risk of opioid-related adverse events (27,53). If opioids are used for CNCP, the treatment regimen should be under the supervision of a specialist, and regular assessment of the patient should take place (32).

In a meta-analysis of 41 randomised controlled trials (RCTs) and a systematic review of 21 RCTs investigating the effectiveness of opioids for CNCP, the authors found no evidence of the effectiveness of long-term opioid therapy for CNCP. However, there was moderate evidence for long-term use of tramadol in patients with osteoarthritis (36). Baldini et al., reviewed the potential adverse effects of long-term opioid use (54). The most prominent adverse effect was constipation, as opioids increase the risk of bowel obstruction, leading to hospitalisation or death (54). Long-term opioid use has also been associated with sleep-disordered breathing such as hypoxemia, carbon dioxide retention and ataxic breathing (54). As for cardiovascular adverse drug reactions, a large cohort study has found that individuals

on opioid therapy compared to those on NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors have a 77% increased risk of developing cardiovascular events, such as heart failure and myocardial infarction (54). Lastly, opioid overdose is a significant issue, where patients prescribed larger doses of opioids are at a greater risk (54). Opioid overdose can potentially lead to life-threatening adverse events such as respiratory depression, hypotension, or bradycardia (54). Studies have shown that opioid-related adverse events such as depression, opioid dependence, and overdose are more common in those taking opioids for long-term compared to those who had short-term use (5,55). Long-term opioid use has also been associated with cognitive decline and increased risks for falling, hip fracture and exacerbation of sleep apnoea (55).

Definition of older adult

Ageing is commonly measured by chronological age, and a person aged ≥65 years is considered as an "older adult" (20,56-60). However, there is no agreed age definition by clinical practice guidelines and recent studies have suggested that defining older adults should not be based on generic definitions and chronological age, but rather establishing a link between the patient's characteristics and the prescribed medications' pharmacology (61). A Japanese study argued that the age boundary of older adults should be changed from 65 years to 75 years or over as the evidence on which the conventional age boundary is based is unknown. Since older adults are commonly defined as adults ≥65 years, this definition was adopted in this thesis (60).

Special considerations for older adults

Although opioid-related adverse events are common amongst patients of all ages, older adults are more vulnerable to develop opioid-related adverse events and their responses to opioids are less predictable when compared to younger adults (62). This propensity is likely due to the age-related physiological changes affecting drug pharmacokinetics and pharmacodynamics. In addition, polypharmacy in older adults is a contributing factor for the increased incidence of opioid-related adverse drug events (63).

In terms of pharmacokinetics in older adults, there are alterations in protein binding, reduction in lean muscle mass and water content and an increase in total body fat, which can affect the volume of distribution of opioids and lead to adverse effects if the dose is not adjusted (63). The age-related loss of function is mostly noticed in the alterations in hepatic and renal

metabolism, where there is marked reduction in metabolism and excretion. This will subsequently affect drug disposition and handling (64).

Pharmacodynamically, older adults have increased sensitivity to opioids and their effects (63). Central nervous system (CNS) adverse effects are significant, where sedation and dizziness increase the risks of falls, fractures and respiratory depression (54,65). Opioid neurotoxicity is also a significant adverse effect in older patients. Other adverse effects related to opioids in older adults include hyperalgesia, intrinsic immunosuppressive effects (which can lead to pneumonia), depression, cognitive decline and effects on the male and female endocrine system (54).

## 1.2 Research questions, aims and objectives

The overarching research question of this thesis is "What are the patterns of opioid use and predictors for persistent opioid use in New Zealanders aged ≥65 years?" The aim of this thesis is to determine the incidence rate and prevalence of opioid use (Study 1) and rates and predictors for persistent opioid use in older New Zealanders (Study 2).

The specific objectives of the study were:

1. To determine the incidence rate of opioid use in older adults (≥65 years) in NZ between 2008 and 2018.

2. To determine the prevalence of opioid use in older adults (≥65 years) in NZ between 2007 and 2018.

3. To determine the rates of persistent opioid (i.e., >90 days continuous use of opioids within a 6-month period) in older adults (≥65 years) without cancer diagnosis between 2013 and 2018.

4. To identify the predictors of persistent opioid use in older adults (≥65 years) without cancer diagnosis between 2013 and 2018.

## 1.3 Significance of the study

Despite the concerns about increasing opioid use and rates of adverse outcomes, there are only a very few population-based studies globally that explored the patterns and predictors of persistent opioid use in older adults. Given the tremendous impact of the opioid epidemic

overseas, particularly in North America, it is of utmost importance to closely monitor the incidence rate, prevalence, rate and predictors of persistent opioid use in NZ. The recent HQSC report showed an increasing rate in opioid use in older adults, NZ European, and women. However, the report did not provide sufficient information about sociodemographic, medication and clinical-related risk factors for persistent opioid use (2). This study is therefore aimed to focus on filling these literature gaps by generating incidence rate and prevalence for opioid use, and investigating rate and predictors of persistent opioid use in the NZ older population. Identifying predictors of persistent opioid use would be one of the first steps in developing interventions to reduce persistent opioid use. There are limited studies exploring patterns and predictors of persistent opioid use in older adults globally. As such, the outputs of this study are important as reporting incidence and prevalence and identifying rate and predictors can inform intervention to reduce risk.

## 1.4 Structure of the thesis

This thesis consists of six chapters: introduction, a literature review, methodology, results, discussion, and conclusions. Chapter 1 comprises of the research background, research questions, aims and objectives, and the significance of the study. Chapter 2 comprises two separate literature reviews for the incidence rate and prevalence of opioid use, and the rate and predictors of persistent opioid use. Limitations and gaps in the literature are also identified. Chapter 3 discusses the methodology adopted for the master's project. This chapter comprises of the study design, sampling and sample size, ethics approval, data sources, study population and eligibility criteria, outcome measures and assessment, opioid exposure assessment and data analysis. Chapter 4 presents the results. The first section provides results on the incidence rate, prevalence and trends of opioid use, and the second section presents the rate and predictors of persistent opioid use. Chapter 5 discusses the findings of this study and links them to previously published studies. This chapter also presents the thesis strengths and limitations as well as implications for medical care and policy and directions for further research. Chapter 6 presents the thesis conclusions.

# 2. LITERATURE REVIEW

## 2.1 Chapter Overview

This chapter presents previous relevant published literature. The chapter begins with an overview of the search strategy and inclusion/exclusion criteria of both sub-studies. The results of the literature review are then organised into five sections; 1) Overview, 2) Incidence rate of opioid use, 3) Prevalence of opioid use, 4) Rate of persistent opioids use, and 5) Predictors of persistent opioid use. The sections contain tables that summarise final articles chosen for each literature review section. Gaps in literature and summary of literature review are then presented. Existing literature on incidence rate and prevalence of opioid use, as well as rates and predictors of persistent opioid use, in older adults is limited. Hence, finding reliable and comparative figures in literature was challenging due to the variation in definitions and methodologies. Overall, this literature review aimed to present, analyse and critically appraise the most relevant literature relating to opioid utilisation amongst older adults.

## 2.2 Methods

### 2.2.1 Search strategy

A literature search was conducted through Medline (Ovid), Scopus and Google Scholar to identify published articles on the incidence rate and prevalence of opioid use, and the rate and predictors of persistent opioid use in older adults. Other databases were also searched such as Embase, Cochrane, International Pharmaceutical abstracts and APA PsycArticles (American Psychological Association). These databases were chosen as they contain credible health-related publications. Additional articles were identified by manually searching the reference lists of articles identified through the database search. Articles up to January 2022 were searched to ensure the inclusion of the latest research. The MeSH terms used are listed in Appendix A. Two separate literature searches were run to retrieve more specific results for both sub-studies and to explore all research questions. The first literature search was aimed to retrieve publications on incidence rate and prevalence of opioid use and was conducted by combining MeSH terms of incidence, prevalence, opioid and old. The second literature search was aimed to retrieve publications on the rate and predictors of persistent opioid use and was conducted by combining MeSH terms of predictors, persistent, opioid and old.

### 2.2.2 Inclusion/exclusion criteria

The final search was limited to human studies and English language, with no date restrictions. This identified the largest range of papers. Relevant publications were screened and selected using the inclusion and exclusion criteria.

Inclusion criterion:

1. Articles examining opioid use in adults (i.e., age ≥18 years old), as limited number of articles reporting opioid use in older adults are limited.

Exclusion criteria:

1. Articles on paediatric population due to their pharmacokinetic and physiological differences compared to the older population.
2. Articles on cancer patients as treatment protocols for chronic cancer pain are different than CNCP. Moreover, one of the main concerns in managing CNCP is the lack of evidence in using persistent opioids. This criterion was only applied for the second literature search.
3. Studies conducted in post-surgical setting as these patients require different treatment regimens compared to non-surgical patients.
4. Articles including methadone for opioid substitution therapy as it is not relevant to this study.
5. Articles whose full text could not be retrieved and unpublished research reports.

## 2.3 Results

### 2.3.1 Overview

As for the first literature search on incidence rate and prevalence of opioid use, a total of 66,301, 103,754 and 53,708 articles were identified in Medline, Scopus and Google Scholar, respectively. Duplicates were removed and inclusion and exclusion criteria were applied. Articles were screened by abstract and title, yielding a total of 338 articles to be reviewed by full text. After screening by full text, a total of 18 articles were initially chosen. Further studies were identified through reference lists of the selected studies. Twenty-five articles were included in the final review (see Figure 1). As for the second literature search on the rate and predictors of persistent opioid use, a total of 11,806, 61,005 and 27,405 articles were identified in Medline, Scopus and Google Scholar, respectively. Duplicates were removed and inclusion and exclusion criteria were applied. Articles were screened by abstract and title, yielding a total

of 255 articles to be reviewed by full text. After screening by full text, a total of 19 articles were initially chosen. Three further studies were identified through reference lists of the selected studies. The final number of studies included in the literature review was 22 articles (see Figure 2). The literature findings are summarised into the two sections in line with the study objectives: Incidence rate and prevalence of opioids use, and rate and predictors of persistent opioid use

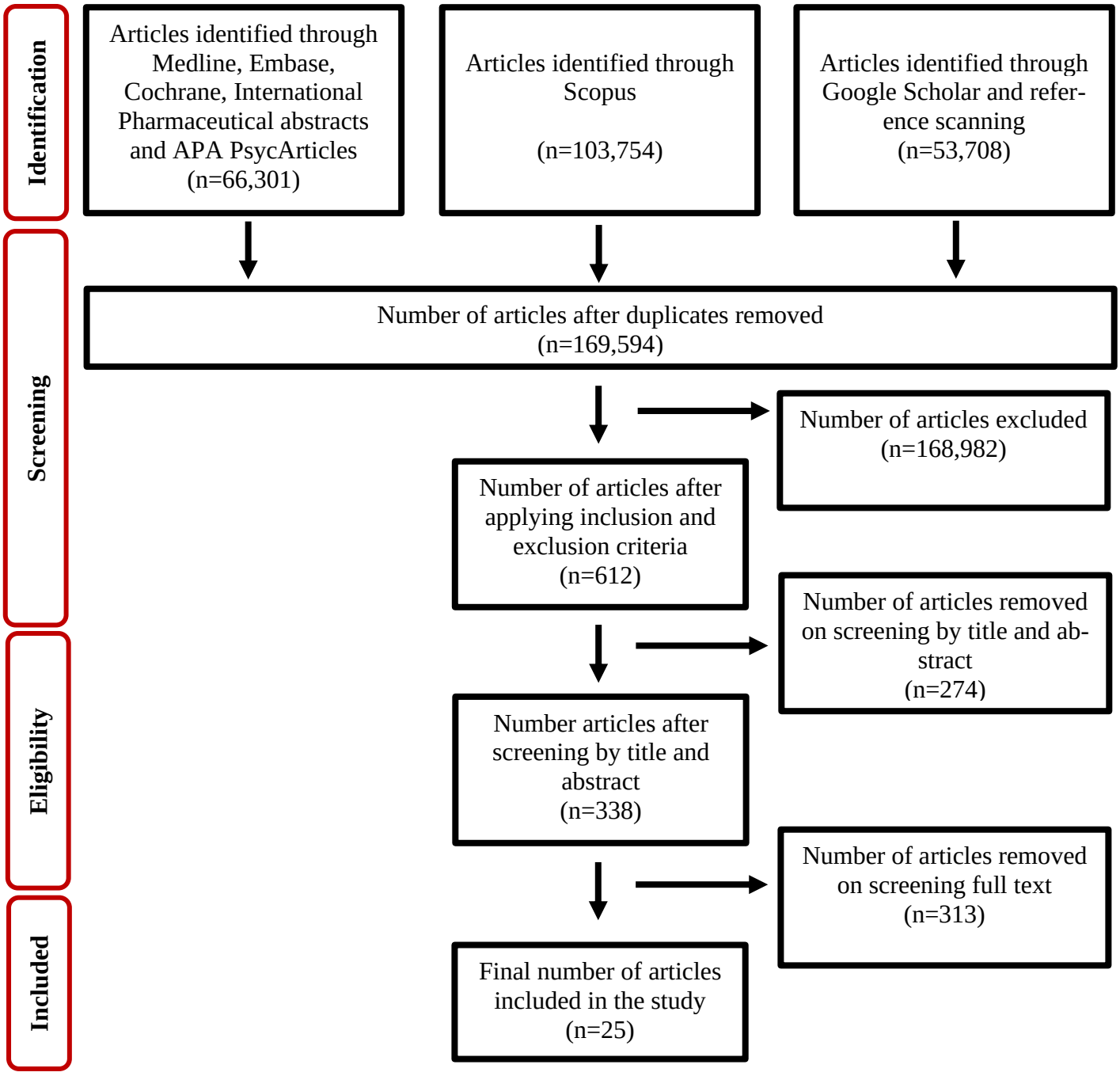


**Figure 1**: Flow chart for literature search on the incidence rate and prevalence of opioid use

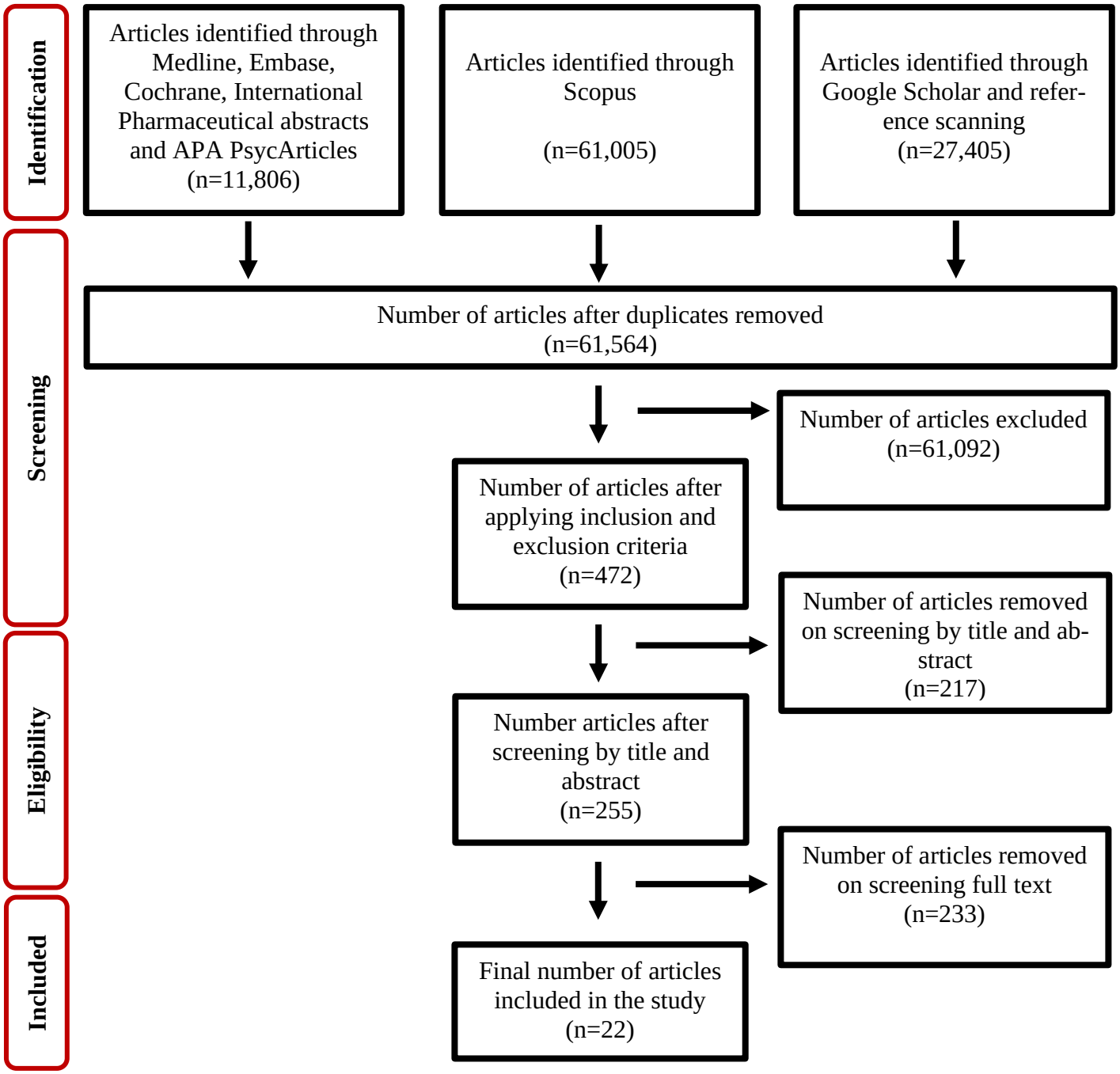


**Figure 2**: Flow chart for literature search on the rate and predictors of persistent opioid use

### 2.3.2 Incidence rate of opioid use

Till present, there is no NZ-based studies reporting incidence rate of opioid use. International studies have reported opioid incidence rates, where some studies reported incidence rates for the older population and others reported those for the general population including patients aged ≥65 years.

In Canada, the percentage of adults being started on opioids has decreased from 9.5% to 8.1% between 2013 and 2018 (66). Although the trends of initiating opioid therapy have dropped from 2013 to 2018, older adults have consistently received more new opioid prescriptions (66). Similarly, the incidence rate in Australia has decreased from 10.7% in 2013/2014 to 10.0% in 2016/2017 (26).

Incidence rates were higher in studies focusing on older population with a specific medical condition. A Canadian study among older adults with Chronic Obstructive Pulmonary Disorder (COPD) (107,109 community-dwelling and 16,207 long-term care resident older adults) between 2003 and 2012 reported the incidence rate of opioid use to be 68.1% and 54.4% among community-dwelling patients and long-term care residents, respectively (67). Another Canadian study investigating the incidence rate of opioid use and adverse respiratory outcomes in older adults reported similar results. The authors of this study reported an incidence rate of 68.2% among 130,979 community-dwelling individuals between 2007 and 2012 (68).

In regard to opioid trends and prescribing patterns, a UK retrospective study found that for 1,968,742 adults who are incident new opioid users, 31.5% of strong opioids were prescribed to patients ≥85 years, compared with 4.1% for weak opioids from 2006 to 2017 (69). Table 2 summarises studies reporting incidence rates of opioid use according to chronological order.

**Table 2:** Summary of the incidence rates of opioid use

| Study | Study setting/participants | Year of incidence rate reported | Incidence rate (%) |
|---|---|---|---|
| Vozoris et al. (2016) | Canadian patients aged 66 and over (n=107,109 community-dwelling and n=16,207 long-term care resident older adults) | 1 April 2003<br>31 March 2012 | 68.1%<br>54.4% |
| Vozoris et al. (2016) | Community-dwelling individuals patients aged 66 and over in Canada (n=130,979) | Between April 1, 2007, and March 31, 2012 | 68.2%. |
| Canadian Institute for Health Information (CIHI) (2019) | The Canadian population: data retrieved from community pharmacies | 2013<br>2018 | 9.5%<br>8.1% |
| Lalic et al. (2019) | Australian population aged 18-99 years old. (n=756,630) | 2013/2014<br>2014/2015<br>2015/2016<br>2016/2017 | 10.7%<br>10.5%<br>10.2%<br>10.0% |
| Jani et al. (2020) | UK adults ≥18 years (n=1,968,742) | 1 January 2006 to 31 December 2017 | 31.5% of strong opioids were prescribed to patients ≥85 years, compared with 4.1% and 3.3% in the weak and moderate opioid respectively |

### 2.3.3 Prevalence of opioid use

The reported prevalence of opioid use ranged widely from 0.5% to 58.1%, depending on the study population and methodologies used. One report has published statistics regarding the prevalence of opioid use in the US. The CDC has published a report regarding the total number and rate of opioid dispensed in the US from 2006–2020. According to this report, opioid dispensing rate has been increasing from 2006 and peaked in 2012 with a dispensing rate of 81.3 prescriptions per 100 persons. The dispensing rate then declined and reached its lowest level in 2020, with a dispensing rate of 43.3 prescriptions per 100 persons (70).

Three US studies reported different prevalences in general adult populations (71-73). The first study (n=47,356) reported that opioid use prevalence has increased from 4.1% in 1999-2000 to 6.8% in 2013-2014 (71). The second study was based on the National Ambulatory Medical Care Survey of 2,846 adults and reported that prevalence of opioid use for CNCP patients to be 33.1% (72). The third study (n=120,481) used electronic health records to evaluate opioid prescribing amongst CNCP patients in a Northern California and the prevalence of all opioid use was 58.1% (73).

In Canada, it was reported that 12.7% of Canadians adults aged ≥15 years have used opioids in 2018 (74). Moreover, 43.9% of adults aged >55 years old have used opioids in 2017 (75); keeping in mind that in Canada, some opioid-containing analgesics are over the counter (76). According to the CIHI, the percentage of Canadians (all age groups) prescribed opioid analgesics has decreased from 14.3% in 2013 to 12.3% in 2018 (66). Another study has investigated the use of opioids in the general population in 2009 where data was obtained from the Canadian Alcohol and Drug Use Monitoring Survey (n=13,032). This study reported that the prevalence of opioid use in adults was 19.2% (77).

As for the Australian adult population, Miller et al., (n=20,426) reported a prevalence of 12% in males and 13.4% in females from 2011 to 2012. This study, however, included patients ≥15 years old (78). Although this study did not strictly meet the inclusion criteria, as the study is based on nationally representative sample of the Australian population, I decided to include it in the review. Another nationally representative Australian study among adults reported a prevalence of 15.8% in 2013/2014 and 16.1% in 2016/2017 (26).

Other studies have also been published on overall prevalence of opioid use. In a systematic review of six studies examining the patterns of opioid prescription in Germany, the prevalence of all opioids use ranged from 0.5% to 5.7% in adults (79). As for the Netherlands, the use of opioids has increased from 4.1% in 2008 to 7.5% in 2017 (80).

Some reports and studies reported opioid prevalence by opioid strength. In NZ, the HQSC report showed that an average of 16.6 per 1000 persons received a strong opioid in 2019 (2). This report also showed that the use of strong opioids increased with age, about 11% of adults aged ≥80 years were dispensed a strong opioid in 2017. Moreover, the prevalence of strong opioids in 2018 was 38.2 and 112.2 per 1000 for older adults aged 65-79 and ≥80 years respectively (2). As for weak opioids, the HQSC also reported that their use has increased with age and about 18% of adults aged ≥80 years were dispensed a weak opioid in 2019 (2). The prevalence per 1000 dispensing of weak opioids in 2018 was 150.6 and 181.5 for older adults aged 65-79 and ≥80 years respectively (2). As for Scotland, a study the prevalence of weak opioids and strong opioids in 2010 was 8.4% and 0.2% respectively (81). An Irish study using the National Administrative Pharmacy Database, which included 32.87% of the total Irish population, found that the greatest increase in opioid use was observed in the older age group of ≥65 years between 2010-2019. In particular, there was a noticeable increase in strong opioid prescribing prevalence over time (20.3% in 2010 versus 23.8% in 2019) (82).

Few studies reported opioid use prevalence in patients with a specific medical condition. Two US studies investigated the prevalence of opioid use amongst patients with musculoskeletal conditions. In one of these studies, among 19,566 adults, 13.1% were identified as prevalent users from 2008-2014 (83). The other study investigating trends in opioids prescribing and co-prescribing of hypnotics from 2001 to 2010 retrieved data from National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey with 35,302 participants. Prevalence of opioid use was reported to be 20.8% combining all years, 28.2% in 2007 and 23.1% in 2010 (84). A cross-sectional study was conducted in Switzerland to investigate the prevalence of treatment among primary care patients with chronic recurrent low back pain from 2015 to 2016 (n=499). The prevalence of opioids use was reported to be 52.5% (85).

There were only a few studies on older adults and they were all US-based, where the prevalence ranged from 3.8% to 21.8%. According to the CDC report, the percentage of older adults (≥60 years) who used opioid analgesics was 9.6% between 2013-2016 (86). The CDC has also recently published a report investigating the prevalence of prescription opioid use among US

adults (n=7,184) with chronic pain in 2019, the prevalence among older adults in 2019 was reported to be 21.8% (87). Another retrospective cohort study using the National Health and Nutritional Examination Survey (n=13,059) reported a prevalence of opioid use of 3.8% from 2005 to 2007 (3). Additionally, a in a cross-sectional study conducted to investigate the frequency of analgesic use in nursing home residents with CNCP between 2007 and 2008, the prevalence of opioid use was found to be 16.2% (88). Table 3 summarises studies reporting prevalence of opioid use according to chronological order.

**Table 3:** Summary of the prevalence of opioid use

| Study | Study setting/participants | Year of reported prevalence | Prevalence |
|---|---|---|---|
| Shield et al. (2013) | Canadian adults ≥15 years<br>(n=13,032) | 2009 | 19.2%. |
| Larochelle et al. (2015) | US Patients co-prescribed opioids and hypnotics from 2001 to 2010 retrieved data from National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (n=35,302) | 2007 - 2010<br>2007<br>2010 | 20.8%<br>28.2%<br>23.1% |
| Ruscitto et al. (2015) | Community-dispensed prescriptions to the Tayside population in Scotland<br>(n=311,881) | 2010 | Weak opioids: 8.4%<br>Strong opioids: 0.2% |
| Fain et al. (2016) | US Nursing home residents with CNCP<br>(n=2.99 million) | 2007 - 2008 | 16.2%. |
| Romanelli et al. (2017) | US patients with CNCP in an ambulatory setting<br>(n=120,481) | 2012 | All opioids: 58.1%<br>Short-acting opioids: 57.4%<br>Long-acting opioids: 7% |
| Miller et al. (2017) | Nationally representative sample of the Australia population<br>(n=20,426) | 2011 - 2012 | Males: 12%<br>Females: 13.4% |
| Sites et al. (2018) | US Adults with musculoskeletal conditions (n=19,566) | 2008-2014 | 13.1% |
| Mojtabai et al. (2018) | US adult participants<br>(n=47,356) | 1999-2000<br>2013-2014 | 4.1%<br>6.8% |
| Kalkman et al. (2019) | The Netherlands population | 2008<br>2017 | 4109 per 100 000 persons<br>7489 per 100 000 persons |
| Oh et al. (2019) | US older adults<br>(n=13,059) | 2005- 2007 | 3.8% |
| Rosner et al. (2019) | German adults (n=ranging from 92,842 to 11,000,000) | 1985 - 2016 | Prevalence ranged from 0.54% to 5.7% |
| Frenk et al. (2019) | US patients aged 60 and over | 2013-2016 | 9.6% |
| Lalic et al. (2019) | Australian population aged 18-99 years old.<br>(n=756,630) | 2013/2014<br>2014/2015<br>2015/2016<br>2016/2017 | 15.8%<br>16.3%<br>16.4%<br>16.1% |
| Lin et al. (2019) | US adult patients (Weighted n=66,198,751; unweighted n=2,846). | 2014 | 33.1% |

| | | | |
|---|---|---|---|
| Rodondi et al. (2019) | Recurrent low back pain among primary care patients in Switzerland (n= 499) | 1 November 2015 – 31 May 2016 | 52.5% |
| Canadian Institute for Health Information (CIHI) (2019) | The Canadian population; data retrieved from community pharmacies | 2013<br>2018 | 14.3%<br>12.3% |
| Rieb et al. (2020) | Canadian adults aged ≥55 years old | 2017 | 43.9% |
| CDC (2021) | US population | 2006–2020 | Opioid dispensing rate in 2012: 81.3 prescriptions per 100 persons.<br>Opioid dispensing rate in 2020: 43.3 prescriptions per 100 persons |
| NZ Health Quality & Safety Commission (2021) | NZ population | 2019 | Strong opioids:<br><br>16.6 per 1000 persons received a strong opioid.<br><br>About 11% of adults aged ≥80 years were dispensed a strong opioid in 2017.<br><br>Prevalence in 2018 was 38.2 and 112.2 per 1000 for older adults aged 65-79 and ≥80 years respectively.<br><br>Weak opioids:<br><br>About 18% of adults aged ≥80 years were dispensed a weak opioid in 2019.<br><br>Prevalence in 2018 was 150.6 and 181.5 for older adults aged 65-79 and ≥80 years respectively. |
| Carrière et al. (2021) | Canadian adults aged ≥15 years | 2018 | 12.7% |
| Dahlhamer et al. (2021) | US adults aged ≥18 years (n=7,184) | 2019 | 21.8% |
| Norris et al. (2021) | 32.87% of the total Irish population | <br>2010<br>2019 | Strong opioids:<br>20.30%<br>23.84% |

### 2.3.4 Rate of persistent opioid use

As mentioned before, the definition of persistent opioid use is inconsistent throughout the literature; however, the majority of the studies defined persistent use as the use of opioids >90 days. Rates reported in studies ranged from 1999 to 2020 and the percentages ranged from 0.9% to 27%, depending on persistent opioid use definition and the study population, with most of them reporting an increase in persistent opioid use among adults and older populations.

Studies that defined persistent opioid use as ≥90 or >90 days use

A study investigating persistent opioid use in opioid-naïve US patients >19 years old (n=2,480,030) reported the rate to be 25% in 2011 (89). Another US study over a decade between 1999-2000 and 2013-2014 reported a sharp increase in persistent opioid use from 1.8% to 5.4% (a 3-fold increase). A quarter of this study population were older adults aged ≥65 years (71). Another study conducted among 180,498 opioid-naïve older Americans reported a prevalence of 6% in 2016 (90). On the contrary, the CIHI reported that the percentage of Canadians became persistent opioid users have decreased from 19.8% in 2013 to 17.6% in 2018. Out of the 17.6% persistent users, about 24% of them were older adults (66).

Studies that defined persistent opioid use as ≥180 days use

In a Norwegian study of 45,837 adults, only 2.9% of the adults used opioids for at least 6 months between 2006 and 2008 (91).

Other definitions

Other studies and reports used more conservative definitions of persistent opioid use. The NZ HQSC defined persistent use as the use of opioids for 6 weeks or longer and has reported that older adults were three times more likely to be dispensed a strong opioid persistently (2). International studies reported different rates of persistent opioid use. The highest rate reported was in the UK, where a study reported that out of 1,968,742 opioid-naïve adults, 14.6% became persistent opioid users. This study defined persistent opioid use as having at least three opioid prescriptions within 90 days, or having one or more opioid prescription lasting at least 90 days (69). Two studies defined persistent use using a group-based trajectory model (GBTM). Using this method, among a nationally representative Australian adults initiating opioids from July 2013 to December 2015, 2.6% were identified as persistent users during a 12-month period (1).

Likewise, a Korean study of opioid use in adult patients (n=15,327) reported that 4.6% of the population to be high-sustained opioid users. Older patients were more commonly represented in the high-sustained users' groups than the early discontinuation group (92). As for the US, a study conducted on adults defined persistent opioid use as ≥6 opioid prescriptions in the 12 months following the initiation month reported that 5% became persistent users (93). The lowest rate was found in Denmark, where the rate of persistent opioid use was reported as 9 per 1000 person-years in a nationally representative sample of patients without cancer. In this study, persistent use was defined as patients dispensed at least one opioid prescription in six separate months within one year (94). Lastly, a Canadian report stated that 43.9% of adults aged ≥55 years old have used opioids in 2017, and 1.1% of them have been using opioids daily or almost daily. However, the duration of use has not been specified (75).

Other studies investigated rates of persistent opioid use in special populations or patients with specific medical condition. For older adults with trauma, a Canadian study investigated the rate of persistent opioid use from April 2004 to March 2014 (n=84,241). In this study, persistent opioid use was defined as filling at least one opioid prescription 305 to 425 days after hospital discharge for trauma and the rate was reported to be 10.9% (95). In case of patients with musculoskeletal conditions, a systemic review and meta-analysis was conducted to investigate rates of persistent opioid use. Different persistent opioid use definitions have been adopted, including specific number of opioid prescriptions within certain duration, episode of opioid prescribing lasting more than 90, 120 and 180 days and opioid treatment discontinuation for a certain period of time. Out of 14 cohorts, 13,263,393 adults were included, and they were classified as high-risk (e.g., concurrent substance use disorder, patients receiving workers' compensation benefits) and low risk populations. Rates of persistent opioid use in high-risk and low risk populations were 27% and 6%, respectively. The overall pooled prevalence was 10.6% (96).

Conversely, a US study defined opioid treatment discontinuation rather than persistent opioid use, where opioid treatment discontinuation was defined as ≥180 days without opioid use. This study reported the rate of persistent use in US adults (n=1,294,247) during 2006–2015 to be 6% (on opioids 1 year later) for patients with at least 1 day of opioid therapy, 13.5% for patients whose first episode of use was for ≥8 days and to 29.9% when the first episode of use was for ≥31 days (97). Table 4 summarises studies reporting rates persistent of opioid use according to chronological order.

**Table 4:** Summary of the rates of persistent opioid use

| Study | Study setting/participants | Definition of persistent opioid use | Year of rate reported | Rate of persistent opioid use |
|---|---|---|---|---|
| Fredheim et al. (2014) | Adult Norwegian population. Data collected from the National Norwegian prescription database for adults (≥20 years) (n=45,837) | ≥180 days | 2006-2008 | 2.9% |
| Deyo et al. (2016) | US patients of all ages filling opioid prescriptions with no opioid fills for the previous 365 days (n=536,767) | ≥6 opioid prescriptions in the 12 months following the initiation month | October 1, 2012 to September 30, 2013 | 5% |
| Ray et al. (2017) | US Opioid-naïve adults >19 years (n=2,480,030) | ≥90 days with either ≥10 opioid fills or ≥120 days-supply of opioids | 2011 | 25% |
| Birke et al. (2017) | A nationally representative sample of the Danish population (n=2015) | Patients dispensed at least one opioid prescription in six separate months within one year | 2012 | 9 per 1000 person-years (0.9%) |
| Shah et al. (2017) | A random 10% sample of commercially insured U.S. adult population<br><br>Mean age: 44.52 years old (n=1,294,247) | Opioid treatment discontinuation was defined as ≥180 days without opioid use | 2006–2015 | 6% on opioids 1 year later for patients with at least 1 day of opioid therapy<br><br>13.5% for patients whose first episode of use was for ≥8 days<br><br>29.9% when the first episode of use was for ≥31 days. |
| Daoust et al. (2018) | Canadian older adults with trauma (n=84,241) | Filling at least 1 opioid prescription 305 to 425 days after hospital discharge. | April 2004 to March 2014 | 10.9%. |
| Mojtabai et al. (2018) | US adult participants of National Health and Nutrition Survey (n=47,356) | ≥90 days | 1999-2000<br>2013-2014 | 1.8%<br>5.4% |

| | | | | |
|---|---|---|---|---|
| Lalic et al. (2018) | A random 10% sample of Australian population who accessed medicines through Australia's Pharmaceutical Benefits Scheme (n=431,963) | Defined persistent use through GBTM; defined by opioid dispensing patterns over 12-month period following opioid initiation | July 2013 to December 2015 | 2.6% |
| Musich et al. (2019) | US Opioid-naïve older adults ≥ 65 years old insured patients (n=180,498) | >90 days | 2016 | 6% |
| Canadian Institute for Health Information (CIHI) (2019) | Canadian adults, data retrieved from community pharmacies | Patients prescribed opioids for 90 days out of a 100-day period. | 2013<br><br>2018 | 19.8%<br>17.6% → Out of the 17.6% of Canadians prescribed persistent opioids, about 24% of them were older adults. |
| Riva et al. (2020) | US Adults (n=13,263,393) | Different persistent opioid use definitions were used, including specific number of opioid prescriptions within certain duration, episode of opioid prescribing lasting more than 90, 120 and 180 days and opioid treatment discontinuation for a certain period of time. | Studies included up until 6 January 2020 | High-risk populations: 27%<br>Low risk populations: 6%<br>Overall pooled prevalence of persistent use: 10.6% |
| Rieb et al. (2020) | Canadian aged >55 years | Duration not specified | 2017 | 1.1% of them have been using opioids daily |
| Jani et al. (2020) | UK adults ≥18 years (n=1,968,742) | Having at least 3 opioid prescriptions within 90 days, or ≥1 opioid prescription lasting at least 90 days | 1 January 2006 to 31 December 2017 | 14.6% |
| Health Quality and Safety Commission New Zealand (2021) | NZ population | ≥6 weeks | 2017 | Older adults aged ≥65 years were three times more likely to be dispensed a strong opioid persistently |
| Yoon et al. (2021) | Korean outpatients prescribed an opioid at least once between January 2009 and December 2013. (n=15,327) | Persistent use was identified through GBTM | January 2009 to 31 December 2013. | 4.6% |

### 2.3.5 Predictors of persistent opioid use

Predictors of persistent opioids use can be broadly classified into four categories: a) Sociodemographic factors, b) opioid-related factors, c) Medication-related factors, d) Co-morbidities.

Sociodemographic factors

*Sex*

Several studies reported that female sex is a predictor of persistent opioid use in older adults and the general adult population (1,3,71,90,92,97-99). In a US study conducted in patients aged ≥65 years, being female was a predictor of persistent use (OR=1.23; 95%CI 1.03–1.46) (3). However, in another US study, females were less likely to be persistent opioid users (OR=0.94; 95%CI 0.87–1.01) than males (89).

*Age*

Likewise, in many studies advanced age was reported as one of the main predictors of persistent opioid use (1,3,69,71,89,90,92,96,97,100,101). In a UK retrospective cohort study, adults who were >75 years old were 4.6 times (OR=4.59; 95%CI 4.48–4.70) and older adults aged 65–74 years were 3.7 times (OR=3.77; 95%CI 3.68–3.85) more likely to become persistent opioid users compared to those younger than 35 years of age (69). Further, in an Australian study, those ≥75 years were 2.5 (95%CI 2.3–2.6) times more likely to be persistent users compared to those aged 18-44 years old (1).

*Socioeconomic status*

Social deprivation was also shown to be a predictor of increased risk of persistent opioid use (1,89,96,102), where studies in the US, UK and Australia have reported that patients living in more deprived areas were more likely to be persistent opioid users. A US study reported an odds ratio of 1.46 (95%CI 1.30–1.64) (89), and a UK study reported an odds ratio of 1.56 (95%CI 1.52–1.59) (69) where adults with lower socioeconomic status have a higher risk of being persistent opioid use. Lastly, in an Australian study conducted by Lalic et al., Concessional status, which is a marker of lower socio-economic status, was found to be a

predictor of persistent opioid use in adults, where Concessional beneficiaries were 1.9 times more likely (95%CI 1.80–2.00) to be persistent users (1).

Opioid-related factors

*Opioid type*

Many studies reported positive association between strong opioid prescription and persistent opioid use (1,3,69,101). In western countries, the sharpest increase for opioids use were seen for strong opioids in older adults, which were often used persistently (101). In a US study, compared to those taking weak opioids, older adults taking strong opioids were 1.3 more likely to be persistent opioid users (3). Similarly, in an Australian study, taking a strong opioid was found to be a stronger predictor (OR=1.51; 95%CI 1.32–1.73) of persistent use in patients ≥85 years old (1). Conversely, in two studies, the use of tramadol, which is a weak opioid, was associated with persistent opioid use in adults (96,97).

*Opioid dose*

As documented by many studies, patients administering a high initial dose of opioids, the risk of transitioning to persistent opioid use is high (1,69,96,97,100). In a US study of a representative sample of opioid-naïve adults, it was found that one of the factors that led to a sharp increase in persistent opioid use was being on an opioid dose of ≥700 mg Oral morphine equivalents (OME) (97). Similarly, an Australian study of the patterns and predictors of opioid use in adult patients (n=431,963) reported that initial prescription of >750mg OME is the strongest predictor of persistent opioid use compared to total OME of >250mg (OR=3.68; 95%CI 3.34–4.06) (1).

*Formulation*

In literature, transdermal formulations have been documented to increase the risk of persistent opioid use (71). An Australian study highlighted that of all the opioids prescribed by physicians, the transdermal formulation was the strongest predictor of persistent opioid use in the general adult population (OR=4.21; 95%CI 3.93–4.51) and in sub-group of patients aged 65–84 years and ≥85 years (OR=4.24; 95%CI 3.85–4.68 and OR=3.47; 95%CI 3.02–3.98, respectively) (1). The use of slow-release formulations has also been shown to increase the likelihood of persistent opioid use in the general and older population (90,97,103). A US study

among opioid-naïve older adults (n=1,294,247) reported that opioid initiation with long-acting opioids was associated with persistent opioid use (97). Another study conducted in the US adults investigating the patterns of immediate-release and extended-release opioid use in the management of chronic pain from 2003 to 2014 included 169,280,456 patients, where 168,315,458 patients filled immediate release formulations and 10,216,570 patients filled extended release/long-acting formulations. This study found that 7% of immediate release formulations users used opioids persistently (≥90 days) compared to 30% for extended-release/long-acting formulations users (103).

*Duration*

Several studies included in a systematic review exploring predictors of persistent opioid use in acute musculoskeletal injuries in adults (n=13,263,393) reported that opioids supply for more than seven days increased the risk of persistent opioid use (96). Another study investigating the association between the characteristics of initial opioid prescription and the likelihood of persistent use in the US adults reported higher likelihood of persistent opioid use when the opioid supply on the first prescription exceeds 10 or 30 days and when the patient received a third prescription (97).

Medication-related factors

The use of pain analgesia, psychiatric and neurological medications with opioids were predictors of persistent opioid use (1,3,69,71,90). Polypharmacy was also a predictor of persistent opioid use. For example, in a US study amongst older adults, patients on five or more medications were 2.5 times more likely to be persistent opioid users (OR=2.52; 95%CI 1.25–5.08) compared to patients taking no medications (3).

*Non-opioid analgesics*

In an Australian study, previous use of non-opioid analgesics (e.g., paracetamol, NSAIDs, and pregabalin) predicted persistence opioid use with an odds ratio of 1.96 (95%CI 1.86–2.05), 1.22 (95%CI 1.17–1.27) and 1.96 (95%CI 1.83–2.10) for paracetamol, NSAIDs and pregabalin, respectively(1). Additionally, in a UK study, adults taking gabapentinoids were 2.5 times more likely to be persistent users (69). Moreover, a systematic review including seven studies also reported that non-opioid medication use (13.2%) predicted persistent opioid use

(51). Similarly, another study reported that the use of NSAIDs contributed to the risk of persistent opioid use in older adults (90).

*Psychiatric and neurological medications*

The use of psychiatric medications including antidepressants and anxiolytics have been well-documented in literature as a risk factor of persistent opioid use (1,3,71,89,90,92,94,96,104). A US retrospective study conducted in older adults reported that antidepressants (OR=1.38; 95%CI 1.14–1.67) and anxiolytic, sedative, or hypnotic agents such as benzodiazepines and barbiturates (OR=2.26; 95%CI 1.69–3.02) are predictors of persistent opioid use (3). Similarly, an Australian study found that previous use of benzodiazepines was a predictor of persistent opioid use (OR=1.48; 95%CI 1.41–1.55) (1). Another US study conducted in older adults also reported the use of benzodiazepines as a strong predictor of persistent opioid use (90). A similar finding was reported by Quinn et al., where patients dispensed benzodiazepines prior to opioid initiation had twice the risk of transitioning to persistent opioid use (104). Lastly, in Denmark, benzodiazepine dispensing was reported to be a predictor of opioid use in adults with CNCP (94). As for neurological medications, a Korean-based study reported anti-epileptics to predict opioid persistence (OR=2.22, 95%CI 1.88–2.63) (92).

Co-morbidities

Co-morbidities, especially mental health and neurological conditions are also strong predictors of persistent opioid use.

*Mental health and neurological conditions*

Mental health conditions and psychotic disorders were reported with a higher risk of persistent opioid use in older adults (90,95) and the general adult population (1,89,92). An Australian and a Korean study specifically reported depression as a predictor of persistent opioid use (OR=1.59; 95%CI 1.52–1.66 and OR=3.55; 95%CI 1.99–6.35, respectively) (1,92). Epilepsy and anxiety disorder were also reported to be predictors of persistent opioid use in a Korean study (OR=10.12; 95%CI 4.72–21.67 and OR=2.10; 95%CI 1.19–3.72, respectively) (92).

*Chronic pain*

In a systematic review examining the predictors of persistent opioid use, chronic pain was consistently identified as a predictor (51). A US study reported that patients with chronic pain

were 2.4 times more likely to be persistent opioid users (95%CI 2.17–2.82) (89). A UK study has also reported increased persistent opioid use among adults suffering from fibromyalgia (OR=1.81; 95%CI 1.49–2.19) and rheumatological conditions (OR=1.53; 95%CI 1.48–1.58) (69). Other medical conditions which predicted persistent use include arthritis (89) and respiratory conditions (e.g., COPD) (89,105). Lastly, in a US study higher number of chronic health conditions predicted persistent opioid use (71).

*Substance use and other co-morbidities*

In adults, substance abuse was reported to be a predictor of opioid use in adults in a US study (OR=2.25; 95%CI 1.89–2.69) (89)**,** a UK study (OR=1.72; 95%CI 1.65–1.79) (69) and a systematic review (96). Suicide and self-harm were also reported to be a predictor of opioid use in adults (OR=1.56; 95%CI 1.52–1.61) (69,96), as well as nicotine dependence (OR=1.65; 95%CI 1.48-1.83) (1) and opioid use disorder (96). Other medical conditions associated with increased persistent use include hypertension (69,89), urinary incontinence (69), Parkinson's disease (89), end-stage renal disease (89) and sleep disorders (92,96). Table 5 summarises studies reporting predictors of persistent opioid use according to chronological order.

**Table 5:** Summary of the predictors of persistent opioid use

| Study | Study setting/participants | Year | Sociodemographic predictors | Opioid-related factors | Medication-related factors | Comorbidities risk factors |
|---|---|---|---|---|---|---|
| Roberts et al. (2013) | US adults aged ≥40 years (n=7,952, mean age: 69 years) | Between January 1, 2006, and December 31, 2010 | | | | Compared to non-COPD patients, COPD patients were more likely to use short-acting (24.2 versus 15.1%) and long-acting opioids (4.4 versus 1.9%). |
| Campbell et al. (2015) | Australian adults (n=1,424) | 2015 | Social deprivation | | | |
| Birke et al. (2017) | A nationally representative subsample of Danish individuals (n=2015) | 2012 | Female sex<br><br>Education | | Use of Benzodiazepines | |
| Ray et al. (2017) | US Opioid-naïve adults >19 years old (n=2,480,030) | 2011 | Compared to Quartile 1 (least deprived):<br><br>Quartile 2: (OR=1.18; 95%CI 1.07–1.30)<br><br>Quartile 3: (OR=1.24; 95%CI 1.12–1.37)<br><br>Quartile 4, most deprived: (OR=1.30; 95% CI 1.15–1.47) | | Use of sedative/hypnotics (OR=1.68; 95%CI 1.54–1.82) | Chronic pain: (OR=2.47; 95%CI 2.17–2.82)<br>Non-opioid substance use disorders: (OR=2.25; 95%CI 1.89–2.69)<br>Psychiatric disorders: (OR=1.20; 95%CI 1.10–1.31)<br>Arthritis: (OR=1.41; 95%CI 1.31–1.52)<br>Hypertension: (OR=1.27; 95%CI 1.17–1.39)<br>Parkinson's disease: (OR=1.08; 95%CI 0.74–1.57)<br>COPD: (OR=1.24; 95%CI 1.09–1.41)<br>End-stage renal disease: (OR=1.04; 95%CI 0.66–1.62) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Shah et al. (2017) | A random 10% sample of commercially insured US adult population<br>Mean age: 44.52 years old (n=1,294,247) | 2006–2015 | Female sex<br>Older patients | Initiated treatment with a long-acting opioid<br>Initiated on higher doses of opioids<br>Initiated on tramadol | | |
| Quinn et al. (2017) | US adults (n=10,311,961) | 2003 to 2013 | | | Benzodiazepines use<br>Psychiatric medications use | Psychiatric conditions |
| Lalic et al. (2018) | Australian adults<br>(n=431 963) | July 2013 to December 2015 | Patients ≥75 years were 2.5 times more likely to be persistent users: (95%CI 2.27–2.64) compared to people aged 18–44 years.<br>Concessional beneficiaries: (OR=1.9; 95%CI 1.80–2.00). | Baseline total OME ≥750 mg compared to a baseline total OME >250: (OR=3.68; 95%CI 3.34–4.06).<br><u>Sub-group aged 65–84 years</u><br>Transdermal formulation: (OR=4.24; 95%CI 3.85–4.68).<br>Being initiated with a baseline total OME ≥750 mg: (OR=2.20; 95%CI 1.84–2.63).<br><u>Sub-group aged ≥85 years</u><br>Transdermal formulation: (OR=3.47; 95%CI 3.02–3.98)<br>Initiated on a strong opioid: (OR=1.51, 95% CI 1.32–1.73). | Previous use of non-opioid analgesics including NSAIDs (OR=1.22, 95%CI 1.17–1.27), paracetamol (OR=1.96; 95%CI 1.86–2.05) and pregabalin (OR=1.96; 95%CI 1.83–2.10)<br>Previous use of benzodiazepines: (OR=1.48; 95%CI 1.41–1.55)<br><u>Sub-group aged 65–84 years</u><br>Prior benzodiazepine use: (OR=1.27; 95%CI 1.18–1.37).<br><u>Sub-group aged ≥85 years</u><br>Prior benzodiazepine use: (OR=1.20, 95%CI 1.06–1.36). | Depression: (OR=1.59; 95%CI 1.52–1.66)<br>Psychotic illness: (OR=2.01; 95%CI 1.87–2.17)<br>Nicotine dependence: (OR=1.65; 95%CI 1.48–1.83) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mojtabai et al. (2018) | US adult participants of National Health and Nutrition Survey<br><br>(n=47 356) | 1999-2000 and 2013-2014 | Older patients | | Patients currently used benzodiazepines | Patients with a painful disabling condition.<br><br>Patients with a larger number of chronic health conditions or poorer self-assessed rating of health. |
| Daoust et al. (2018) | Canadian older adults with trauma (n=84,241) | April 2004 to March 2014 | Female sex | Opioid use before the injury, and opioid use within 3 months after injury<br><br>Opioid prescription filled within 3 months: (OR=2.57; 95%CI 2.36–2.80) | | History of depression in the year before trauma |
| Hwang et al. (2018) | US adults (n=169,280,456) | 2003 to 2014 | | Extended-release/long-acting formulations | | |
| Musich et al. (2019) | US Opioid-naïve older adults ≥65 years insured patients (n=180,498) | 2016 | Low income<br><br>Older adults<br><br>Female sex | Long-acting opioids<br><br>Use of tramadol | Use of benzodiazepines, muscle relaxants, NSAIDs, prescription sleep medications and antipsychotics. | New or chronic back pain.<br><br>New onset depression and/or anxiety |
| Oh et al. (2019) | US older adults (n=13,059) | 2005- 2007 | Female sex: (OR=1.23; 95%CI 1.03–1.46) | | Use of antidepressant agent: (OR=1.38 95%CI 1.14–1.67). | Hypertension: (OR=1.44; 95%CI 1.20–1.72)<br>Urinary incontinence: (OR=1.45; 95%CI 1.19–1.78) |
| Jani et al. (2020) | UK adults ≥18 years (n=1,968,742) | 1 January 2006 to 31 December 2017 | Older age (compared to <35 years):<br>≥75 years: (OR=4.59; 95%CI 4.48–4.70). | Morphine Milligram Equivalents (MME)/day at initiation: (OR 1.08; 95%CI 1.07–1.08). | Gabapentinoid use: (OR 2.52, 95%CI 2.43–2.61). | Fibromyalgia: (OR=1.81; 95%CI 1.49–2.19).<br>Rheumatological conditions: (OR=1.53; 95%CI 1.48–1.58). |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | 65–74 years: (OR=3.77; 95%CI 3.68–3.85).<br>Social deprivation (Quintile 5/most deprived compared to quintile 1/least deprived):<br>(OR=1.56; 95%CI 1.52–1.59). | | | Substance abuse: (OR=1.72; 95%CI 1.65–1.79).<br>Suicide/self-harm: (OR=1.56; 95%CI 1.52–1.61). |
| Riva et al. (2020) | US, Australia and Malaysian adults<br>(n=13,263,393) | Studies included until 6 January 2020 | Older age<br>Lower educational level<br>Lower socioeconomic status | Higher MME per day<br>Opioid prescriptions lasting more than 7 days<br>Tramadol use | Co-prescription of benzodiazepine | Sleep disorders<br>History of suicide, opioid use disorder<br>Past or current substance use disorder |
| Karmali et al. (2020) | Different settings for each study | January 2007 to July 2018 | Age (eight models)<br><br>Sex (eight models) | Opioid dose at baseline (four models) | | Arthritis (four models)<br>Chronic pain<br>Tobacco use<br>Drug disorders<br>Mental health disorders |
| Weesie et al. (2020) | US older adults (n=283,600) | 2005–2017 | Oldest age group (>85 years) compared to younger older adults. | | | |
| Yoon et al. (2021) | Korean outpatients prescribed an opioid at least once between January 2009 and 31 December 2013.<br><br>(n=15,327) | January 2009 to 31 December 2013. | Female sex: (OR=1.35; 95%CI 1.10–1.65).<br><br>Age; 65–74 years: (OR=3.48; 95%CI 2.76–4.39).<br><br>Age; >75 years: (OR=3.48; 95%CI 2.76–4.39). | | Antiepileptics: (OR= 2.22; 95%CI 1.88–2.63).<br><br>Antidepressants: (OR= 1.84; 95%CI 1.54–2.19). | Epilepsy: (OR=10.12; 95%CI 4.72–21.67)<br>Depression: (OR=3.55; 95%CI 1.99–6.35).<br>Sleep disorder: (OR=3.03, 95%CI 1.70–5.38).<br>Anxiety disorder: (OR=2.10, 95%CI 1.19–3.72). |

## 2.4 Limitations and gaps in literature

Several limitations and gaps in literature were identified. There are a limited number of older population-based studies with some studies sampling special groups or patients with a specific medical condition (e.g., patients with COPD and musculoskeletal injuries, trauma patients). This limited the generalisability of the findings to the general older population (67,68,95,96). The definition of persistent opioid use varied between studies as previously explained. Moreover, opioid prescription records were obtained from pharmacy claim databases, but information on the consumption of opioids was missing, hence, it is unknown whether the patient has actually taken the medicine as prescribed or not (69,82,92). Further, the use of opioids that were not dispensed by a recent prescription (e.g., leftover medicine from hospitalisations or medication sharing) may not have been considered. In some studies, information regarding socioeconomic status, education level, comorbidities, use of non-opioid medicines, and history of alcoholism was not obtained. Therefore, the association of these factors with the transition to persistent opioid use may have been underestimated. In addition, the use of over-the-counter opioids (such as codeine) was not taken into account, which might have underestimated the overall utilisation of weaker opioids (69). Lastly, a selection bias may have occurred in some of the studies as participants who were excluded had a higher rate of co-morbidities, as well as a higher rate of opioid/strong opioid usage at baseline. This could potentially lead to the underestimation of opioid usage in this cohort (3).

## 2.5 Summary of literature review

The review has revealed large gaps in literature in the incidence rate and prevalence of opioid use and the rate and predictors of persistent opioid use in older adults in NZ and globally. Incidence rate, prevalence and rate of persistent opioid use rates vary widely, depending on the methodologies used. As for predictors, the most common factors reported in literature include advanced age, being female, formulation, mental health medications and mental health conditions. Overall, there is an apparent gap in literature since there is no NZ specific study on persistent opioid use in the older population; hence we do not know how we compare to the rest of the world. Thus, it is important to conduct a NZ specific study to explore the patterns and predictors of persistent opioid use in the NZ older population.

# 3. METHODOLOGY

## 3.1 Chapter Overview

The first section of this chapter describes a general overview of the study design, sampling and sample size, ethics approval and data sources. Then the methodologies for the two sub-studies forming the thesis are described. Detailed information on the study population, eligibility criteria, opioid exposure assessment, outcome measures, and data analysis are discussed for both sub-studies.

## 3.2 Study design

This is a population-based, retrospective cohort study, which was conducted using routinely collected administrative healthcare claims data. Retrospective cohort study design was chosen for several reasons, including the low cost, less time-consuming nature of this design, and readily availability of information on several study variables. This thesis has two different but related sub-studies: 1) Incidence rate and prevalence of opioid use in general older adults in NZ; and 2) The rate and predictors of persistent opioid use in older adults without cancer diagnosis. The methodologies of these studies are described below.

## 3.3 Sampling and Sample size

All older New Zealanders (≥65 years) who had at least one dispensing for any opioid medication during the study period and met eligibility criteria for each sub-study were included. It should be noted that the two sub-studies had different eligibility criteria. As all eligible individuals were included in both studies, no sample size calculations were required.

## 3.4 Ethics approval

This research was reviewed on the NZ Health and Disability Ethics Committee online site and considered out of scope for review given the retrospective nature of the database study and use of completely de-identified health data.

## 3.5 Data sources

The data for this research were obtained from a number of national administrative healthcare databases, including the National Health Index (NHI), Primary Health Organisation (PHO)

enrolment data, Pharmaceutical Collection (Pharms), National Minimum Datasets (NMDS), the Mortality Collection (MORT), The National Non-Admitted Patients Collection (NNPAC) and NZ Census data. All the databases were anonymously linked using encrypted NHI numbers. The data linking was conducted by a professional data analyst, using SQL server. Each database is briefly described below.

NHI is a unique identifier assigned to every person in NZ who uses health support services. The NHI number is stored along with the person's demographic details such as sex, age, date of birth, deprivation index, and ethnicity (106).

PHO enrolment data has a national collection which holds patient enrolment data in the primary healthcare system. The PHO enrolment collection was used to get data on primary care enrolment (107).

Data on medication use were obtained from the Pharms database. Pharms is a data warehouse supporting the management of pharmaceutical subsidies, where claim and payment information from pharmacists for subsidised dispensed medicines can be obtained. Information on opioid dispensing including opioid type, strength, formulation and preparation was obtained from this database (108). In addition, information on opioid start date and discontinuation date as well as opioid switch date were obtained from the Pharms database. As mentioned above, Pharms was also used to identify baseline other medications use.

NMDS is a national collection of public hospital discharge statistical information (109). The database contains coded clinical data for inpatients and information on hospital stay dates, medical procedures and diagnoses. NMDS was primarily used to obtain baseline co-morbidities that could potentially predict persistent opioid use, number of hospitalisations, and Charlson Comorbidity Index (CCI). In NMDS, primary and secondary diagnoses are coded according to the international classification of diseases - Australian Modified version (ICD-10AM) (110).

MORT is a national database that classifies the underlying cause of death for all deaths registered in NZ (111). MORT was used to identify patients who died from any or a particular cause. MORT uses ICD-10AM classification for mortality coding.

NNPAC is the national database used to capture patients' information on outpatient/emergency department (ED) visits (112). This database was used to determine the Number of outpatient/ED visits within 365 days prior to the index date.

The NZ population Census data were used to determine population denominators in calculation of the incidence rate and prevalence of older adults opioid use. Table 6 summarises the type of information obtained from each database by study type.

**Table 6:** Summary of data sources

| | **Database type** | | | | | | | **Study period** |
|---|---|---|---|---|---|---|---|---|
| | **NHI** | **PHARMS** | **PHO** | **NMDS** | **NNPAC** | **MORT** | **NZ Census** | |
| **Data type** | Socio-demographics | Medication use | Primary care enrolment | Hospitalisation and diagnosis | Outpatient and ED visits | Mortality | Population census | |
| Study 1 | ✓ | ✓ | ✓ | NA | NA | ✓ | ✓ | 2007-2018 |
| Study 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | NA | 2013-2018 |

NHI: National Health Index
PHARMS: Pharmaceutical Collection
PHO: Primary Health Organisation
NMDS: National Minimum Datasets
NNPAC: The National Non-Admitted Patients
MORT: The Mortality Collection
NA: Non-applicable

## 3.6 Study 1: Incidence rate and prevalence of opioid use in older adults

### 3.6.1 Study Population

The cohort for study 1 consisted of all older adults (≥65 years old) in NZ who had an opioid dispensing episode from 1st January 2007 to 31st December 2018 using dispensing records in the Pharms Collection. Patients with missing data on age and sex were excluded to reduce selection bias.

### 3.6.2 Opioid exposure assessment

All opioid types available in NZ were included. However, opioid combination products (e.g., paracetamol and codeine) were excluded due to the low dose of codeine and the potential risk of confounding. Paracetamol and codeine combination could also be sold by the pharmacist over-the-counter. Moreover, other over-the-counter opioid-containing medications (e.g., pholcodine and anhydrous morphine) were excluded as this data were not captured in the Pharms database.

### 3.6.3 Data Analysis

Medication incidence rate was estimated using data from all patients whose record indicates at least one opioid prescription from 1st January 2008 to 31st December 2018 and medication prevalence was estimated using data from all patients whose record indicates at least one opioid prescription from 1st January 2007 to 31st December 2018.

Incidence rate of opioid use

The annual incidence rate of opioid use was calculated by dividing the total number of individuals newly prescribed with at least one opioid medication per calendar year, by the total older adult population on the 1st of July of that particular calendar year. A one-year window before the first prescription was used as a screening period to exclude prevalent users, hence why incidence calculations started from 2008 and not 2007. Thus, the numerator was the sum of all older patients with their first opioid prescription during the specified study year who had not received any opioid prescription during the one-year window before the specified study year, and the denominator was the total number of older NZ population on the 1st of July of the study year (mid-year Census population estimates were used to compensate for death, migration, and immigration in a given year). The overall annual incidence rate of opioid use was expressed per 1000 persons.

Sex specific incidence rate by opioid type was calculated by dividing the total number of male or female individuals newly prescribed with at least one weak or strong opioid medication per calendar year or the opioid drug of interest, by the total male or female population. For example, the incidence rate of morphine male users in 2013 was calculated by dividing the numerator (males with a prescription of morphine in 2013 without a prescription in 2012) by the denominator (the total number of males on 1 July 2013). The incidence rate was expressed per 1000 persons.

The annual incidence rate of opioid use by type of opioid was calculated by dividing the total number of individuals newly prescribed with the opioid of interest per calendar year, by the total older adult population in a given calendar year. For example, the incidence rate of morphine users in 2013 was calculated by dividing the numerator (individuals with a prescription of morphine in 2013 without a prescription in 2012) by the denominator (the total number of individuals in the population on 1 July 2013). The incidence rate of specific opioid was expressed per 1000 persons.

The annual incidence rate of strong and weak opioid use by sex was calculated by combining the number of male or female strong or weak opioid users and dividing them by the total number of male or female population in a given calendar year. For example, the incidence rate of strong opioid use in males in 2013 was calculated by dividing the numerator (total number of males with a prescription of a strong opioid in 2013 without a prescription in 2012) by the denominator (the total number of males in the population on 1 July 2013). The incidence rate was expressed per 1000 persons.

The annual incidence rate of opioid use by strength was calculated by combining the number of opioid type users (strong or weak) per calendar year and dividing it by the total older adult population in a given calendar year. For example, the incidence rate of strong opioid use in 2013 was calculated by dividing the numerator (individuals with a prescription of morphine, oxycodone, fentanyl or pethidine in 2013 without a prescription in 2012), by the denominator (the total number of individuals in the population on 1 July 2013). The incidence rate was expressed per 1000 persons.

Prevalence of opioid use

The annual prevalence of opioid use was calculated by dividing the total number of individuals prescribed with at least one opioid medication per calendar year, by the total older adult population on the 1st of July of that particular calendar year. Thus, the numerator was the sum of all older patients with at least one opioid prescription during the specified study year, and the denominator was the total number of older NZ population on the 1st of July of the study year. Prevalence was expressed per 1000 persons.

Sex specific prevalence by opioid type was calculated by dividing the total number of male or female individuals prescribed with at least one opioid medication per calendar year or the opioid drug of interest, by the total male or female population on the 1st of July of that particular year. For example, the prevalence of morphine male users in 2013 was calculated by dividing the numerator (males with a prescription of morphine in 2013) by the denominator (the total number of males in the population on 1 July 2013). Prevalence was expressed per 1000 persons.

The annual prevalence of a specific opioid type was calculated by dividing the total number of individuals who prescribed the opioid of interest per calendar year by the total older adult population in this calendar year. For example, the prevalence of morphine users in 2013 was

calculated by dividing the numerator (individuals with a prescription of morphine in 2013) by the denominator (the total number of individuals in the population on 1 July 2013). Prevalence was expressed per 1000 persons.

The annual prevalence of strong and weak opioid use by sex was calculated by combining the number of male or female strong opioid users and dividing them by the total number of male or female population on the 1st of July of that particular year. For example, the prevalence of strong opioid use in males in 2013 was calculated by dividing the numerator (total number of males with a prescription of a strong opioid in 2013), by the denominator (the total number of males in the population on 1 July 2013). Prevalence was expressed per 1000 persons.

The annual prevalence of opioid use by strength was calculated by combining the number of opioid type users (strong versus weak) per calendar year and dividing it by the total older adult population on the 1st of July of that particular year. For example, the prevalence of strong opioid use in 2013 was calculated by dividing the numerator (individuals with a prescription of morphine, oxycodone, fentanyl or pethidine in 2013), by the denominator (the total number of individuals in the population on 1 July 2013). Prevalence was expressed per 1000 persons.

## 3.7 Study 2: The rate and predictors of persistent opioid use in older adults in NZ

### 3.7.1 Study Population

The cohort for study 2 consisted of all older adults (≥65 years) in NZ who initiated a new opioid episode from 1 January 2013 to 31 December 2018, using dispensing records in the Pharms database. Patients can enter the cohort any time from January 1, 2013, the earliest index date, until June 30, 2018, the latest index date. Patients may therefore have different index dates due to the open nature of the cohort entry. To allow for at least 6 months follow-up after cohort entry, the last possible date of cohort entry was June 30, 2018. However, patients were followed until December 31, 2018. An individual can only enter the cohort once, if they had multiple opioid dispensings at different years of the study period, only their first period was included. Mortality data were only available until 2018, thus data for 2019-2021 could not be analysed. Further, to avoid the potential impact of very long-term follow-up period on persistent opioid use rate estimate and predictors, in consultation with the supervisory team, we decided to use five years of data instead of 12 years of data as the incidence rate/prevalence calculations.

### 3.7.2 Eligibility Criteria

Patients were included if they met the following criteria:

- Age 65 years or older at the index date
- Had at least one inpatient, outpatient or emergency department hospital visits for any health condition between 1 January 2013 and 31 December 2018. This criterion was needed as information on co-morbidities and number of hospital visits/admissions could not be obtained for those without hospital visits during the study period.

Patients were excluded based on the following criteria:

- Those younger than 65 years of age
- Patients with any cancer diagnosis one year before the index date (ICD-10AM codes: C00-C97, D10-D50) or within 6 months after the index date. This is because the focus of study 2 is on persistent opioid use among non-cancer patients.

### 3.7.3 Opioid exposure assessment

Persistent opioid use is defined as continuously filling any number of opioid prescriptions or dosing between 91 and 180 days after the index opioid prescription episode during the study period. Continuous use is defined as multiple opioid prescription claims with no period >45 days between opioid fill dates. This threshold was chosen because it is unlikely that an individual would receive opioids for >90 days in a 6-month period for acute pain conditions. Patients with ≤ 90 days of opioid use in 6 months period were considered as non-persistent opioid users. The first day of the opioid prescription fill date during the study period was considered as the start of an opioid use episode and was defined as the index date. All eligible individuals were followed up for 6 months after the index date.

All opioid types available in NZ were included; however, as has been described above, opioid combination products were excluded. Another excluded opioid was methadone. In NZ, methadone is indicated for moderate to severe chronic pain, treatment for opioid dependence (opioid substitution) and intractable cough in palliative care (42). The indication of methadone prescribing could not be obtained from the Ministry of Health dispensing records, therefore, opioid substitution and intractable cough in palliative care indications could not be excluded from the records. Over-the-counter products containing opioids were also not included for their low opioid doses and that these data are not captured in Pharms database (e.g., cough and cold products containing codeine, pholcodine and Anhydrous Morphine cough syrups).

Since patients were on different opioid types with different potencies, the patient's daily prescribed doses were standardised by converting to oral morphine equivalence (OME) in milligrams as per conversion factors and adding together the OME for the total load. This will account for overall opioid exposure relative to morphine. The total quantity dispensed per opioid was used irrespective of duration or instructions used on the prescription. The OME formula and conversion factors are shown in Table 7 (1,113):

OME = Pack Strength × OME conversion factor × Quantity dispensed (1)

**Table 7:** OME formula conversion factors

| **OME conversion factors** | |
|---|---|
| Morphine | 1 |
| Oxycodone | 1.5 |
| Fentanyl Patch | 7.2 |
| Pethidine | 0.4 |
| Dihydrocodeine | 0.1 |
| Codeine | 0.1 |
| Tramadol | 0.1 |

### 3.7.4 Outcome assessment

The primary outcome of interest was persistent opioid use. Alternative definition of persistent opioid use was used for sensitivity analysis (see sensitivity analysis section below).

Potential Predictors of persistent opioid use

Based on the literature review in Chapter 2, my experience, professional judgement as a clinical pharmacist and discussions with the supervisory team, potential predictors of persistent opioid use have been identified. The potential predictors included sociodemographic, opioid-related factors, other medications use, co-morbidities and healthcare utilisation-related factors. These predictors are briefly discussed below (see Appendix B for detailed definition of each predictor under each group of factors).

*Sociodemographic factors*

Sociodemographic factors included age at index date, sex, prioritised ethnicity (Māori, NZ European, Pacific people, Asian, Other, or Unknown), and socioeconomic deprivation index (using the NZ Deprivation Index) at index date. Prioritised ethnicity is used when an individual self-identifies with two or more ethnicities (individual being allocated to a single ethnic group based on the ethnic group they identified with order of priory; Māori, Pacific, Asian then European/Other (114)). The NZ Deprivation Index measures the socioeconomic deprivation level in each small area based on nine census variables, where decile 1 refers to is the least deprived areas and decile 10 is the most deprived areas (115).

*Opioid-related factors*

Variables included opioid type, opioid strength (weak versus strong opioids), total oral OME and formulations (i.e., injectables and slow-release dosage forms).

*Medication-related factors*

Medication classes investigated as potential predictors included antihypertensives, antidiabetics, anti-gout medications, antiepileptic drugs, non-opioid analgesics, anxiolytics, sedatives and hypnotics, antipsychotics, mood stabilisers, antidepressants, Parkinson's and dementia medications. Medication use is defined as any prescription for medication of interest within 365 days prior to the index date. Medications were identified using Chemical ID codes in the Pharms database.

*Co-morbidities*

Baseline medical and psychiatric conditions were identified from NMDS database using ICD-10AM diagnosis codes. Co-morbidities investigated as potential predictors included CCI score, sleep disorders, mental health, neurological, chronic pain, cardiovascular, respiratory, autoimmune conditions, sleep disorders, chronic kidney and liver disease, diabetes mellitus, gout, osteoarthritis, soft tissue disorders, substance abuse, alcohol-related conditions, obesity and suicide and self-harm. Baseline medical conditions were identified by the presence of ≥1 inpatient claim within 3-year prior to the index date using ICD-10AM diagnosis codes. Validated ICD-10AM codes from literature were used for the definition of each medical

condition. We also used medication prescription as proxy indicator for some co-morbidities (see Appendix B).

*Healthcare utilisation factors*

Other potential predictors included the number of outpatient/ED and inpatient visits within 365 days prior to the index date.

### 3.7.5 Data analysis

Primary Analysis

The baseline characteristics of persistent and non-persistent opioid users were compared using descriptive statistics. Chi-squared test was used to compare baseline characteristics of categorical variables. Multivariable logistic regression models were used to identify predictors of persistent opioid use. Adjusted odds ratios (AOR) from logistic regression models were used to compare relative odds of persistent opioid use between comparison groups. P-values of <0.05 were considered statistically significant. Statistical Package for the Social Sciences (SPSS) version 27 was used for data analyses. As the focus of study 2 was on determining the rates and predictors of "new" persistent opioid use, we only included opioid-naïve patients, defined as patients who did not fill opioid prescription within 6 months prior to the index date.

Sensitivity analysis

Several sensitivity analyses were conducted to test the robustness of the study results. Given the lack of consensus on the definition of opioid-naïve, the primary analyses was repeated by changing the look-back window time for the definition of opioid-naïve from 6 month to 3 month and 12 months. In another sensitivity analysis, given the varying definitions of persistent opioid use in the literature, the primary analysis was repeated by changing the definition of persistent opioid use. For this sensitivity analysis, persistent opioid users were defined as those who had an opioid dispensing at index date and who had continuously dispensed opioids for at least 120 days within 6 months following the index date.

# 4. RESULTS

## 4.1 Chapter overview

This chapter presents the findings of Studies 1 and 2. The chapter is divided into two sections; Incidence rate and prevalence of opioid use in older adults and rate and predictors of persistent opioid use in older adults. The first section presents data on the incidence rate and prevalence of opioid use in older adults. Data for incidence rate and prevalence are presented separately and in the following order: 1) Overall incidence rate/prevalence of opioid use, 2) Overall incidence rate/prevalence of opioid use by type of opioid, 3) Incidence rate/prevalence of opioid use by sex and opioid strength, 4) Incidence rate/prevalence of opioid dispensing by specific opioid type. The second section describes the characteristics of the study cohort, then present the primary analysis and sensitivity analysis results of study 2.

## 4.2 Incidence rate and prevalence of opioid use in older adults

### 4.2.1 Incidence rate of opioid use

Overall incidence rate of opioid use

Figure 3 shows the overall incidence rate of opioid use amongst NZ older population from 2008 to 2018. In total, 820,349 older adults were initiated on opioids between 2008 and 2018. The trend for the incidence rate shows a steady increase until 2015, where it reached its peak, then the rate fluctuated afterwards. The incidence rate then slightly decreased in 2018.

The overall incidence rate ranged between 74.3 per 1000 persons in 2008 and 86.3 per 1000 persons in 2018, where the lowest incidence rate was in 2008 (74.3 per 1000 persons) and the highest in 2015 (89.4 per 1000 persons).

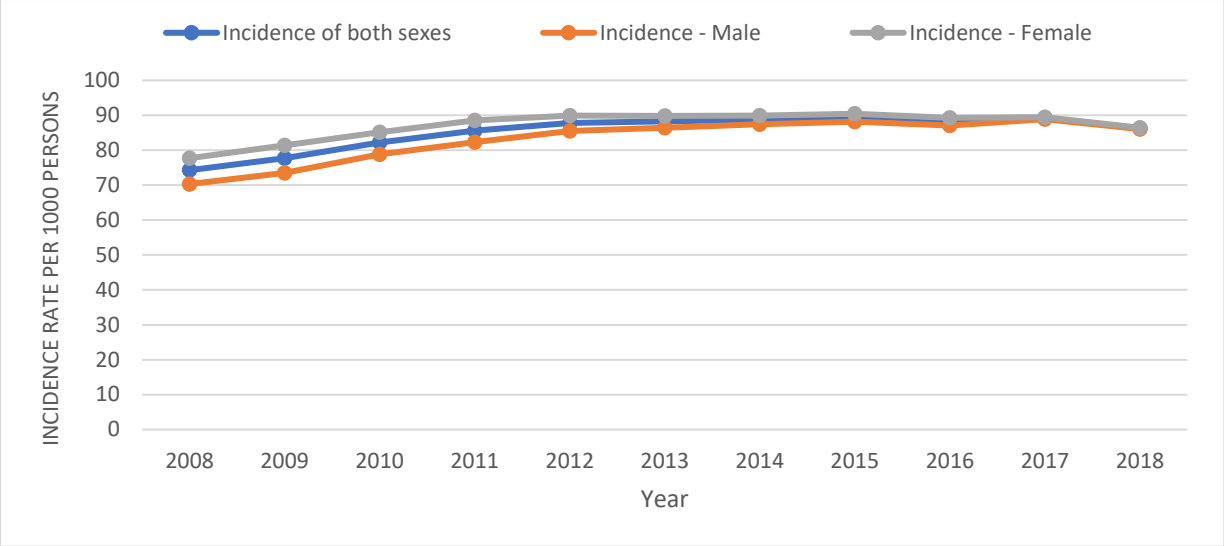


**Figure 3:** The overall incidence rate of opioid use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

Overall incidence rate of opioid use by opioid type

As shown in the figure 4, the most newly initiated opioid in each year was codeine, while the incidence rate of pethidine was the lowest. The two most frequently initiated opioids belong to weak opioids (codeine and tramadol). Codeine incidence rate reached its peak in 2017 (52.7 per 1000 persons). Tramadol (35.7 per 1000 persons), morphine (20.4 per 1000 persons), oxycodone (12.5 per 1000 persons), and dihydrocodeine (5.0 per 1000 persons) incidence rates were highest in 2013, 2017, 2011, and 2008, respectively. Fentanyl (4.2 per 1000 persons) and pethidine (0.4 per 1000 persons) incidence rates were highest in 2016 and 2008 respectively.

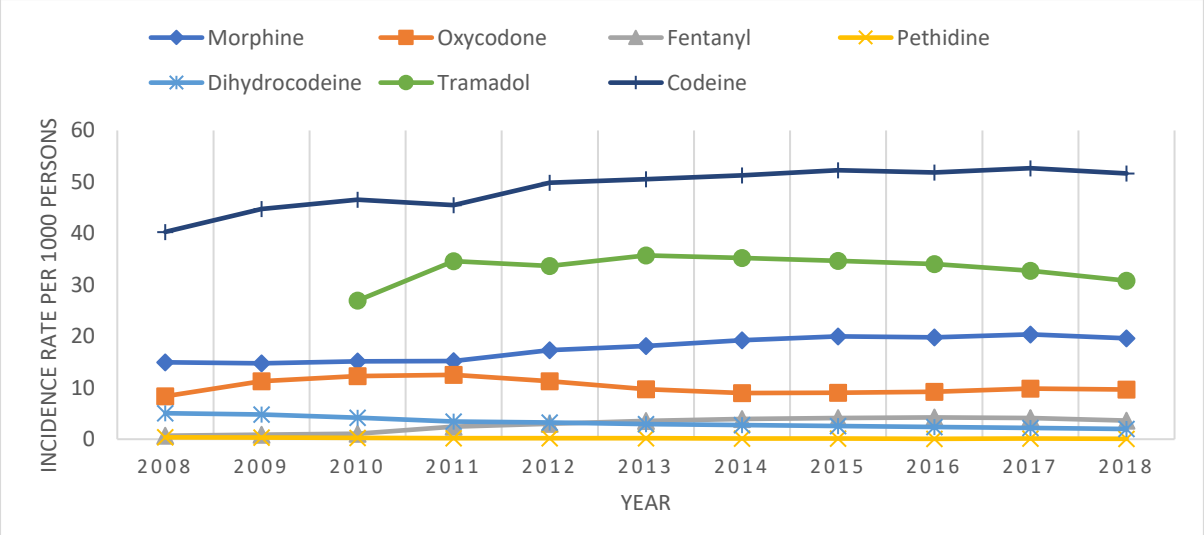


**Figure 4:** The incidence rate of opioid use by opioid type in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

Incidence rate of opioid use by sex and opioid strength

Figure 5 illustrates a comparison between strong and weak opioid use. It was observed that the incidence rates of weak opioid use (codeine, dihydrocodeine and tramadol), both in males and females, were higher than the incidence rate of strong opioid use (morphine, oxycodone, pethidine and fentanyl). Incidence rates were higher among females than males for both strengths of opioids. The highest incidence rates of strong opioid use in males and females were observed in 2017 (31.6 per 1000 persons and 37.0 per 1000 persons, respectively), whereas the lowest incidence rates were observed in 2008 (22.6 per 1000 persons and 25.8 per 1000 persons, respectively). As for weak opioids, the highest incidence rate of weak opioid use in males was observed in 2017 (87.6 per 1000 persons) and in 2013 for females (91.8 per 1000 persons), whereas the lowest incidence rates were observed in 2008 for males and females (41.2 per 1000 persons and 48.9 per 1000 persons, respectively).

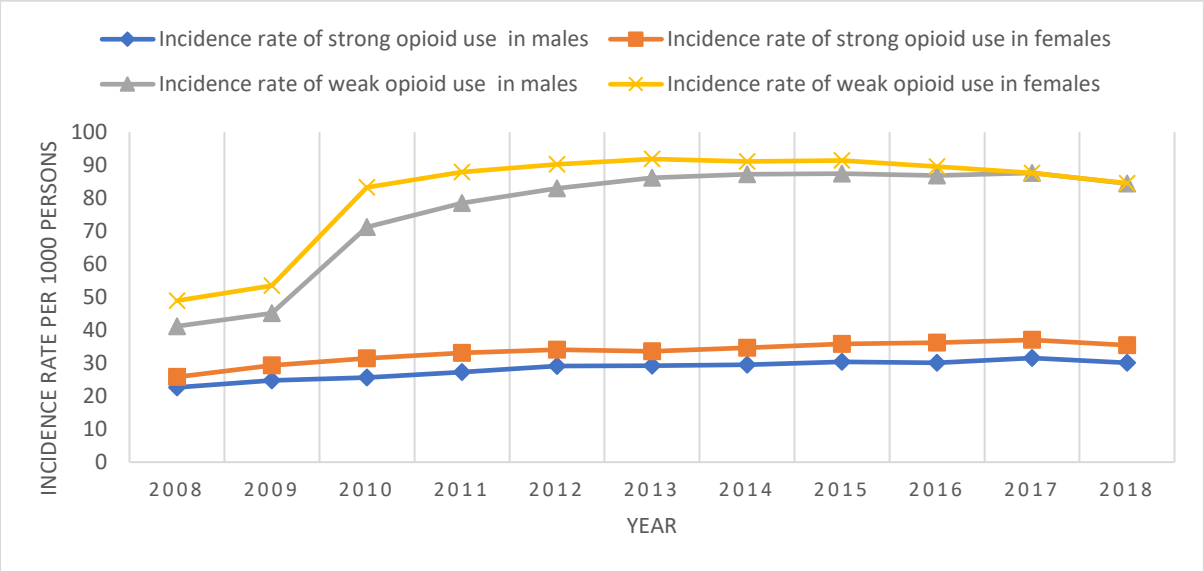


**Figure 5:** Comparison between strong and weak opioid use incidence rates in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

Incidence rate of opioid use by strength of opioid

*Strong Opioids – combined*

As shown in figure 6, morphine was the most commonly initiated strong opioid in each year during the study period, while pethidine was the lowest newly initiated strong opioid in each year. As noticed, morphine decrease was accompanied by oxycodone increase and vice versa. Incidence rate for fentanyl gradually increased after 2010, while the incidence rate of pethidine was steady during the study period.

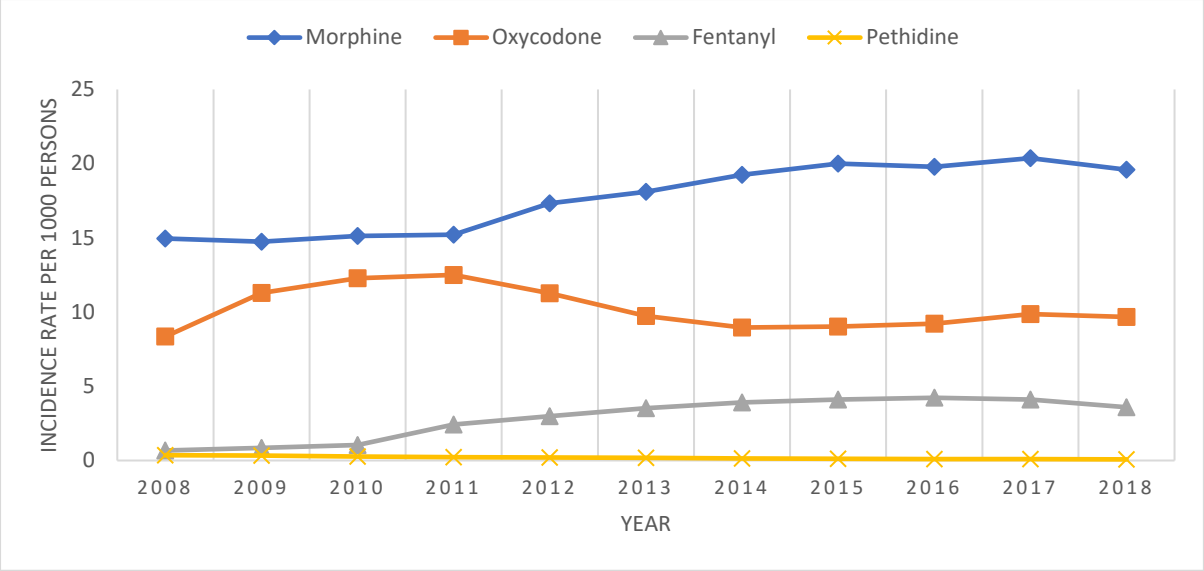


**Figure 6:** The incidence rate of strong opioid use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

*Morphine*

Morphine incidence rate ranged from 15.0 per 1000 persons in 2008 to 19.6 per 1000 persons in 2018, where the lowest rate was 14.7 per 1000 persons in 2009 and the highest rate was 20.4 per 1000 persons in 2017. The incidence rate was relatively steady between 2008 and 2011, then gradually increased after 2011. Females had higher incidence rates than males throughout the study period (see Figure 7).

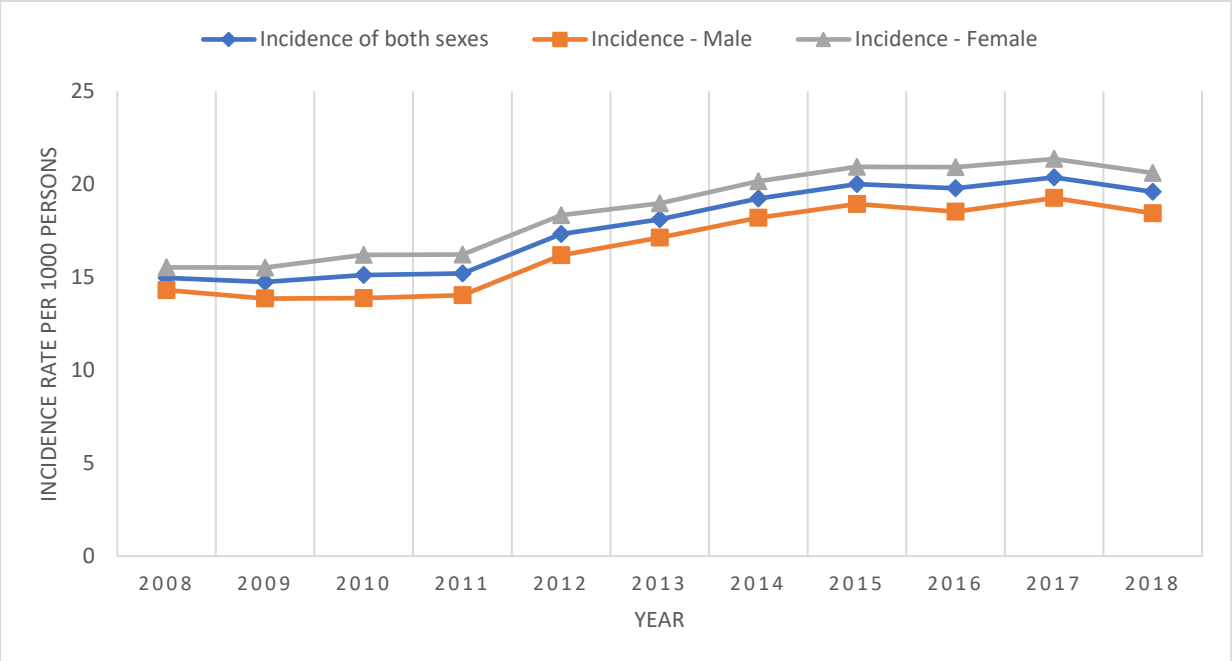


**Figure 7:** The incidence rate of morphine use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

*Oxycodone*

The incidence rate of oxycodone ranged from 8.3 per 1000 persons in 2008 to 9.7 per 1000 persons in 2018. The lowest incidence rate was 8.3 per 1000 persons in 2008, whereas the peak was observed in 2011 (12.5 per 1000 persons). The incidence rates for both males and females has gradually increased from 2008 to 2011, then the incidence rate gradually decreased between 2012-2014 and then plateaued starting from 2015 (see Figure 8).

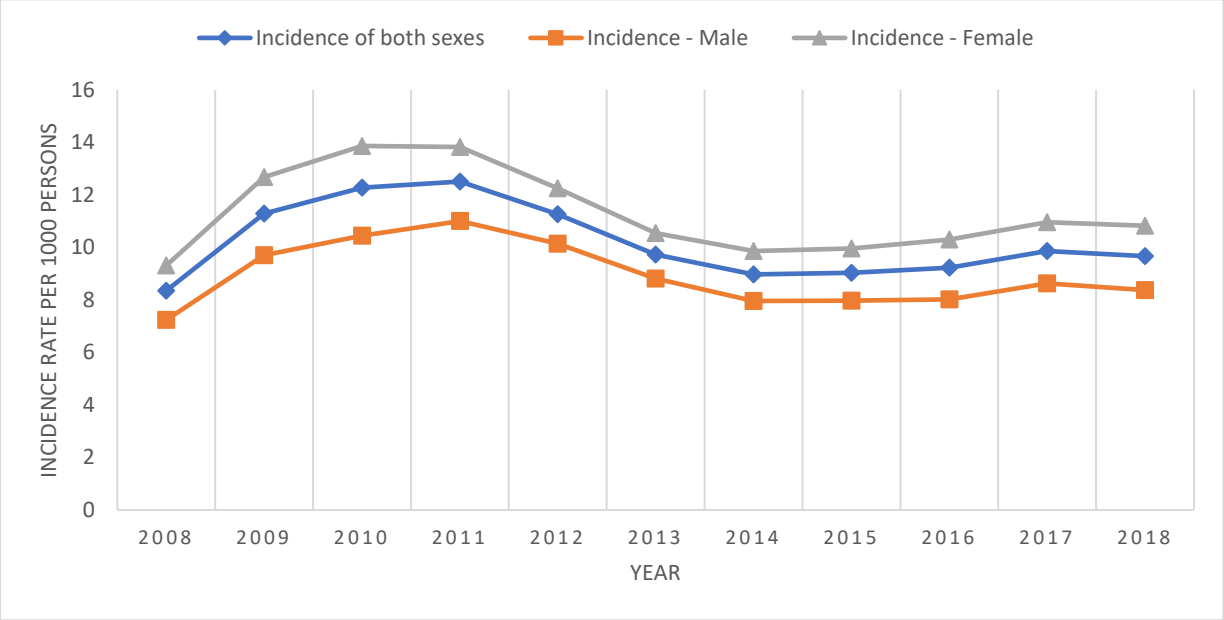


**Figure 8:** The incidence rate of oxycodone use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

*Fentanyl*

Figure 9 illustrates fentanyl incidence rate, where it ranged between 0.7 per 1000 persons in 2008 and 3.6 per 1000 persons in 2018. The peak incidence rate was observed in 2016 as 4.2 per 1000 persons and the lowest rate was observed in 2008 as 0.7 per 1000 persons. The incidence rate was relatively steady from 2008 to 2010, then it started rising from 2011, where incidence rate for females started exceeding males.

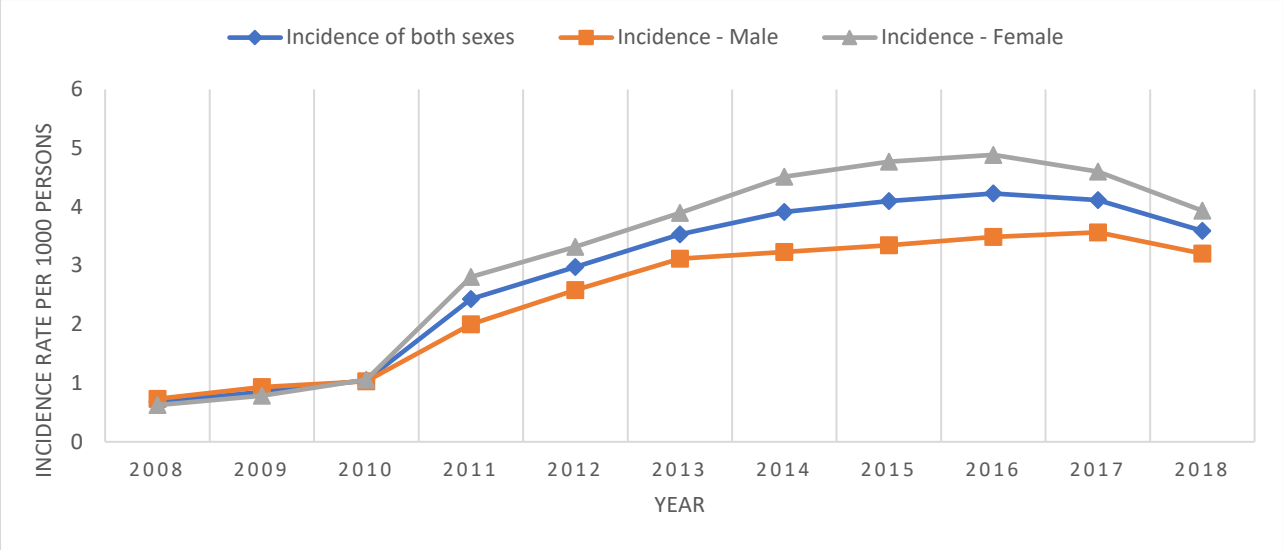


**Figure 9:** The incidence rate of fentanyl use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

*Pethidine*

Pethidine incidence rate was the lowest compared to other opioids in this study where it ranged from 0.4 per 1000 persons in 2008 to 0.08 per 1000 persons in 2018. The peak and lowest incidence rates were observed in 2008 (0.4 per 1000 persons) and in 2018 (0.08 per 1000 persons), respectively. The incidence rate for pethidine gradually dropped over the study period, and the incidence rate of females was higher for most of the study period except in 2013 and 2014 (see Figure 10).

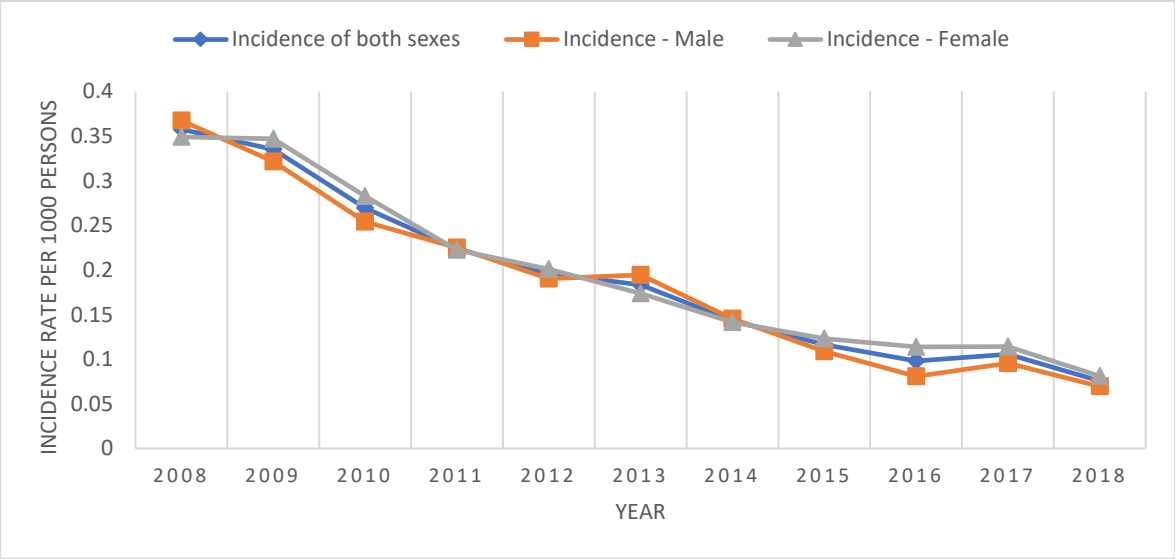


**Figure 10:** The incidence rate of pethidine use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

*Weak opioids – combined*

As shown in the figure 11, codeine was the most commonly initiated weak opioid throughout the study period, while dihydrocodeine was the lowest newly initiated weak opioid. It is noticeable that the decline in codeine incidence rate in 2011 was accompanied by an increase in tramadol incidence rate.

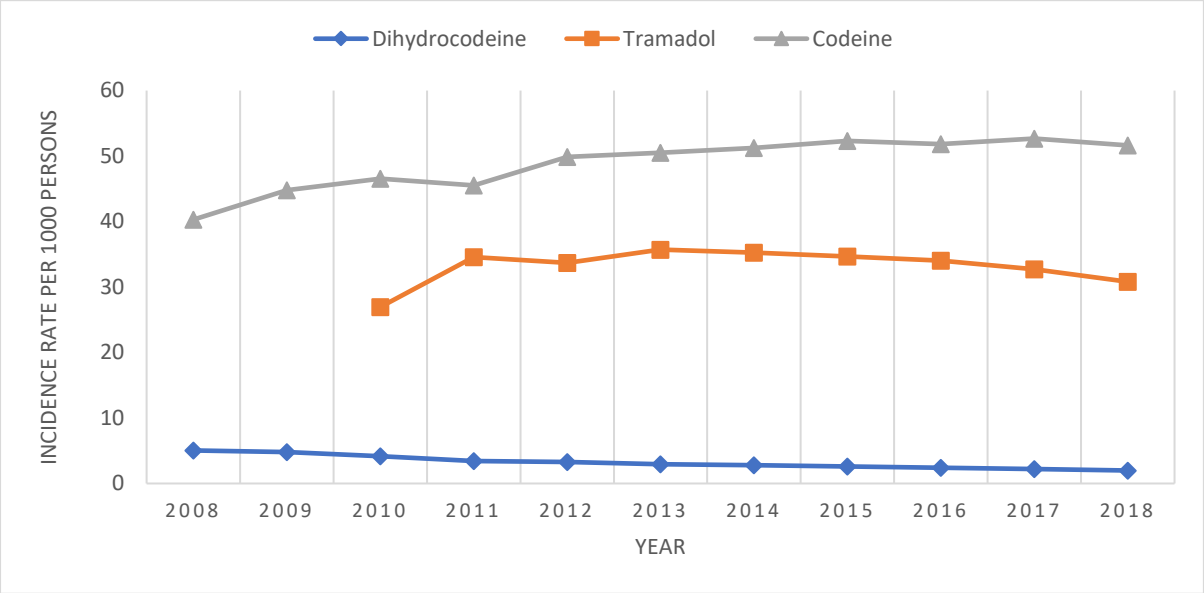


**Figure 11:** The incidence rate of weak opioid use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

*Dihydrocodeine*

The incidence rate of dihydrocodeine ranged from 5.0 per 1000 persons in 2008 to 2.0 per 1000 persons in 2018 (lowest to highest rate: 2.0 per 1000 in 2018 and 5.0 per 1000 in 2008). The incidence rate has been gradually dropping over time. Females had a higher incidence rate than males (see Figure 12).

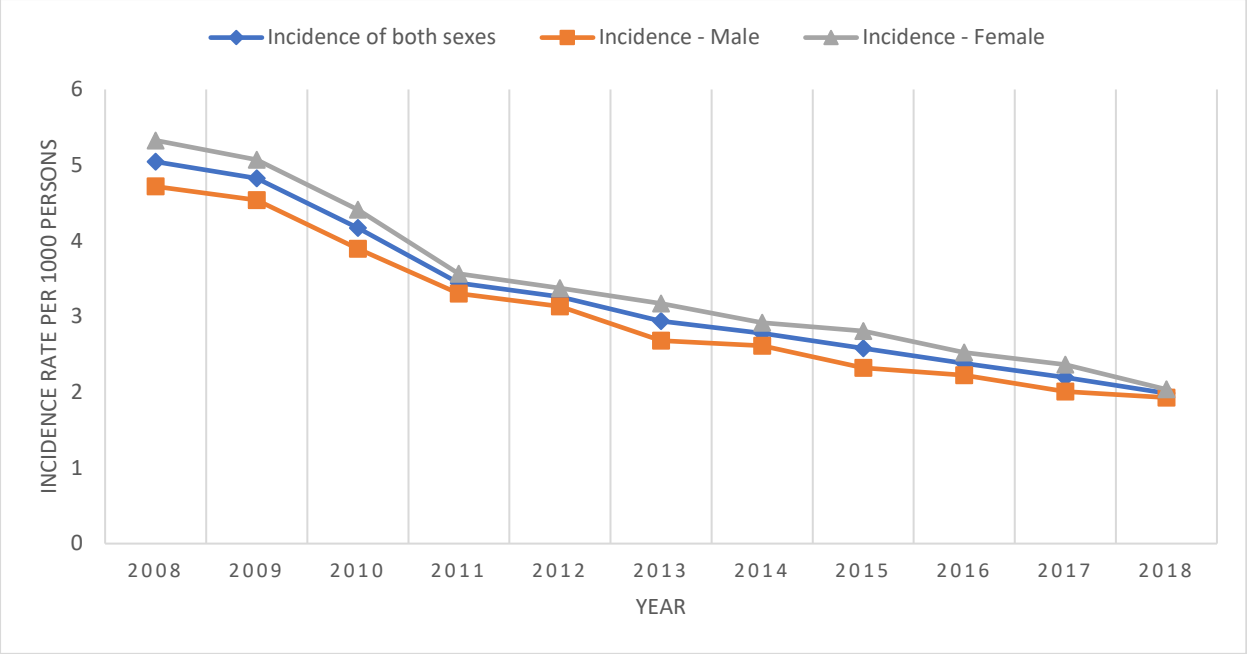


**Figure 12:** The incidence rate of dihydrocodeine use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

*Tramadol*

Tramadol was funded in NZ since 1 June 2010, hence why dispensing data prior to this date were not available. Tramadol incidence rate ranged from 27.0 per 1000 persons in 2010 to 30.8 per 1000 persons in 2018. The peak (35.7 per 1000 persons) and lowest rates (27.0 per 1000 persons) were observed in 2013 and 2010, respectively. The incidence rate showed significant increase between 2010 and 2011 then a slight decline was observed in 2012. The rate started to rise again in 2013 then this rise was followed by a steady decrease in 2014 and thereafter. Male incidence rate surpassed female incidence rate starting from 2012 (see Figure 13).

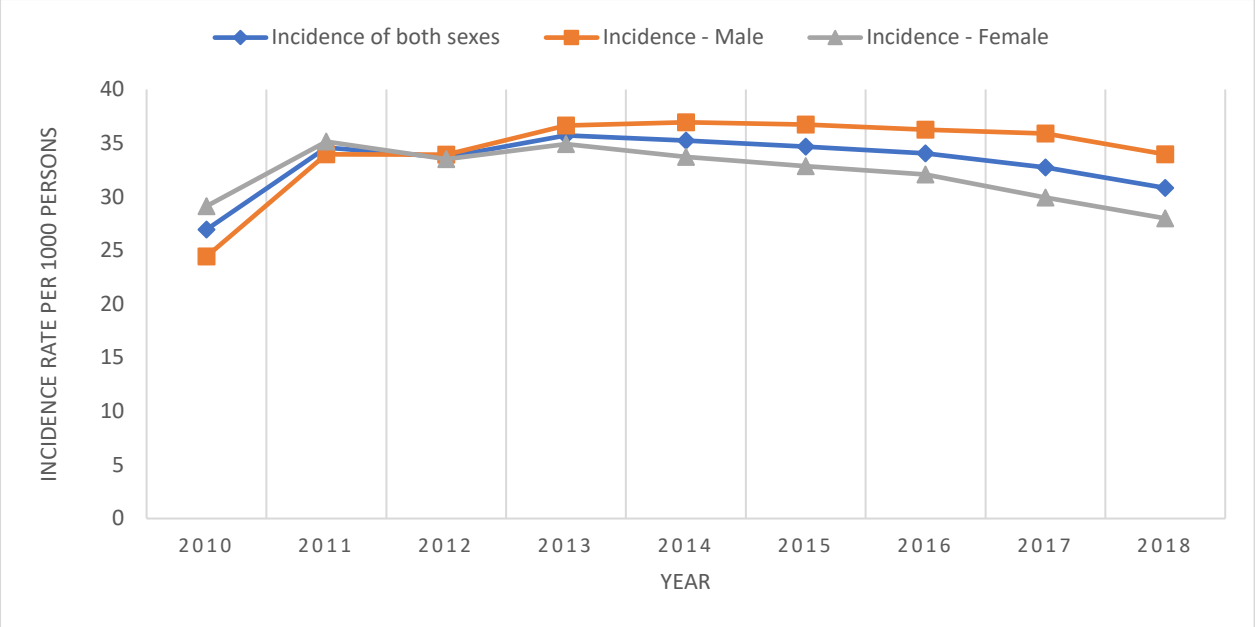


**Figure 13:** The incidence rate of tramadol use in male and female older adults, as rates per 1000 persons, from 2010 to 2018.

*Codeine*

Codeine incidence rate ranged between 40.3 per 1000 persons in 2008 and 51.7 per 1000 persons in 2018. The lowest (40.3 per 1000 persons) and highest (52.7 per 1000 persons) incidence rates were observed in 2008 and 2017, respectively. The data showed steady increase in the incidence rate of codeine during the study period, apart from a slight decrease in 2011. Females had higher incidence rate than males (see Figure 14).

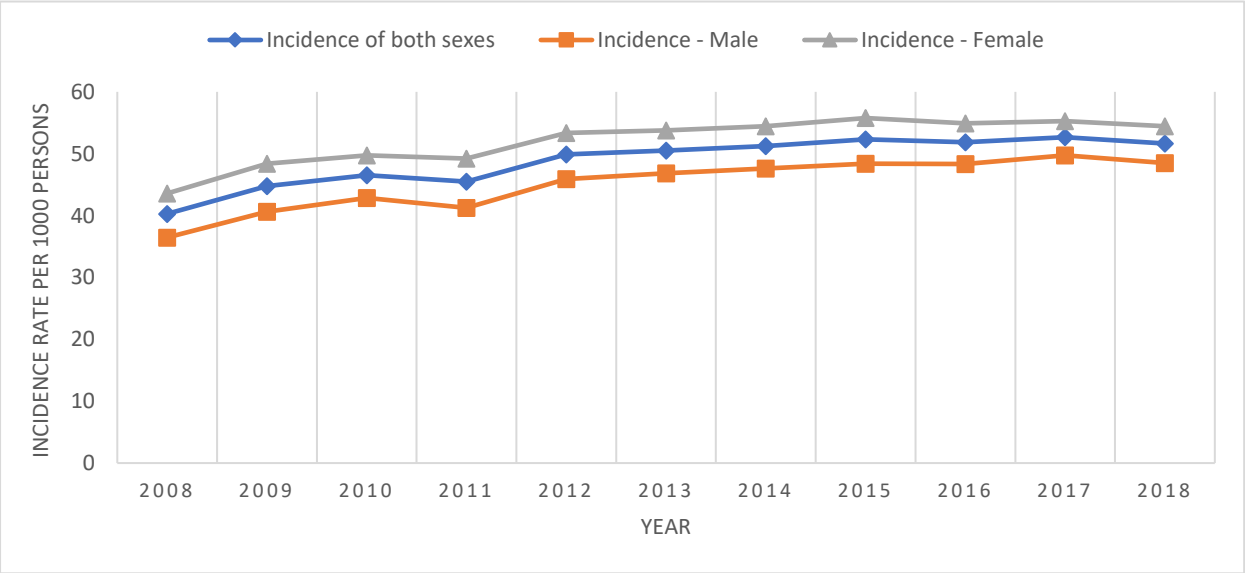


**Figure 14:** The incidence rate of codeine use in male and female older adults, as rates per 1000 persons, from 2008 to 2018.

### 4.2.2 Prevalence of opioid use

Overall prevalence of opioid use

As shown in Figure 15, the overall prevalence of opioid use amongst older adults increased steadily over time till 2015, where it reached its peak. The prevalence then slightly fluctuated and a slight decrease was observed in 2018. The overall prevalence of opioid use ranged from 153.4 per 1000 persons in 2007 to 181.5 per 1000 persons in 2018. The lowest (153.4 per 1000 persons) and highest (186.5 per 1000 persons) overall prevalence were observed in 2007 and 2015, respectively.

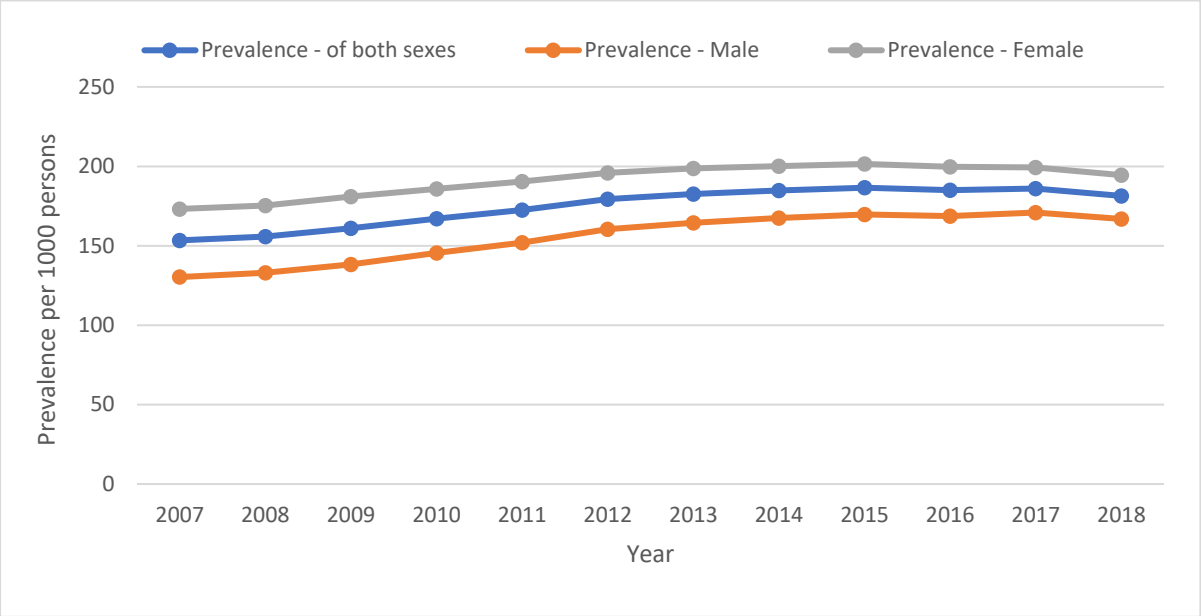


**Figure 15:** The overall prevalence of opioid use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

Overall prevalence of opioid use by opioid type

The prevalence of opioid use by opioid type between 2007 and 2018 is presented in figure 16. The prevalence of codeine was the highest throughout the study period, while the prevalence of pethidine was the lowest. Codeine prevalence reached its peak in 2017 (80.3 per 1000 persons). Tramadol (53.7 per 1000 persons), morphine (28.5 per 1000 persons), oxycodone (18.5 per 1000 persons), and dihydrocodeine (8.5 per 1000 persons) prevalence were highest in 2014, 2017, 2011, and 2007, respectively. Fentanyl (6.7 per 1000 persons) and pethidine (0.7 per 1000 persons) prevalence were highest in 2017 and 2007, respectively.

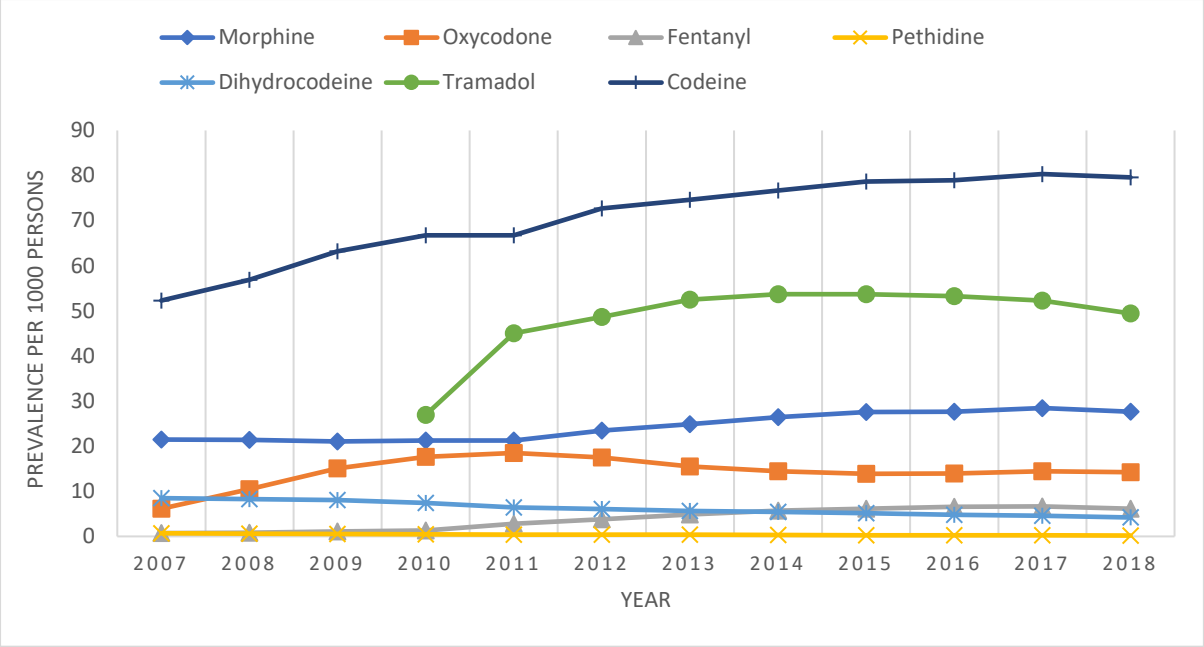


**Figure 16:** The prevalence of opioid use by opioid type in male and female older adults, as rates per 1000 persons, from 2007 to 2018

Prevalence of opioid use by sex and opioid strength

Figure 17 shows a comparison between strong and weak opioid use. The prevalence of weak opioid use (codeine, dihydrocodeine and tramadol), both in males and females, was higher than the prevalence of strong opioid use (morphine, oxycodone, pethidine and fentanyl). Females had higher prevalence than males for both strong and weak opioids use throughout the study period. There is a noticeable increase in the weak opioid use after 2009. The highest prevalence of strong opioid use in males and females was observed in 2017 (43.5 per 1000 persons and 55.4 per 1000 persons, respectively), whereas the lowest prevalence was observed in 2007 (26.5 per 1000 persons and 31.2 per 1000 persons, respectively). As for weak opioid use, the highest prevalence for males was observed in 2017 (129.4 per 1000 persons) and highest prevalence for females was observed in 2015 (146.5 per 1000 persons), whereas the lowest prevalence for males and females were observed in 2007 (52.4 per 1000 persons and 68.0 per 1000 persons, respectively).

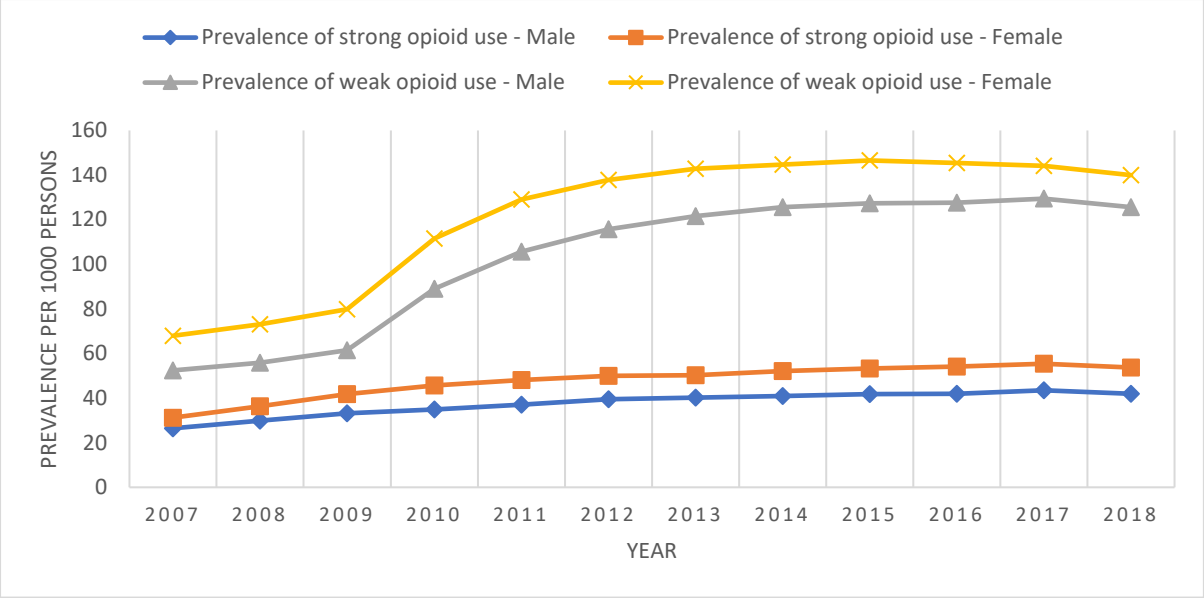


**Figure 17:** Comparison between prevalence of strong and weak opioid use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

Prevalence of opioid use by strength of opioid

*Strong opioids – combined*

As shown in Figure 18, the prevalence of morphine was highest throughout the study period, while the prevalence of pethidine was the lowest. The steady decrease in morphine prevalence was accompanied by a steady increase in oxycodone prevalence and vice versa. The prevalence of fentanyl use showed gradual increase after 2010 while the prevalence of pethidine was steady during the study period.

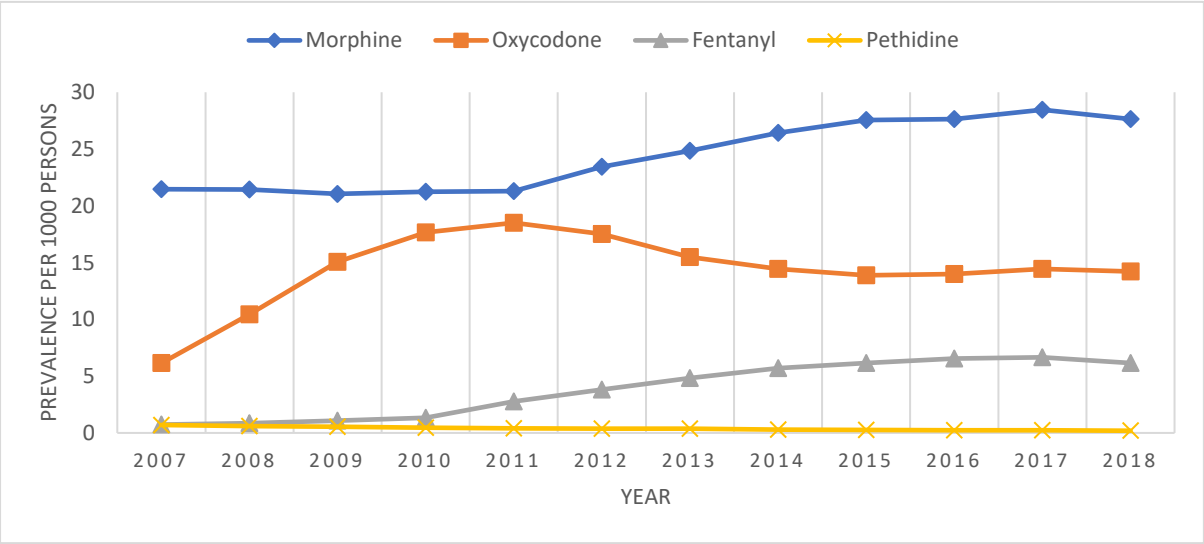


**Figure 18:** The prevalence of strong opioid use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

*Morphine*

Morphine prevalence ranged from 21.5 per 1000 persons in 2007 to 27.6 per 1000 persons in 2018 with the highest prevalence being 28.5 per 1000 persons in 2017 and the lowest prevalence being 21.1 per 1000 persons in 2009. The prevalence was relatively steady between 2007 and 2011, then a gradual increase occurred starting from 2012. Females had higher prevalence than males throughout the study period (see Figure 19).

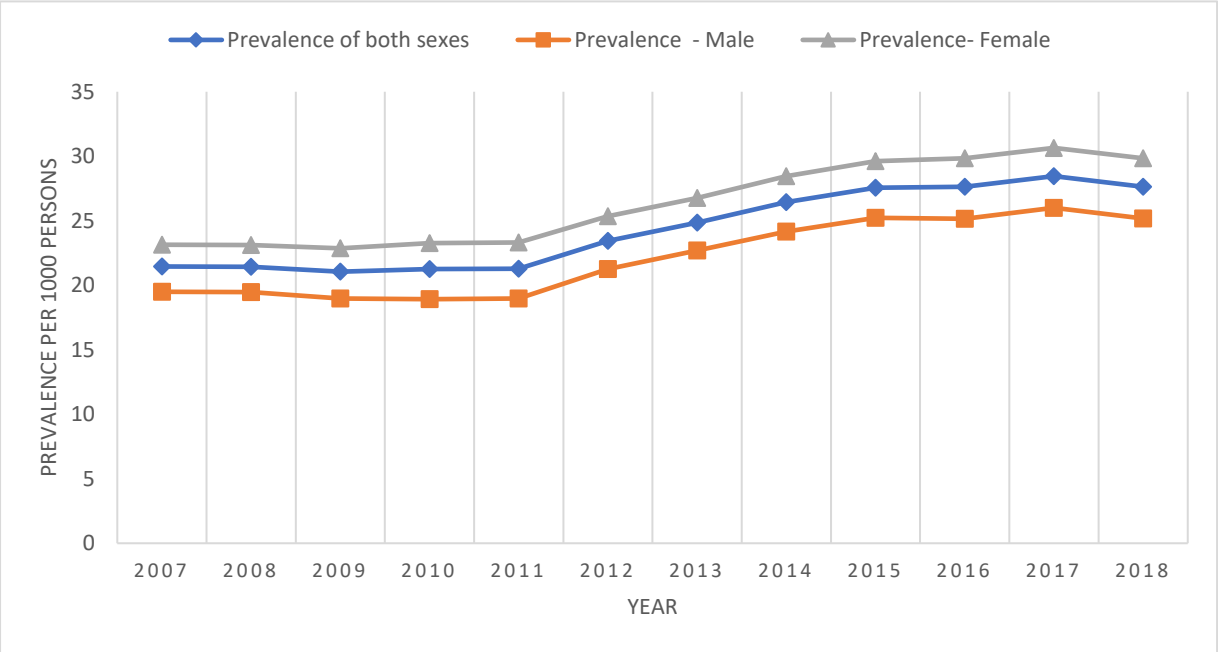


**Figure 19:** The prevalence of morphine use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

*Oxycodone*

The prevalence of oxycodone ranged from 6.1 per 1000 persons in 2007 to 14.2 per 1000 persons in 2018. The lowest (6.1 per 1000 persons) and highest (18.5 per 1000 persons) prevalence were observed in 2007 and 2011, respectively. Oxycodone prevalence had gradually increased from 2007 to 2011 where it reached its peak, then the prevalence declined. Females had higher prevalence than males throughout the study period (see Figure 20).

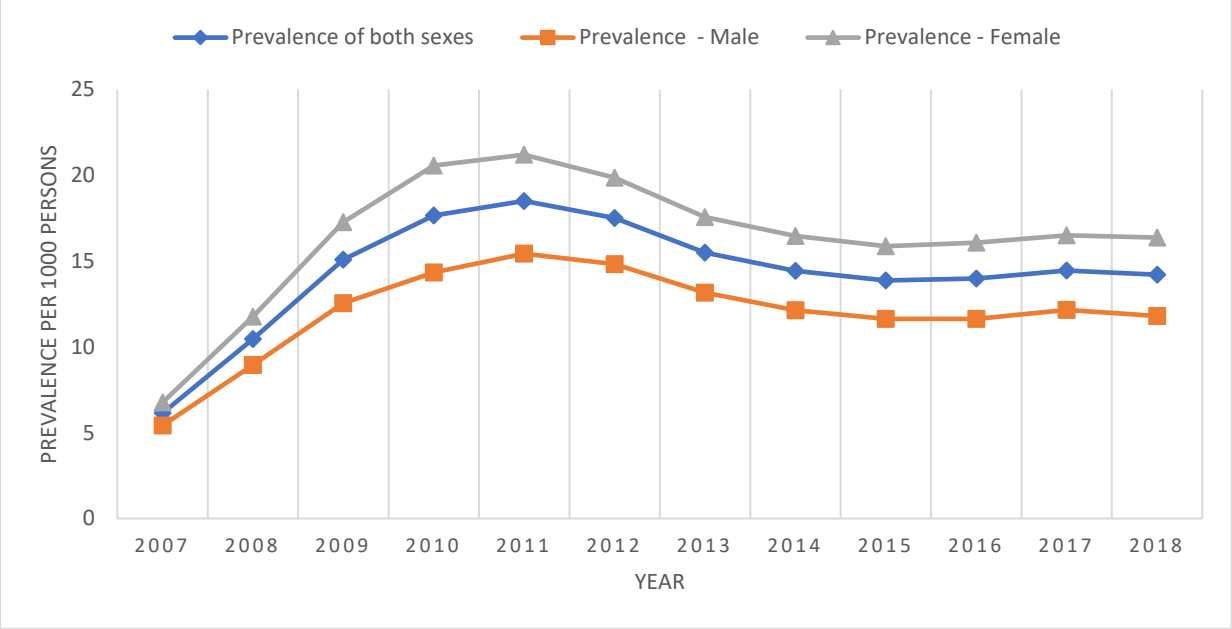


**Figure 20:** The prevalence of oxycodone use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

*Fentanyl*

As shown in Figure 21, fentanyl prevalence ranged from 0.7 per 1000 persons in 2007 to 6.2 per 1000 persons in 2018. The highest prevalence was observed in 2017 (6.7 per 1000 persons) and the lowest prevalence was observed in 2007 (0.7 per 1000 persons). Fentanyl prevalence was relatively steady between 2007 and 2010 for both male and females, then started increasing. It is noticeable that the prevalence of female use started exceeding male use after 2010.

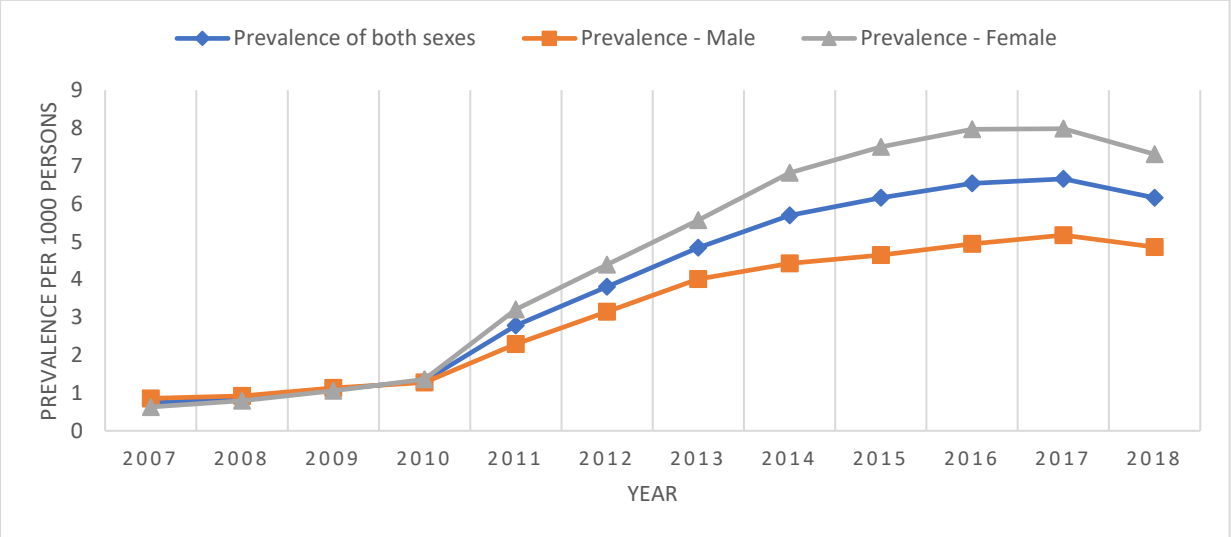


**Figure 21:** The prevalence of fentanyl use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

*Pethidine*

The use of pethidine in older adults was low as shown in Figure 22, where it ranged from 0.7 per 1000 persons in 2007 to 0.2 per 1000 persons in 2018. The highest prevalence was in 2007 (0.7 per 1000 persons) and the lowest prevalence was in 2018 (0.2 per 1000 persons). The prevalence has been gradually dropping over time. Females had slightly higher prevalence than males.

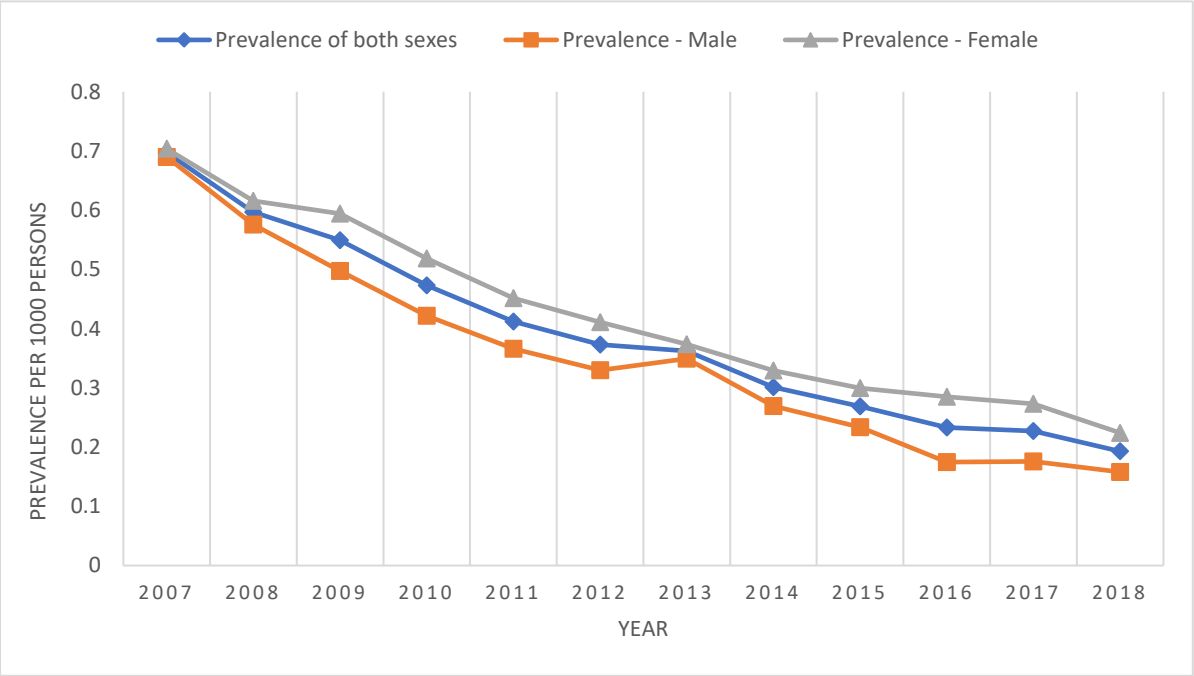


**Figure 22:** The prevalence of pethidine use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

*Weak opioids – combined*

Similar to incidence rates of weak opioids, the prevalence of codeine was highest during the study period while the prevalence of dihydrocodeine was the lowest. The prevalence of codeine showed steady increase, while the prevalence of dihydrocodeine slightly decreased over time. Tramadol prevalence was increasing starting from 2011 (see Figure 23).

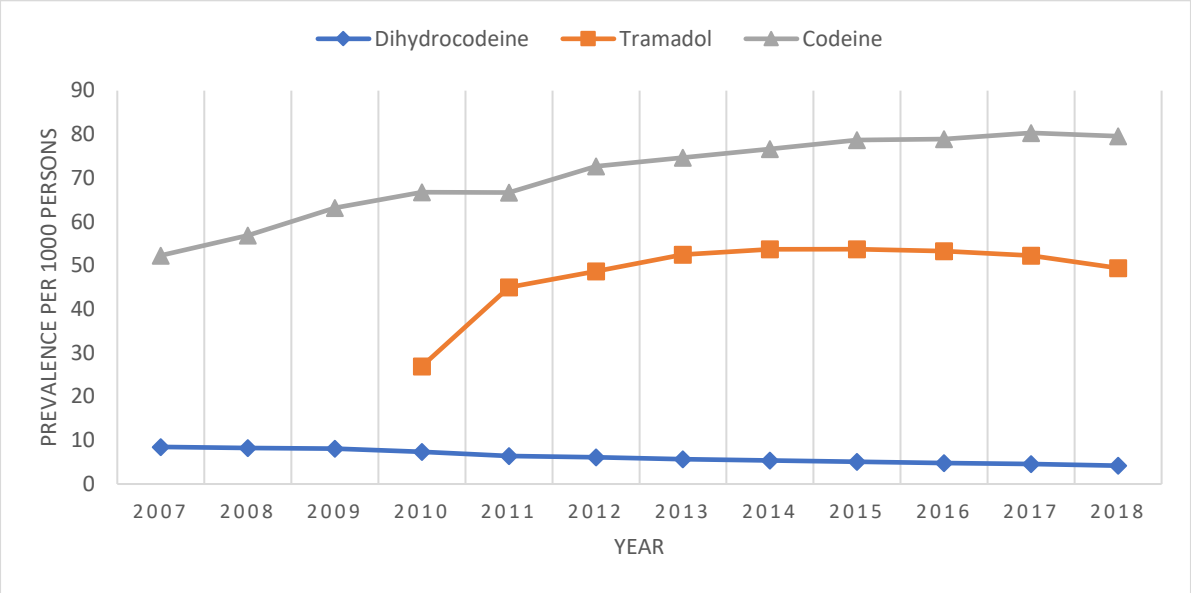


**Figure 23:** The prevalence of weak opioid use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

*Dihydrocodeine*

The prevalence of dihydrocodeine ranged from 8.5 per 1000 persons in 2007 to 4.2 per 1000 persons in 2018. The lowest and highest prevalence were observed in 2018 (4.2 per 1000 persons) and 2007 (8.5 per 1000 persons), respectively. Prevalence has been gradually dropping over time, and females had higher prevalence than males (see Figure 24).

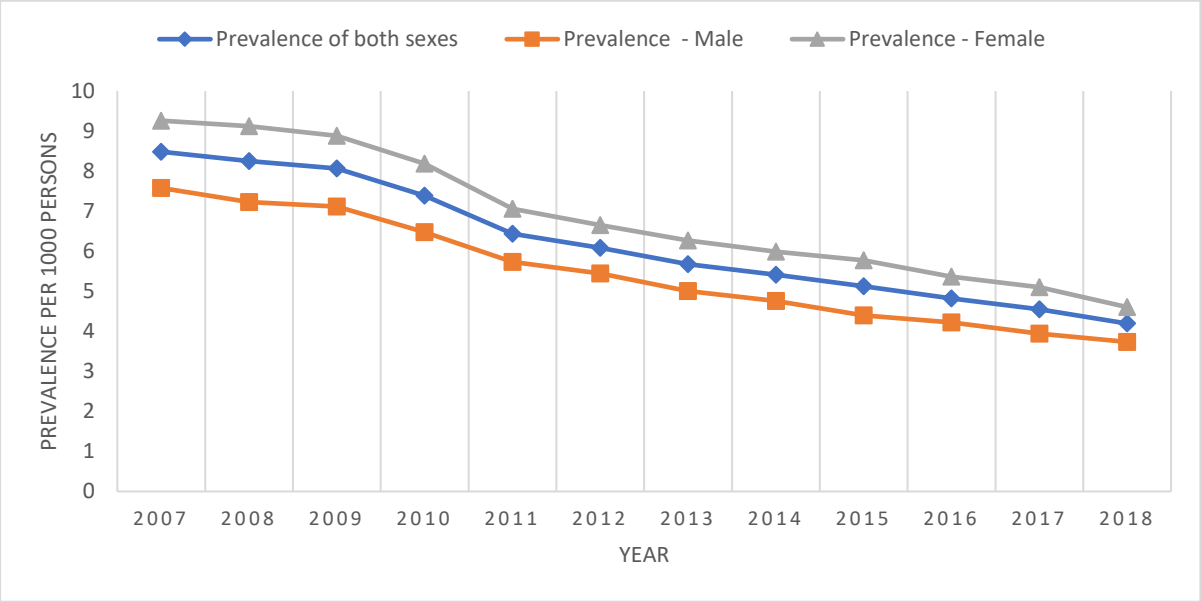


**Figure 24:** The prevalence of dihydrocodeine use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

*Tramadol*

As shown in Figure 25, tramadol prevalence ranged from 27.0 per 1000 persons in 2007 to 49.4 per 1000 persons in 2018. The highest prevalence was observed in 2014 (53.7 per 1000 persons) and the lowest prevalence was observed in 2010 (27.0 per 1000 persons). Tramadol prevalence showed significant increase after 2010, peaked in 2014, then started slightly decreasing after 2014. Females had higher prevalence than males till 2013, then the prevalence of males surpassed female use.

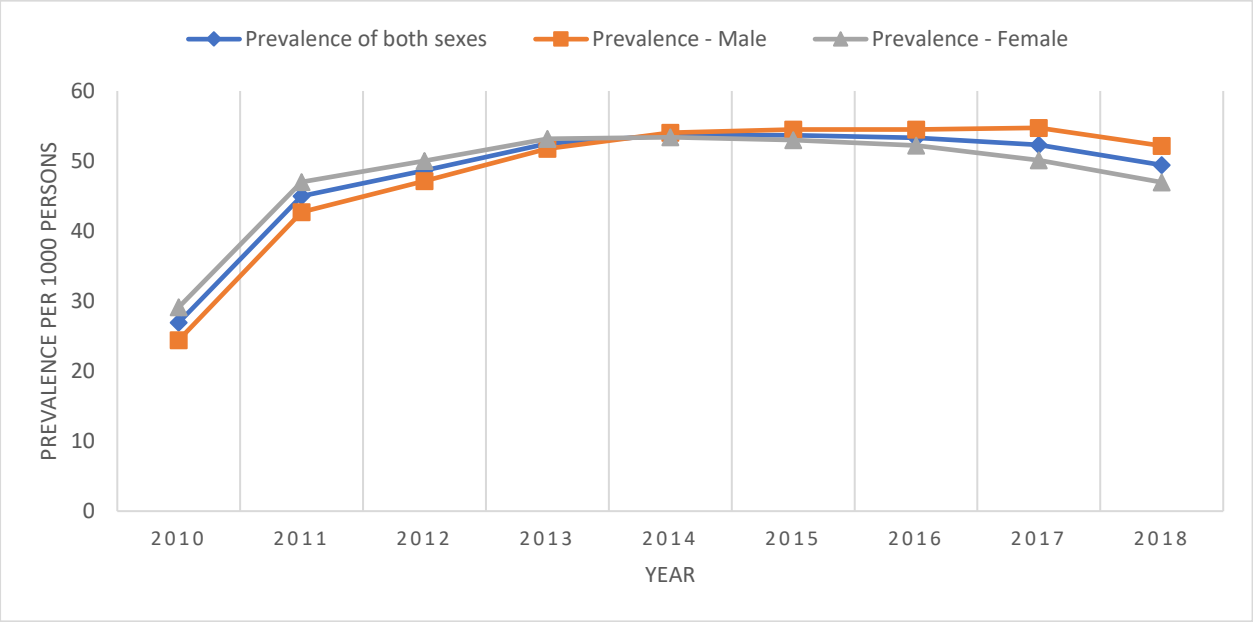


**Figure 25:** The prevalence of tramadol use in male and female older adults, as rates per 1000 persons, from 2010 to 2018.

*Codeine*

Codeine prevalence ranged from 52.3 per 1000 persons in 2007 to 79.6 per 1000 persons in 2018, where the lowest prevalence was 52.3 per 1000 persons in 2007 and the highest prevalence was 80.3 per 1000 persons in 2017. The data showed a steady increase in prevalence of codeine over time. Females had higher prevalence than males (see Figure 26).

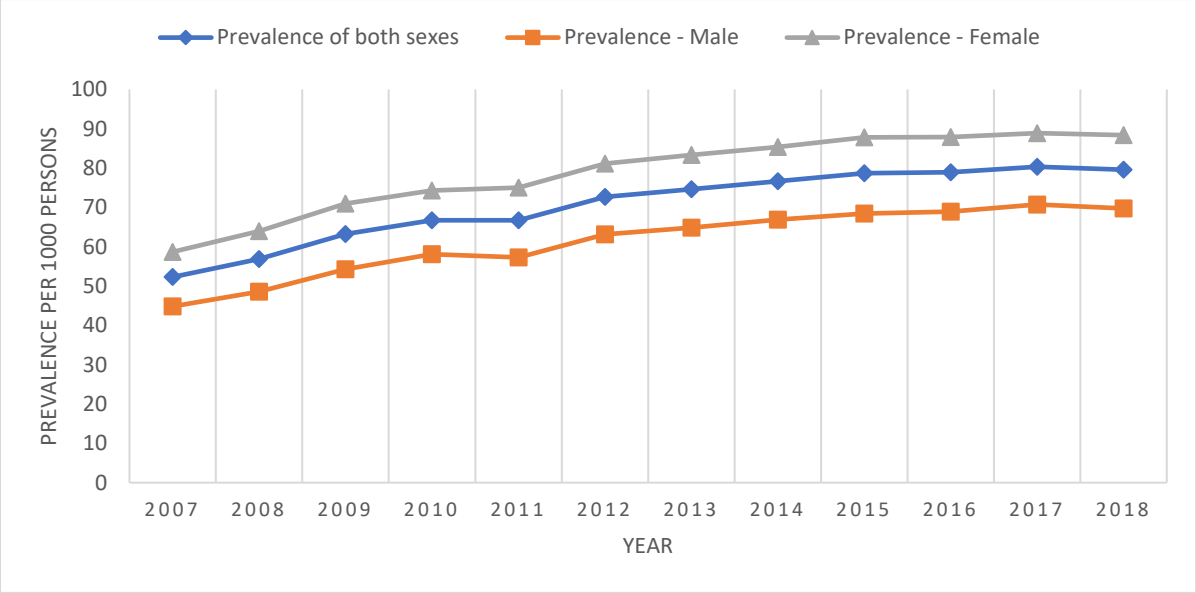


**Figure 26**: The prevalence of codeine use in male and female older adults, as rates per 1000 persons, from 2007 to 2018.

## 4.3 Rate and Predictors of persistent opioid use in older adults in NZ

### 4.3.1 Baseline characteristics of the study cohort

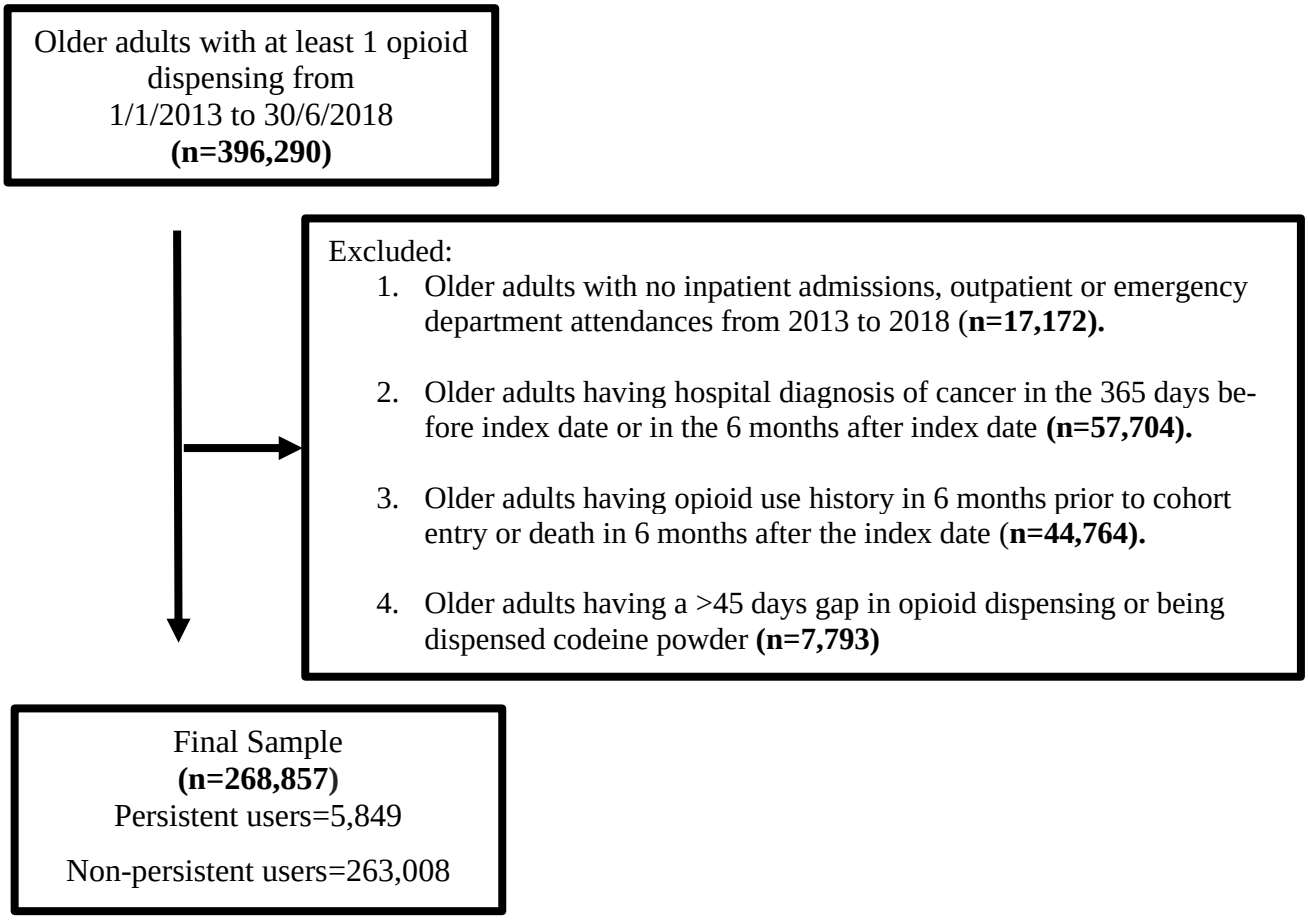


**Figure 27:** Sample selection flowchart for Study 2

As shown in Figure 27, overall, 396,290 older adults filled at least one opioid prescription during the study period. From this initial population, 17,172 patients were excluded due to lack of either inpatient or outpatient/ED visits history during the study period. A further 57,704 patients were excluded due to cancer diagnoses within 365 before or 6 months after index date; 44,764 patients were excluded due to opioid use history in 6 months prior to cohort entry or death in 6 months after the index date. Further, 7,793 patients were excluded due to >45 days gap in opioid dispensing or because they were dispensed codeine powder. After these exclusions, the final study populations included 268,857 opioid-naïve non-cancer patients.

As shown in Table 8, those who initiated opioids use were mostly NZ Europeans (84.8%), females (54.9%), 65-74 years of age (58.6%), and lived in areas with deprivation index quintile 4 (23.5%). Most patients (64.7%) had no inpatient admissions 365 days prior to index date, while 42.4% of them had 3 or more outpatient or ED visits in 365 days prior to index date. Initial opioid prescriptions were most often codeine (56.4%), tramadol (30.4%) or morphine (5%). Initial prescriptions for most patients were weak opioids (90.2%), and the strength of initial prescriptions for 25% of the patients were 51-90 MME/day. Only 0.5% of study participants used injectable preparations, while 7.9% used slow-release preparations. The most frequent comorbidities included hypertension (13.1%), diabetes (9.2%), osteoarthritis (4.8%), chronic kidney disease (4.0%), and respiratory disorders (3.9%). Most patients had zero CCI score (82.5%). Common other medications used included non-opioid analgesics (68.5%), antihypertensives (68%), antidepressants (21.5%), antidiabetic medications (14.1%), and anxiolytics, sedatives and hypnotics (19.8%).

**Table 8:** Baseline characteristics of the study participants

| Variables | All<br>N=268,857<br>n (%) | Persistent users<br>N= 5,849<br>n (%) | Non-persistent users<br>N= 263,008<br>n (%) | $\chi^2$ test<br><br>p-value |
|---|---|---|---|---|
| **Female** | 147,596 (54.9) | 3,568 (61.0) | 144,028 (54.8) | <0.001 |
| **Age in years** | | | | |
| 65-74 years | 157,530(58.6) | 2,757(47.1) | 154,773(58.8) | <0.001 |
| 75-84 years | 78,521(29.2) | 1,525(26.1) | 76,996(29.3) | |
| >85 years | 32,806(12.2) | 1,567(26.8) | 31,239(11.9) | |
| **Ethnicity** | | | | |
| European | 227,942(84.8) | 5,261(89.9) | 222,681(84.7) | <0.001 |
| Māori | 17,189(6.4) | 395(6.8) | 16,794(6.4) | |
| Pacific | 9,136(3.4) | 74(1.3) | 9,062(3.4) | |
| Asian | 12,777(4.8) | 96(1.6) | 12,681(4.8) | |
| Other | 1,538(0.6) | 17(0.3) | 1,521(0.6) | |
| Missing | 275(0.1) | 6(0.1) | 269(0.1) | |
| **Deprivation Index** | | | | |
| Quintile 1 (least deprived) | 46,667(17.4) | 797(13.6) | 45,870(17.4) | <0.001 |
| Quintile 2 | 50,527(18.8) | 952(16.3) | 49,575(18.8) | |
| Quintile 3 | 56,484(21.0) | 1,213(20.7) | 55,271(21.0) | |
| Quintile 4 | 63,205(23.5) | 1,630(27.9) | 61,575(23.4) | |
| Quintile 5 (most deprived) | 51,599(19.2) | 1,235(21.1) | 50,364(19.1) | |
| Missing | 375(0.1) | 22(0.4) | 353(0.1) | |
| **Cohort entry year** | | | | |
| 2013 | 66,947(24.9) | 1,200(20.5) | 65,747(25.0) | <0.001 |
| 2014 | 53,962(20.1) | 964(16.5) | 52,998(20.2) | |
| 2015 | 47,341(17.6) | 918(15.7) | 46,423(17.7) | |
| 2016 | 42,470(15.8) | 931(15.9) | 41,539(15.8) | |
| 2017 | 40,133(14.9) | 1,153(19.7) | 38,980(14.8) | |
| 2018 | 18,004(6.7) | 683(11.7) | 17,321(6.6) | |
| **No. of outpatient/ED visits** | | | | |
| 0 | 71,869(26.7) | 1,103(18.9) | 70,766(26.9) | <0.001 |
| 1-2 | 82,899(30.8) | 1,413(24.2) | 81,486(31.0) | |
| 3+ | 114,089(42.4) | 3,333(57.0) | 110,756(42.1) | |
| **No. of inpatient admissions** | | | | |
| 0 | 173,893(64.7) | 3,150(53.9) | 170,743(64.9) | <0.001 |
| 1-2 | 77,495(28.8) | 1,858(31.8) | 7,5637(28.8) | |
| 3+ | 17,469(6.5) | 841(14.4) | 16,628(6.3) | |
| **Opioid type** | | | | |
| Codeine | 151,725(56.4) | 2,135(36.5) | 149,590(56.9) | <0.001 |
| Oxycodone | 9,015(3.4) | 640(10.9) | 8,375(3.2) | |
| Fentanyl | 1,200(0.4) | 380(6.5) | 820(0.3) | |
| Pethidine | 231(0.1) | 5(0.1) | 226(0.1) | |
| Morphine | 13,430(5.0) | 1,059(18.1) | 12,371(4.7) | |
| Dihydrocodeine | 3,645(1.4) | 208(3.6) | 3,437(1.3) | |
| Tramadol | 81,711(30.4) | 1,187(20.3) | 80,524(30.6) | |
| Multiple | 7,900(2.9) | 235(4.0) | 7,665(2.9) | |
| **Opioid strength** | | | | |
| Weak opioid | 242,630(90.2) | 3,644(62.3) | 238986(90.9) | <0.001 |
| Strong Opioid | 26,227(9.8) | 2,205(37.7) | 24022(9.1) | |

| | | | | |
|---|---|---|---|---|
| **Total OME** | | | | |
| ≤50 MME/day | 39,656(14.7) | 976(16.7) | 38,680(14.7) | <0.001 |
| 51-90 MME/day | 67,214(25.0) | 832(14.2) | 66,382(25.2) | |
| 91-120 MME/day | 26,762(10.0) | 455(7.8) | 26,307(10.0) | |
| 121-200 MME/day | 66,735(24.8) | 1,317(22.5) | 65,418(24.9) | |
| >200 MME/day | 67,579(25.1) | 2,265(38.7) | 65,314(24.8) | |
| Missing | 911(0.3) | 4(0.1) | 907(0.3) | |
| **Injectable preparation** | 1,230(0.5) | 60(1.0) | 1,170(0.4) | <0.001 |
| **Slow-release preparation** | 21,256(7.9) | 1,958(33.5) | 19,298(7.3) | <0.001 |
| **Comorbidities** | | | | |
| CCI | | | | |
| 0 | 221,744(82.5) | 3,825(65.4) | 217,919(82.9) | <0.001 |
| 1 | 17,867(6.6) | 572(9.8) | 17,295(6.6) | |
| 2 | 18,253(6.8) | 835(14.3) | 17,418(6.6) | |
| ≥3 | 10,993(4.1) | 617(10.5) | 10,376(3.9) | |
| Hypertension | 35,308(13.1) | 1,080(18.5) | 34,228(13.0) | <0.001 |
| Heart failure | 9,563(3.6) | 451(7.7) | 9112(3.5) | <0.001 |
| Diabetes | 24,623(9.2) | 711(12.2) | 23912(9.1) | <0.001 |
| Respiratory disorder | 10,567(3.9) | 535(9.1) | 10,032(3.8) | <0.001 |
| Mental disorder | 4,390(1.6) | 281(4.8) | 4,109(1.6) | <0.001 |
| Dementia/Alzheimer | 5,328(2.0) | 464(7.9) | 4,864(1.8) | <0.001 |
| Parkinson Disease | 1,270(0.5) | 85(1.5) | 1,185(0.5) | <0.001 |
| Seizures | 1,510(0.6) | 100(1.7) | 1,410(0.5) | <0.001 |
| Suicide attempt and self-harm | 473(0.2) | 38(0.6) | 435(0.2) | <0.001 |
| Chronic pain | 3,497(1.3) | 190(3.2) | 3,307(1.3) | <0.001 |
| Soft tissue disorders | 8,021(3.0) | 274(4.7) | 7,747(2.9) | <0.001 |
| Gout | 2,063(0.8) | 89(1.5) | 1,974(0.8) | <0.001 |
| Osteoarthritis | 12,978(4.8) | 326(5.6) | 12,652(4.8) | 0.007 |
| Alcohol related condition | 2,091(0.8) | 90(1.5) | 2,001(0.8) | <0.001 |
| Rheumatoid arthritis | 728(0.3) | 38(0.6) | 690(0.3) | <0.001 |
| Lupus | 45(0.0) | 4(0.1) | 41(0.0) | 0.016 |
| Substance abuse | 7519(2.8) | 367(6.3) | 7,152(2.7) | <0.001 |
| Obesity | 3,435(1.3) | 114(1.9) | 3,321(1.3) | <0.001 |
| Chronic Kidney Disease | 1,0879(4.0) | 417(7.1) | 10,462(4.0) | <0.001 |
| Chronic liver disease | 380(0.1) | 17(0.3) | 363(0.1) | 0.002 |
| **Other Medications used** | | | | |
| Antihypertensives | 182,727(68.0) | 4,089(69.9) | 178,638(67.9) | 0.001 |
| Antidiabetics | 37,920(14.1) | 814(13.9) | 37106(14.1) | 0.677 |
| Gout medications | 26,931(10.0) | 587(10.0) | 26344(10.0) | 0.961 |
| Antiepileptics | 13,350(5.0) | 951(16.3) | 12399(4.7) | <0.001 |
| Non-opioid analgesics | 184,155(68.5) | 5,060(86.5) | 179,095(68.1) | <0.001 |
| Antipsychotics | 9,069(3.4) | 741(12.7) | 8,328(3.2) | <0.001 |
| Mood stabilisers | 5,485(2.0) | 276(4.7) | 5,209(2.0) | <0.001 |
| Antidepressants | 57,761(21.5) | 2,320(39.7) | 55,441(21.1) | <0.001 |
| Parkinson medications | 4,237(1.6) | 217(3.7) | 4,020(1.5) | <0.001 |
| Dementia medications | 2,655(1.0) | 167(2.9) | 2,488(0.9) | <0.001 |
| Anxiolytics, sedatives and hypnotics | 53,112(19.8) | 2,039(34.9) | 51,073(19.4) | <0.001 |

### 4.3.2 Rates of persistent opioid use

Of the total 268,857 patients who initiated opioid use during the study period, 5,849 (2.2%) transitioned to persistent opioid users. In chi-squared analysis, compared to non-persistent users, persistent users had a higher percentage of NZ Europeans, females, oldest patients (>85 years), patients living in most deprived areas of Auckland (quintile 4 or 5), and strong opioids users. In addition, compared to non-persistent users, a higher percentage of persistent users had ≥3 outpatient/ED visits and ≥3 inpatient stays. Co-morbidities and other medications used (except antidiabetics) were also more common among persistent opioid users than non-persistent users (see Table 8).

### 4.3.3 Primary analysis results of predictors of persistent opioid use

As shown in Table 9, several factors were found to be significant predictors of persistent opioid use in older adults. Several negative predictors/protective factors were also identified, where they decrease the risk of developing persistent opioid use.

Sociodemographic factors

Compared to NZ Europeans, Pacific People, Asian and Other Ethnicities were associated with a lower risk of developing persistent opioid use (Pacific People: AOR=0.442; 95% CI 0.349–0.561, Asian: AOR=0.449; 95% CI 0.365–0.553, Other Ethnicities: AOR=0.521; 95% CI 0.319–0.852). The odds of persistent opioid use were 1.9 times higher for the oldest adults (>85 years) compared to those aged 65-74 years (AOR=1.92; 95% CI 1.788–2.077). Further, older adults who were living in more deprived areas were more likely to be persistent opioid users compared to those who were living in the least deprived area (Quintile 5: AOR=1.4; 95% CI 1.267–1.535; quintile 4: AOR=1.353; 95% CI 1.237–1.480; and quintile 3: AOR=1.169; 95% CI 1.064–1.284).

Opioid-related factors

With respect to morphine milligram equivalent doses, compared with older adults receiving ≤50 mg/day of morphine (or equivalents), those prescribed opioids at daily doses of >200 mg/day (AOR=1.784; 95% CI 1.608–1.978) and 121-200 mg/day (AOR=1.175; 95% CI 1.061–1.301) had a much higher risk of persistent opioid use. Conversely, those receiving 51-90 mg/day were 15.7% less likely to be persistent users (AOR=0.843; 95% CI 0.759–0.935) compared to those receiving ≤50 mg/day.

Older adults prescribed injectable opioid preparations were 61.9% less likely to be persistent users compared to those who did not (AOR=0.381; 95% CI 0.287–0.506). Further, those who were prescribed tramadol were 25.9% less likely to be persistent users compared to codeine users (OR=0.741; 95% CI 0.682–0.806). Older adults prescribed multiple opioids were also 27.5% less likely to be persistent users compared to codeine users (AOR=0.725; 95% CI 0.591–0.888).

Compared to codeine, fentanyl use was significantly associated with persistent opioid use (AOR=3.61; 95% CI 2.632–4.952). Similarly, there was strong association between slow-release preparation use and persistent opioid use (AOR=3.024; 95% CI 2.780–3.289). Further, the odds of persistent opioid use were 2 times higher among strong opioid users compared to weak opioid users (AOR=2.029; 95% CI 1.551–2.653).

Medication-related factors

Patients taking antiepileptics (AOR=2.065; 95%CI 1.886–2.262), non-opioid analgesics (AOR=2.045; 95%CI 1.889–2.214), antipsychotics (AOR=1.962; 95% CI 1.775–2.168), antidepressants (AOR=1.50; 95% CI 1.413–1.593), anxiolytics, sedatives and hypnotics (AOR=1.305; 95%CI 1.227–1.389), Parkinson's medications (AOR=1.466; 95%CI 1.233–1.742), or dementia medications (AOR=1.305; 95% CI 1.087–1.565) were more likely to become persistent opioid users than those who did not. Conversely, mood stabilisers use was negatively associated with persistent opioid use (AOR=0.731; 95% CI 0.627–0.852).

Medical condition-related factors

Patients with higher CCI scores were more likely to become persistent opioid users than those with zero CCI score (CCI ≥3: AOR=2.094; 95% CI 1.782–2.460, CCI=2: AOR=1.756; 95% CI 1.575–1.958; and CCI=1: AOR=1.523; 95% CI 1.349–1.720). Those with respiratory disorders (AOR=1.137; 95% CI 1.006–1.285), substance abuse disorders (AOR=1.522; 95% CI 1.347–1.720), and chronic pain (AOR=1.350, 95% CI 1.145–1.593) had higher odds of persistent opioid use than those who did not have those conditions. Conversely, hypertension (AOR=0.835, 95% CI 0.764–0.912) and osteoarthritis (AOR=0.866, 95% CI 0.767–0.977) diagnosis were negative associated with persistent opioid use.

Healthcare utilisation factors

Lastly, those who had 3+ Outpatient/ED visits within one year before the index date were more likely (AOR=1.114; 95% CI 1.027–1.209) to become persistent opioid users compared to those with no outpatient/ED visits. Unexpectedly, compared to patients with no prior inpatient admissions, those who had 1-2 inpatient hospital admissions were less likely to become persistent opioid users (AOR=0.816; 95% CI 0.762–0.874).

**Table 9:** Multivariable logistic regression model examining the predictors of persistent opioid use in opioid-naïve older adults in New Zealand

| | B | Adjusted Odds ratio | 95% C.I | | p-value |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| **Sociodemographic factors** | | | | | |
| **Female (Ref=Male)** | 0.030 | 1.031 | 0.973 | 1.092 | 0.307 |
| **Age Group (Ref=65-74 years)** | | | | | |
| 75-84 years | -0.027 | 0.974 | 0.910 | 1.042 | 0.441 |
| >85 years | 0.656 | 1.927 | 1.788 | 2.077 | <0.001 |
| **Ethnic Group (Ref=European)** | | | | | |
| Māori | 0.078 | 1.082 | 0.966 | 1.211 | 0.173 |
| Pacific | -0.816 | 0.442 | 0.349 | 0.561 | <0.001 |
| Asian | -0.800 | 0.449 | 0.365 | 0.553 | <0.001 |
| Other | -0.651 | 0.521 | 0.319 | 0.852 | 0.009 |
| **Deprivation Index (Ref=Quintile 1)** | | | | | |
| Quintile 2 | 0.046 | 1.047 | 0.949 | 1.156 | 0.360 |
| Quintile 3 | 0.156 | 1.169 | 1.064 | 1.284 | 0.001 |
| Quintile 4 | 0.302 | 1.353 | 1.237 | 1.480 | <0.001 |
| Quintile 5 | 0.333 | 1.395 | 1.267 | 1.535 | <0.001 |
| **Healthcare utilisation factors** | | | | | |
| **Number of outpatient/ED visits (Ref=No Visit)** | | | | | |
| 1-2 Outpatient/ED visits | -0.077 | 0.926 | 0.851 | 1.007 | 0.071 |
| 3+ Outpatient/ED visits | 0.108 | 1.114 | 1.027 | 1.209 | 0.009 |
| **Number of inpatient admissions (Ref= No inpatient admission)** | | | | | |
| 1-2 Inpatient admissions | -0.203 | 0.816 | 0.762 | 0.874 | <0.001 |
| 3+ Inpatient admissions | -0.094 | 0.910 | 0.822 | 1.008 | 0.072 |
| **Opioid-related factors** | | | | | |
| **Opioid type (Ref = Codeine)** | | | | | |
| Oxycodone | -0.176 | 0.839 | 0.628 | 1.121 | 0.235 |
| Fentanyl | 1.284 | 3.610 | 2.632 | 4.952 | <0.001 |
| Morphine | 0.210 | 1.234 | 0.930 | 1.637 | 0.145 |
| Dihydrocodeine | -0.037 | 0.964 | 0.810 | 1.146 | 0.677 |
| Tramadol | -0.299 | 0.741 | 0.682 | 0.806 | <0.001 |
| Multiple | -0.322 | 0.725 | 0.591 | 0.888 | <0.001 |
| **Opioid strength (Ref=Weak opioid)** | | | | | |
| Strong Opioid | 0.707 | 2.029 | 1.551 | 2.653 | <0.001 |
| **OME (Ref = ≤50 MME/day)** | | | | | |
| 51-90 MME/day | -0.171 | 0.843 | 0.759 | 0.935 | 0.001 |

| | | | | | |
|---|---|---|---|---|---|
| 91-120 MME/day | 0.006 | 1.006 | 0.884 | 1.145 | 0.924 |
| 121-200 MME/day | 0.161 | 1.175 | 1.061 | 1.301 | 0.002 |
| >200 MME/day | 0.579 | 1.784 | 1.608 | 1.978 | <0.001 |
| **Injectable preparation** | -0.964 | 0.381 | 0.287 | 0.506 | <0.001 |
| **Slow-release preparation** | 1.107 | 3.024 | 2.780 | 3.289 | <0.001 |
| **Co-morbidities** | | | | | |
| CCI score (Ref = CCI 0) | | | | | |
| CCI 1 | 0.421 | 1.523 | 1.349 | 1.720 | <0.001 |
| CCI 2 | 0.563 | 1.756 | 1.575 | 1.958 | <0.001 |
| CCI ≥3 | 0.739 | 2.094 | 1.782 | 2.460 | <0.001 |
| Hypertension | -0.181 | 0.835 | 0.764 | 0.912 | <0.001 |
| Heart failure | -0.106 | 0.900 | 0.784 | 1.033 | 0.134 |
| Diabetes | -0.075 | 0.928 | 0.815 | 1.056 | 0.258 |
| Respiratory disorder | 0.128 | 1.137 | 1.006 | 1.285 | 0.040 |
| Mental disorder | 0.018 | 1.019 | 0.883 | 1.175 | 0.801 |
| Dementia/Alzheimer | 0.036 | 1.036 | 0.896 | 1.198 | 0.631 |
| Parkinson Disease | -0.085 | 0.918 | 0.694 | 1.215 | 0.551 |
| Seizures | 0.224 | 1.252 | 0.993 | 1.578 | 0.058 |
| Chronic pain | 0.300 | 1.350 | 1.145 | 1.593 | <0.001 |
| Soft tissue disorders | 0.081 | 1.084 | .948 | 1.241 | 0.239 |
| Gout | 0.322 | 1.380 | 1.086 | 1.753 | 0.008 |
| Osteoarthritis | -0.144 | 0.866 | 0.767 | 0.977 | 0.019 |
| Alcohol related condition | 0.118 | 1.125 | 0.894 | 1.415 | 0.315 |
| Substance abuse | 0.420 | 1.522 | 1.347 | 1.720 | <0.001 |
| Obesity | 0.100 | 1.105 | 0.894 | 1.365 | 0.356 |
| CKD | -0.059 | 0.942 | 0.827 | 1.074 | 0.374 |
| **Other Medications used** | | | | | |
| Antihypertensives | -0.032 | 0.968 | 0.910 | 1.031 | 0.314 |
| Antidiabetics | -0.002 | 0.998 | 0.899 | 1.107 | 0.967 |
| Gout medications | -0.072 | 0.931 | 0.845 | 1.025 | 0.143 |
| Antiepileptics | 0.725 | 2.065 | 1.886 | 2.262 | <0.001 |
| Non-opioid analgesics | 0.715 | 2.045 | 1.889 | 2.214 | <0.001 |
| Anxiolytics, sedatives and hypnotics | 0.266 | 1.305 | 1.227 | 1.389 | <0.001 |
| Antipsychotics | 0.674 | 1.962 | 1.775 | 2.168 | <0.001 |
| Mood stabilisers | -0.313 | 0.731 | 0.627 | 0.852 | <0.001 |
| Antidepressants | 0.406 | 1.500 | 1.413 | 1.593 | <0.001 |
| Parkinson medications | 0.383 | 1.466 | 1.233 | 1.742 | <0.001 |
| Dementia medications | 0.266 | 1.305 | 1.087 | 1.565 | 0.004 |

The following patients were excluded from analysis:

- Patients with opioid exposure within 6 months before the index date
- Those who died within 6 months after the index date
- Patients with cancer diagnosis 365 days before or 6 months after index date
- Pethidine users (n=317)

### 4.3.4 Sensitivity analyses results

In the sensitivity analysis (see Appendix C) when the look-back period was changed to 3 months or 12 months, the predictors of persistent opioid use remained largely consistent with the main analysis results. However, for the 3-month look-back period, older adults with seizure diagnosis had higher odds of persistent opioid use (AOR=1.265; 95% CI 1.007–1.590). Lastly, in the sensitivity analysis where persistent opioid use was defined as at least 120 days of opioid supply during the 6 months period, the predictors of persistent opioid use remained the same except for small changes in magnitude of the odds ratios. However, older patients taking anti-gout medications had lower odds of persistent opioid use (AOR=0.901; 95% CI 0.814–0.998) than those who did not.

# 5. DISCUSSION

## 5.1 Chapter overview

In this chapter, the results of the studies 1 and 2 will be discussed. The chapter is organised as follows: The first section discusses the incidence rate and prevalence of opioid use in NZ older adults. The second section discusses findings of the rate of persistent opioid use in NZ older adults. The third section discusses predictors of persistent opioid use. The fourth section discusses the sensitivity analyses results. The fifth, sixth and seventh sections are on strengths and limitations of this study, implication for clinical practice and policy, and directions for further research, respectively. Comparing our findings with other international studies was difficult due to methodological and healthcare system differences between countries and differences in study populations. Therefore, comparing specific figures was not possible, but rather comparing overall trends.

## 5.2 Overall incidence rate and prevalence of opioid use in NZ older adults

The overall incidence rate of opioid use in NZ older adults showed a steady increase from 2008 and it peaked in 2015, then the rate fluctuated thereafter. A slight decrease was observed in 2018. The incidence rate of codeine use was the highest across all years, followed by tramadol, morphine, oxycodone, dihydrocodeine (from 2008 to 2012) and fentanyl (from 2013 to 2018). The incidence rate of pethidine use was the lowest across all years.

All previous studies reporting incidence rates and trends of opioid use were conducted on the general populations that included older adults, rather than older adults specific. In Australia, the incidence rate of opioid use was 107 per 1000 persons in 2013/2014 and 100 per 1000 persons in 2016/2017, which was slightly higher compared to the findings of the present study (26). In Canada, the proportion of adults initiated on opioids decreased from 95 per 1000 persons to 81 per 1000 persons between 2013 and 2018; however, older adults have consistently received more new opioid prescriptions than younger adults (66). Similar trends were observed in the present study, where the incidence rate decreased from 88.3 per 1000 persons in 2013 to 86.3 per 1000 persons in 2018; however, the decrease in this study was less compared to the Canadian study.

Other studies in the literature did not explicitly report the overall incidence rate of opioid use; however, incidence trends over time were reported. Regarding the weak opioids, a systematic

review and meta-analysis of 34 studies investigated the trends of opioid prescribing in Australia (116). They reported similar results to the present study, where codeine and tramadol were the most commonly prescribed opioids (116). The same systematic review, however, reported a significant overall increase in opioid prescribing in Australia from 1990 to 2017, primarily driven by increases in strong opioid prescribing (e.g., fentanyl, oxycodone and buprenorphine) (116). These findings were different from the findings of the present study where weak opioid prescribing contributed to the overall significant increase in opioid use in older adults.
Regarding the strong opioids, a UK study investigating the patterns and trends of opioid use reported that opioid use has substantially increased between 2006 and 2017, where older patients were mostly initiated on stronger opioids (69). A similar trend was observed in the present study where the incidence rate of strong opioid use has increased from 2008 to 2017.

The overall prevalence of opioid use in the present study showed a steady increase from 2007 and it peaked in 2015, then the rate fluctuated thereafter. A slight decrease in prevalence was observed in 2018. The prevalence of codeine use was the highest across all years, followed by tramadol, morphine, oxycodone (from 2008 onwards), dihydrocodeine (from 2007 to 2013) and fentanyl (from 2014 to 2018). The prevalence of pethidine use was the lowest across all years.

The prevalence of opioid use in US older adults was previously investigated and the proportion of adults aged ≥60 years who used opioids was nearly double than that of the present study (96 per 1000 persons versus 182.7-185.1 per 1000 persons in 2013-2016, respectively) (86). Other studies reported prevalence of opioid use in the general populations which included older adults. An Australian study reported approximately 16% of the adult population used opioids each year between 2013/2014 and 2016/2017, which was similar to the findings of the present study; while the prevalence of opioid use increased by 0.6% during this period (158.1 per 1000 persons in 2013/2014 and 161.2 per 1000 persons in 2016/2017) (26). In-line with the present study, codeine and tramadol were among the top three most commonly prescribed opioids in this Australian study (26). The prevalence of weak opioid use is higher than the prevalence of strong opioid use. A possible reason for this observation is that strong opioids have more restrictions in terms of quantity prescribed in NZ, where prescribers are only allowed to prescribe a month supply versus three months supply for weak opioids. Lastly, previous Dutch study reported that the prevalence of opioid use in the general population has increased from 41.1 per 1000 persons in 2008 to 74.9 per 1000 persons in 2017 (80). These findings are

congruent with the findings of the present study, where it showed a similar trend of increasing prevalence of opioid use.

Previous studies have reported prevalence in the general population by different strengths of opioids. For example, the NZ HQSC report showed that the use of both strong and weak opioids increased with age, and females were dispensed more opioid analgesics than males (2). This report showed that the prevalence of weak opioids was higher than strong opioids, which was also similar to what the present study has found. Another study in Scotland reported that the prevalence of weak opioids in 2010 was 82 per 1000 persons, whereas the prevalence of strong opioids was 36 per 1000 persons (81). This study reported that opioid use increased with age and was more common in females. These findings are consistent with the findings in the present study, where the prevalence of weak opioids was higher than strong opioids and female use was higher than male use. On the other hand, a study in France reported that strong opioid prevalence in the general population has increased from 5.4 to 11 per 1000 persons between 2004 and 2017, while the prevalence of weak opioids has decreased from 191 per 1000 persons to 171 per 1000 persons in adult patients (117). While the French study reported an overall increase in opioid use, the trends of strong and weak opioid use are not consistent with the findings of the present study. The present study showed an overall increase in prevalence for both weak (except for dihydrocodeine) and strong opioids (expect for pethidine and oxycodone). In addition, unlike the present study's findings, a systematic review of German studies found that fentanyl was the most prescribed strong opioid in adult population outpatient settings (79).

In general, some factors might have contributed to the rise of incidence rate and prevalence of opioid use in NZ. Firstly, the rise in the older adult population. Secondly, the possibility of the increase in the older adult population with more chronic pain and more contraindications to other analgesic medication such as NSAIDs.

Incidence rate and prevalence by opioid type

*Morphine*

Morphine incidence rate and prevalence remained relatively stable between 2008 and 2011, then started to increase. This increase was accompanied by oxycodone decrease in incidence rate and prevalence. A possible explanation to this trend is that prescribers switched patients from oxycodone to morphine after the campaign launched by the Capital and Coast District

Health Board (CCDHB) aiming to reduce oxycodone prescribing in NZ. This campaign reminded prescribers that morphine is still the first-line opioid for CNCP unless the patient is intolerant (118). In the present study, morphine was found to be the third most commonly used opioid in older adults. In a Netherlands study, morphine was the fourth most commonly used opioid from 2008 to 2017 in general adult population (80).

*Oxycodone*

The trend of oxycodone use in the present study showed a steady increase from 2007 to 2011, where it reached its peak, then it gradually declined and plateaued. International studies also showed an increase in oxycodone use in the general adult population. In Australia, oxycodone was the second most common opioid initiated (237 per 1000 persons) (26) and a systematic review have reported a significant rise in oxycodone use until 2017 (116). Similarly in the Netherlands, oxycodone users have quadrupled from 5.7 to 25.7 per 1000 persons from 2008 to 2017 and was the second most used opioid (80). As for the UK, oxycodone use has rose 30-fold from 2006 to 2017 (69). Likewise, in France, the prevalence of oxycodone increased from 32 to 390 per 1000 persons between 2004 and 2017 (117). Our findings align with the HQSC report, where oxycodone prevalence per 1000 dispensing has significantly decreased by 27% since 2011 (2).

The oxycodone rise can be explained by referring back to when it was launched. Oxycodone was introduced into NZ in the early 2000s, where it was regarded by many prescribers as new and improved strong opioid analgesic with lesser adverse effects and possibly none of the stigma associated with morphine and its safety (119). Moreover, the promotion of oxycodone started in the early 2000 where it was heavily marketed, but the advertisements did not provide guidance on its rational and appropriate use. The advertisements strongly suggested that oxycodone is superior to other opioid analgesics without providing any evidence to support this (120). In 2012, the CCDHB launched a campaign to reduce oxycodone use as the first choice of strong opioids in primary and secondary care, which focused on CNCP patients. This campaign resulted in a decrease in oxycodone prescribing in both primary and secondary care (118). Suboptimal practice was also found in Switzerland, where a study was conducted to investigate the appropriateness of oxycodone use in older adults for non-cancer pain. In this study, 26% of the study participants were initiated oxycodone without trialling any other analgesic in the 12 months prior to oxycodone initiation (121). The results of the study conducted in Switzerland align with an Australian study where general practitioners often

prescribe opioids preferentially for treating new episodes of lower back pain without trialling paracetamol (122).

*Fentanyl*

In the present study an increase in fentanyl incidence rate and prevalence was observed since over time. These findings are in congruence with the HQSC report, where they reported an increase in fentanyl prevalence. Moreover, in the HQSC report, fentanyl use has significantly increased with age, where older adults aged 65-79 had a rate of dispensing of 4 per 1000 persons, while older adults aged ≥80 years had a rate of dispensing of 20.3 per 1000 persons (2). However, the HQSC report stated that the prevalence has decreased after 2016 (2) while the present found a decrease after 2017. International studies reported increase in fentanyl use as well in the general population. A systematic review conducted in Australia have shown that fentanyl prescriptions continued to escalate since 2000 (116). In the Netherlands, fentanyl was the third most commonly used opioid from 2008 to 2017 (80). Whereas in the UK, fentanyl use has increased between 2006 and 2012, then plateaued till late 2017 (69). On the other hand, the prevalence of fentanyl use remained steady in France between 2004-2017 (117).
In NZ, fentanyl patches became fully funded without special authority from February 2011 (123). Special Authority is an application process where prescribers can request for medication funding for a particular patient (124). The absence of funding restrictions can explain the rise of incidence rate and prevalence of fentanyl in 2011 in the present study.

*Pethidine*

The use of pethidine in older adults was found to be the lowest in the present study and both incidence rate and prevalence steadily decreased over the study period. The reason for low pethidine prescription rates could be due to its toxic metabolite norpethidine that can accumulate with impaired renal function (125,126). Moreover, neurotoxicity associated with pethidine use is dose related, hence why pethidine is not recommended to be used for periods greater than 24 to 36 hours (125). Pethidine is also usually prescribed by midwives for women's health (i.e., intrapartum analgesia) (127) and not commonly prescribed in outpatient settings.

*Dihydrocodeine*

Dihydrocodeine incidence rate and prevalence have been declining in the present study; however, my findings are different compared to international studies. In the UK,

dihydrocodeine was the second most commonly used opioid between 2006 and 2017, where its use increased between 2006 and 2012, then plateaued till late 2017 (69). This study, however, was not specifically conducted on older adults.

*Tramadol*

Tramadol was the second highest opioid used in the present study. It is worth-noting that out of all opioids included in this study, tramadol is the only non-controlled drug. This may explain the sudden increase in incidence rate and prevalence, where tramadol has less restrictions than controlled drugs in NZ. International studies conducted on the general population also align with our findings; in the Netherlands, tramadol was the most commonly prescribed opioid from 2008 to 2017 (80). Similar findings were reported in the UK, where tramadol was amongst the most common used opioids between 2006 and 2017 (69). In Australia, tramadol was the third most commonly initiated opioid between 2013 and 2017 (26). A possible reason as to why tramadol use is widespread is that prescribers and possibly patients perceive it as being a "weak" opioid. Although tramadol presents fewer concerns regarding dependence compared to strong opioids, it can lead to toxicity in overdose due to its dual action at the opioid and the serotonin/norepinephrine receptors, where the latter is not blocked by naloxone (81).

*Codeine*

Codeine was the most commonly used opioid in the present study with a steady increase over the study period. Similar results were reported in international studies conducted in the general population, where codeine was amongst the most commonly used opioid in the UK between 2006 and 2017, where it has increased 5-fold during this period (69). A systematic review conducted in Australia have shown that codeine is the most prevalent opioid (116). Moreover, the prevalence of codeine use has increased by 150% from 2004-2017 in France (117). Although codeine is a controlled drug in NZ, it is classified as class C, where quantity restrictions are less compared to Class A and B. Codeine can be prescribed for 3 months, rather than 1 month. Since codeine is a weak opioid, this could potentially be a reason as to why its incidence rate and prevalence were high, where prescribers are reluctant to prescribe strong opioids for older adults.

Incidence rate and prevalence by Sex

In this study, higher rates of incidence and prevalence of opioid use were observed among females than males, which is consistent with other international studies (81). It has been reported in literature that females are more likely to develop chronic medical conditions, especially musculoskeletal conditions that lead to chronic pain or nociceptive stimuli, including fibromyalgia, osteoarthritis, lower back pain, and inflammatory arthropathies (128-130). This finding was backed up by large scale epidemiological studies, where a higher prevalence of chronic pain was reported among women than men (130).

Females are also more likely to report acute and chronic pain (131), have frequent and longer pain duration (130,131), have more severe and anatomically diffused pain (132) and higher use pain-relieving medications, even with equal pain frequency and severity with men (133).
Furthermore, females are more likely to have co-morbidities that can impact the risk of developing chronic pain. This occurs through the modulation of pain perception or an impact on behavioral response, which may result in increasing opioids use (128). For example, a study conducted to investigate the effect of sex on morphine consumption has found that women reported higher level of pain intensity and required higher morphine dose to achieve a similar degree of pain relief than men (134). Another study has also shown that female gender and older age are linked to having lower pressure pain threshold, however, the gender differences seem to diminish with aging (135). However, the data presented above should be considered cautiously, as most studies were done on healthy general adult populations rather than older adults with chronic pain. Healthy volunteers may not have similar physiological and/or psychological response to painful stimuli compared to older patients with chronic pain and co-morbidities. Further studies are needed to precisely determine sex differences in pain response and opioid use among older adults.

## 5.3 Rate of persistent opioid use in NZ older adults

This study also investigated the rate of persistent use of opioids amongst opioid-naïve older adults. Due to different reports and studies reporting prevalent persistent users rather than incident persistent users and using different methodologies, comparing rates was difficult. As has been described in the results section, 2.2% of older adults without cancer were identified as persistent opioid users (n=5,849). There is a lack of data regarding rate of non-post-operative persistent opioid use in older adults with CNCP. However, a few NZ and international studies

have published rates of persistent opioid use based on close, but not similar criteria of the present study.

In NZ, the rate of persistent strong opioid use among older adults (which is defined by the HQSC as use of 6 weeks or more) was three times higher compared to younger adults (2). However, this rate is referring to prevalent persistent users rather than incident persistent users. In the US, an observational study reported that between 2005 and 2017, more than 30% of patients aged ≥85 years used strong opioids longer than 3 months (71). Another US study reported that prevalence of persistent opioid use has increased from 1.8% in 1999/2000 to 5.4% in 2013/2014, where 25% of these users were older adults (3). However, the above comparisons should be cautiously interpreted. None of the above studies designed to particularly examine persistent opioid use among opioid-naïve and cancer-free older patients. Given the potential risks of persistent opioid use, healthcare providers should be aware of individuals at greater risk for progressing to persistent opioid use. It is widely documented that persistent opioid use is associated with a multitude of adverse effects and harms, which includes overdose, motor vehicle accidents, addiction, opioid misuse, and death (5), the findings from this study can be useful to health care providers to reduce the risk and harms by identifying the characteristics associated with persistent opioid use in older adults, to prevent inappropriate opioid use and improve benefit-risk assessment.

## 5.4 Predictors of persistent opioid use in NZ older adults

The types of predictors and protective factors of persistent opioid use assessed include sociodemographic factors, opioid-related factors, medication-related factors, co-morbidities and healthcare utilisation factors. The use of fentanyl, strong opioids, slow-release preparations, presence of three or more co-morbidities and the use of anti-epileptics, and non-opioid analgesics were the strongest predictors of persistent opioid use.

<u>Sociodemographic factors</u>

*Age*

A positive association was found between advanced age (≥85 years) and persistent opioid use. The odds of persistent opioid use were two times higher than the youngest old (65-74 years). This finding is consistent with existing literature (129,136-138). In line with the present study's finding, a study that investigated the use of opioids in older adults between 2005 and 2017

reported that patients in the oldest age group (>85 years) were more likely to be prescribed opioids compared to younger older adults (101). In addition, a study contacted by Lalic et al., showed that older age is a predictor of persisted opioid use (1). Oh et al., also reported positive association between age and persistent opioid use for all opioids (OR=1.83; 95% CI 1.28–2.61) and for strong opioids (OR=2.10; 95% CI 1.34–3.28) (3). A possible explanation to this finding is the high prevalence of chronic pain in older adults (23). The decline in organ function, especially hepatic and renal function affects opioid clearance and subsequently, older adults are more susceptible to adverse drug reactions (20). Prescribing opioids in the very old population requires the skill of a knowledgeable prescriber to navigate through different variables including polypharmacy, co-morbidities and physiological changes (20).

*Socioeconomic Status*

In line with previous studies (69,89,102), in the present study, older adults living in most deprived areas (Quintile 3, 4 and 5) were more likely to be persistent users compared to those living in the least deprived area (Quintile 1). This finding can be explained by many factors. Firstly, the risk of having CNCP is higher in lower socioeconomic areas, which could result in the use of more opioid analgesics (139-141). Secondly, factors like social segregation, poverty concentration, the physical structure of the environment may influence the prevalence of pain and co-morbidities (142,143). Other issues include the lack or difficulty of accessing alternative treatment options (e.g., physiotherapy) or accessing pain treatment specialist due to high cost (144). Another study conducted in the UK had similar results, where more deprived areas had more prevalence of opioid dispensing and identified factors such as lack of time spent on patient care as a potential reason to this finding (145).

*Ethnicity*

The present study results showed that the odds of persistent opioid use were lower among Pacific People, Asian or Other ethnic groups as compared to NZ Europeans. In line with the present study, the HQSC had similar results, where Pacific and Asian people had less prevalence of all opioids compared to NZ Europeans from 2011 to 2019 (2). There are a few potential interpretations for this. For instance, NZ Europeans might have been over-prescribed opioids or ethnic minorities having poorer access to pain treatment or opioid analgesics (146). Further research is required to better understand the relationship between ethnicity and persistent opioid use.

Opioid-related factors

*Fentanyl*

In the main analysis and all sensitivity analyses, the initiation of fentanyl was found to be the strongest predictor of persistent opioid use. In NZ, fentanyl is available in patch and injection formulations. It is worth noting that the patch formulation allows controlled delivery of fentanyl for up to 72 hours (147). Moreover, transdermal patches have a lower onset of action, therefore they are not used to manage acute pain (148). Although it is unknown what formulation of fentanyl older adults were administered in this study, it is more likely that the transdermal formulation was used more since the injection formulation is used for acute pain rather than chronic pain. Moreover, fentanyl injections are short-acting and are used to treat breakthrough pain (149). An Australian study investigating the predictors of persistent opioid use found that in the sub-group aged ≥65 years, being initiated on a transdermal formulation was the strongest predictor (1). Another Australian study exploring the safety of opioid patch initiation in Australian residential aged care found that 34% of older adults who were initiated on fentanyl patch were opioid-naïve, which raises a safety concern (150). In NZ, fentanyl is indicated for the management of chronic non-cancer pain in opioid tolerant patients where other conservative protocols of analgesia have been trialled first (151). Transdermal fentanyl patches should not be used for opioid-naïve patients and should only be used in patients who demonstrated tolerance who are already receiving opioids due to its high potency (152). Initiation of fentanyl transdermal patches in the opioid-naïve patients has been associated with adverse effects such as rare cases of significant respiratory depression and/or death, even at low doses of fentanyl especially in older adults (151). Furthermore, fentanyl pharmacokinetics can be altered in older adults due to decreased fentanyl clearance, muscle wasting and poor fat stores (153).

In general, older adults can be more sensitive to fentanyl compared to younger adults due to its prolonged half-life and reduced clearance. Therefore, patients and prescribers should carefully observe signs of fentanyl toxicity and reduce dose when necessary (151). Although fentanyl doses are unknown in this study, the initiation of fentanyl in older adults should follow the approach of "start low and go slow". Though, significant limitation of fentanyl patches is the lack of flexibility in dose titration. In general, treatment of chronic pain with fentanyl patches remains controversial and further research is needed to establish guidelines for the treatment of CNCP with fentanyl (153).

*Slow-release preparations*

The initiation of a slow-release opioid preparation was the second strongest predictor of persistent opioid use. Slow-release formulations include Long-acting (LA) morphine, LA oxycodone, LA tramadol, LA dihydrocodeine and sustained-release fentanyl patch. Similarly, a US study conducted on opioid-naïve older adults reported that patients initiated on long-acting opioids had a higher risk of becoming persistent opioid users (97). Another study investigating the patterns of immediate-released and extended-release opioid use in the management of chronic pain from 2003 to 2014 in US adults reported that 30% of persistent opioid users were on extended-release/long-acting formulations, compared to 7% for immediate release formulations (103).

Guidelines for pain management recommend the use of slow-release preparations in patients suffering from chronic pain as they provide sustained analgesia for 12 to 24 hours. They also provide more consistent plasma concentration of drug and minimise fluctuations which can contribute to end-of-dose breakthrough pain. Moreover, they provide more consistent pain control, especially at night-time, which may improve pain-related sleep-disturbances (154). These reasons can potentially explain why slow-release preparations can be a predictor of persistent opioid use. Thus, prescribers need to be careful when initiating slow-release formulations as there is a high risk of continuing opioids long-term, which can have negative consequences on older patients.

*Strong opioids*

In the present study, the odds of persistent opioid use among strong opioid users were two times higher than weak opioid users. Likewise, Oh et al., reported that strong opioids were a predictor of new persistent opioid use among older adults. In this study, older adults using strong opioid were 27% more likely to be persistent users (AOR=1.27; 95% CI 1.04–1.56) compared to those taking weak opioids (3). Furthermore, an Australian study reported that the use of strong opioids was a strong predictor of persistent opioid use in patients ≥85 years (OR=1.51; 95% CI 1.32–1.73) (1). These findings have important clinical implications as the use of strong opioids can pose a risk on older patients. The evidence for the benefits of persistent strong opioid use is limited and several risks has been reported and documented. Older adults on strong opioids, especially high doses, are at risk of developing adverse effects including CNS effects (e.g., decrease in cognitive function, over sedation), GI effects

(constipation and bowel obstruction) and are at a greater risk of falls and fractures (155). Prescribers should be cautious when prescribing strong opioids and the lowest possible dose for the shortest possible time should be used. Monitoring and assessing the need for strong opioid analgesics is also necessary for older adults as they are at higher risk of clinically relevant complications (156).

*Opioid dose*

In the present study, those prescribed opioids at daily doses of 120-200 mg/day and >200 mg/day had a much higher risk of persistent opioid use than those taking ≤50 mg/day of morphine (or equivalents). These findings are consistent with the literature. In a recent US study, an OME of ≥700 mg initial prescription predicted persistent opioid use for up to 3 years (97). Similarly, in an Australian study initial prescription of total OME ≥ 750 mg was found to be a predictor (OR=2.20, 95% CI 1.84–2.63) of persistent opioid use in older patients (1). Recommendations from recent guidelines on opioid dosing is to start low and go slow, i.e., prescribers should initiate opioids at lower starting doses with slower titration, longer dosing interval and most importantly, more frequent monitoring of side effects and reviewing benefit of therapy continuation at each stage (9). Since prescribed dose was not available in the present study, it was not possible to evaluate concordance with dosing recommendations (1). It is well-documented in literature that higher opioid doses are associated with higher risks of serious harm (157). A meta-analysis reported that for every 15 patients prescribed a high dose opioid, one will present to the emergency department, which highlights the health and economic burden of high dose opioid prescription (157). There is some heterogeneity in international guidelines regarding dose thresholds that warrant caution (15,158,159). For example, US national guidelines advise re-assessment of patients exceeding 50 MME/day and that doses should not exceed 90 MME per day (15), whereas Faculty of Pain Medicine in the UK advises that harms outweigh benefits when patients are prescribed more than 120 MME/day (160). Moreover, there is minimal evidence-based guidance on how to taper, reduce or discontinue opioids in chronic pain. Prescribers could fail to taper doses as they could be guided by patients, who may think their pain will not be controlled by non-opioid analgesics, fear worsening pain or withdrawal symptoms, or may lack healthcare or social support. Alternatively, transitioning to persistent opioid use can be driven by "clinical inertia", where prescribers continue to issue repeat prescriptions, and assume therapy effectiveness without regular patient review (161). Strategies and methods that promote safe opioid prescribing practice are needed to prevent

undesired clinical consequences (157). Multiple regulations have been put in place to reduce the high-risk prescribing practices in the US including prescription drug monitoring programmes and caps on opioid prescribing that limit the duration and dose of prescriptions; however, the effectiveness of these interventions is still under investigation (157). Investing in resources and monitoring systems in NZ could potentially reduce the number of older adults on high dose opioids.

*Tramadol*

In the present study, tramadol users were less likely to become persistent users when compared to codeine users, which can be expected for several reasons. Firstly, tramadol has a minimal affinity for μ-opioid receptor, which is deemed to be a relatively safe opioid with lower abuse potential compared to other opioids (162). Secondly, the effects of persistent opioid intake on the development of dependence, tolerance and addiction are reduced with tramadol (163,164). However, a recent US study investigating persistent use of tramadol after acute pain episode had different results. The study reported that patients receiving tramadol alone after surgery had a similar risk of persistent opioid use when compared to other short-acting opioids such as hydrocodone and oxycodone (165). However, these results are in a surgical setting, which is different from the population-based setting in this study. Another US study investigating the risk of persistent opioid use found that tramadol was associated with a 13.7% risk of persistent use at one year compared with 4.7-8.9% of other short-acting opioids (97).

*Multiple opioid use*

In the present study, it was found that the use of multiple opioids was a protective factor against the use of opioids persistently compared to the use of codeine alone. Since the risk of polypharmacy is high in older patients, prescribers might have prescribed multiple opioids to reduce the pain effectively, then discontinued opioids to reduce polypharmacy in older adults.

*Injectable preparations*

In this study, the use of injectable preparations was a protective factor against persistent use of opioid. Potential reasons as to why injectable preparations is a protective factor could include patient convenience, immediate-release formulation and subsidy issues. Injectables are immediate-release preparations, where they are used for breakthrough pain rather than

continuous pain. Moreover, intravenous infusions over 24 hours are not subsidised (e.g., morphine, oxycodone, fentanyl and tramadol) and this might have prevented physicians from prescribing injectable formulations (38-40,46).

Medication-related factors

*Antiepileptics*

Opioids are one of the drug classes that can lower seizure threshold and have been associated with seizures (166). In the present study, increased risk of persistent opioid use was observed among older adults who were taking antiepileptics. Similarly, in another study conducted by Terman et al., investigating polypharmacy in 20,146 US patients with epilepsy, 16% of patients with epilepsy reported at least using one opioid, 6% reported a combination of opioid and benzodiazepine, and 7% reported an opioid plus a gabapentinoids (167). The reasons for higher persistent opioid use in epileptic patients are still unclear; however, it is more likely to be a combination of reasons including increased pain prevalence and psychiatric illness. It is also worth-noting that in the US, around 70,000 deaths occur annually due to drug overdose in epilepsy patients, where two-thirds of these are related to opioid analgesics (168). This implies that prescribers should take extra care and pay more attention to safe opioid prescribing habits in patients with epilepsy, to prevent adverse events such as drug-drug interactions, overdose, abuse or addiction (169).

*Non-opioids analgesics*

The use of non-opioid analgesics was found to be a predictor of persistent opioid use in the present study. Likewise, a US study has reported that the use of NSAIDs in older adults was a predictor of persistent opioid use (90). In addition, in an Australian study previous use of non-opioid analgesics predicted persistence use of opioids, where paracetamol, NSAIDS, and pregabalin users were more likely to be persistent opioid users (1). It is worth-noting that opioids can interact with non-opioid analgesics (e.g., pregabalin with opioids analgesics), this interaction involves increased risk of CNS depression (170). A Cross-sectional hospital-based study examining the association between CNS depressants use (e.g., opioids) and cognitive function in older patients reported that in older patients, both CNS depressants and co-morbidities have an influence on cognitive function. Older adults are also more sensitive to

negative outcomes like cognitive impairment and falls partly due to age-related renal and hepatic function decline and polypharmacy (64,171-173).

*Antipsychotics*

The present study has shown that older adults on antipsychotics are more likely to be persistent opioid users. Psychotic illness has been reported to be a predictor of persistent opioid use (OR=2.01; 95% CI 1.87–2.17) (1). One study in the US conducted by Reid et al., reported that some geriatricians prescribe opioid analgesics to older patients with substantial psychiatric co-morbidity, cognitive and functional impairments, which is a big concern (35). Co-prescribing opioids and antipsychotics can be tricky. A study investigating risks of co-prescribing opioids and antipsychotics has concluded that the use of sedating antipsychotics with opioids was associated with an increased risk of overdose compared to non-sedating antipsychotics. Prescribers should be vigilant when co-prescribing these two medication classes together in older adults, and if co-prescription is necessary, then prescribing a non-sedating antipsychotic is preferred if possible (174).

*Antidepressants*

In line with previous studies, the present study has shown that the use of antidepressants was a predictor of persistent opioid use. A UK study done on older adults reported that antidepressants was a predictor of persistent opioid use (69). Furthermore, it is documented that depression is associated with developing chronic pain (175) and that patients with depression were likely to be taking opioids regardless of their pain severity (176). Moreover, an Australian study reported that patients with mental illness are at a greater risk of persistent opioid use (1), which is consistent to other US studies (99,104) and support current guidelines stating that prescribers should exert extreme caution when prescribing opioids in patients with mental health comorbidities (49). All these findings are particularly important since a study found that patients who were in a depression remission period and started opioids had double the risk of depression recurrence (177). It is also worth-mentioning that antidepressants are not only used for depression, but also in other mental health conditions such as generalised anxiety disorder, obsessive compulsive disorders and bipolar disorder. They are also used in non-mental health disorder such as smoking cessation and neuropathic pain (unapproved indication) (178-180). However, the evidence behind the use of antidepressants in combination with opioids in neuropathic pain has not been established. Therefore, further studies are needed to

investigate the outcomes of antidepressant prescribing in older adults taking opioids to establish the risk-benefit ratio of these complex medication profiles (180). Prescribers need to be particularly cautious when co-prescribing opioids with antidepressants, especially sedating antidepressants for their risk of anticholinergic side effects, drowsiness, and consequently higher risk of falls and fractures (181).

*Parkinson's disease medications*

In this study, it was found that older adults prescribed anti-Parkinson's mediations had a higher risk of being persistent opioid users. Patients with Parkinson's disease can suffer from chronic pain, where opioids can be prescribed. However, opioids should be used with extreme caution due to the risk of neuropsychiatric and GI side effects. In Parkinson's disease, care must be exercised when prescribing pain reliefs. Ideally, medications that induce anticholinergic side effects should be avoided (182). It is also noted that some antiparkinsonian medications already have anti-cholinergic effects (e.g., benztropine, entacapone) (183). According to the American Parkinson Disease Association, some opioids need to be avoided such as tramadol. Moreover, other opioids analgesics should ideally be avoided if patients are on Monoamine oxidase inhibitors (MAOIs) due to the potential interaction (184).

*Dementia medications*

As for older patients prescribed anti-dementia medications, the present study has shown that they were more likely to be persistent opioid users. Pain is common amongst older patients suffering from Alzheimer's disease and dementias (185). Older adults with dementia are specifically vulnerable because of inherent difficulties when treating and assessing pain (3). A study conducted in Denmark investigating opioid use in older adults with dementia reported that opioid use has rose steadily with age and specifically pronounced amongst patients with dementia (32%) and nursing home residents (41%). The study also found that patients with dementia were more likely to be prescribed multiple opioid prescriptions with higher doses compared with patients without dementia. However, a recent study by Oh et al., reported that patients with dementia were 27% less likely to be incident persistent users (OR= 0.73; 95% CI 0.57–0.92) and 54% less likely to be prevalent persistent users (OR=0.46; 95% CI 0.32–0.68) (3). Another potential reason explaining the higher risk of persistent opioid use is that analgesics, including opioids, can be used to treat behavioural and psychological symptoms of dementia (186).

In general, opioids can be problematic in patients with dementia due to risk of sedation and their association with mental health functioning reduction (33). It is worth-noting that under-treating pain in older adults can lead to serious implications such as depression, anxiety or agitation, further research need to be conducted to address the patterns of opioids use in older adults with dementia. This is important as little data exists to support evidence of opioid prescribing for older patients with dementia and that very few older adults are included in analgesic trials with dementia (187).

*Anxiolytics*

It was found that patients on benzodiazepines were more likely to be persistent opioid users in the present study, which is similar to what has been reported in literature. Benzodiazepines should be avoided in older patients based on the American Geriatric Society's Beers Criteria (188). In spite of the evidence of a multitude of risks, the use of benzodiazepines among older adults is common (189,190). The use of anxiolytics, sedatives or hypnotic agents has also been associated with persistent opioid use. A US study investigating opioid use in older adults found positive association between the use of these agents and long-term use of all opioids (OR=2.26; 95% CI 1.69–3.02), as well as strong opioids (OR=2.51; 95%CI 1.76–3.57) (3,71). Similarly, an Australian study found that previous use of benzodiazepines was a predictor of persistent opioid use in older patents (1). A similar finding was reported by Quinn et al., where patients dispensed benzodiazepines prior to opioid analgesics initiation had double the risk of transitioning to persistent opioid use (104). These findings have an important clinical implication since the overdose risk of co-prescribing benzodiazepines and opioids is high, and further research is needed to investigate the benefits versus harms with benzodiazepine co-prescribing and the effect of using both medications together on opioid-related adverse events (3). This is particularly important as older adults with polypharmacy who are exposed to both opioids and benzodiazepines may be vulnerable and at higher risk of adverse events (191). Following opioids, benzodiazepines are the second medication class associated with drug overdose mortality, and while opioids are the first class, benzodiazepines are mostly commonly combined with opioids in such deaths (192). Hence why the Food and Drug administration (FDA) has recently issued a "black box warning" to alert prescribers of potential respiratory depression and death caused by concurrent use of benzodiazepines and opioids (193). Hence, this implies that primary care prescribers need to re-assess patients who are co-prescribed benzodiazepines and opioids in order to avoid initiating benzodiazepines in the first place. If

the combination is deemed necessary, benzodiazepines should be taken for short-term use only (157).

*Mood stabilisers*

In the present study, patients on mood stabilisers including sodium valproate, carbamazepine, lamotrigine and lithium have been found to be less likely to be persistent opioid users. Lithium has been documented to decrease inflammation (194), reduce painful cluster headaches (195) and is neuroprotective (196). Some studies have reported that lithium affects morphine-induced analgesia in mice (197,198) and reduced morphine dependence and tolerance (199).

As for carbamazepine, the American Psychiatric Association guidelines only supported carbamazepine as the mood stabiliser with robust efficacy in chronic pain (200). This could be a potential explanation why carbamazepine users are less likely to be persistent opioid users. It should be noted that mood stabilisers in this study include lithium carbonate, carbamazepine, sodium valproate and lamotrigine. Therefore, we could not specify which mood stabiliser had the most effect on chronic pain and is a protective factor against persistent opioid use. More studies are needed to investigate the effect of each mood stabiliser on chronic pain in older adults and whether there is an association between mood stabilisers and persistent opioid use.

Co-morbidities

*Number of medical conditions*

In this study, patients with higher CCI score had higher odds of persistent opioid use. In line with the present study's findings, a recent US study investigating the future persistent opioid use among hospitalised patients in a US hospital reported adult patients who progressed to persistent opioid use therapy one year post discharge had a higher CCI score on hospital admission (201). Another study aligning with the present study's findings reported that patients with higher number of chronic health conditions are more likely to be persistent users (71).

*Chronic pain*

Unsurprisingly, chronic pain has been associated with persistent opioid use in this study. In a systematic review assessing risk factors of persistent opioid use, chronic pain was consistently identified as a predictor of persistent opioid use (51). This finding is concerning as the evidence

of long-term opioid use for the management of CNCP is limited. In addition to the lack of evidence on long-term efficacy, the risk of opioid harm is well documented in older adults (8). Recently, the CDC published guidelines to improve safety and efficacy of chronic pain treatment, where they increased the requirement of monitoring the risks of opioid use in older adults. However, these guidelines lacked detailed guidance on actual opioid prescribing (15). Improvements in the training of prescribers are required to optimise care and minimise inappropriate opioid prescribing in older adults (202).

*Respiratory disorder*

In the present study, respiratory disorder was a significant predictor of persistent opioid use. Opioids are commonly prescribed for COPD patients for the treatment of pain and refractory dyspnoea. On the other hand, it is advised that older adults avoid taking them due to their well-documented risk of respiratory events (i.e., respiratory depression). It is reported in literature that patients with COPD are more likely to receive opioids compared to patients without COPD (105). A Canadian study conducted to investigate the incidence rate of opioid use in older adults with COPD reported that 68.1% of community-dwelling patients and 54.4% of long-term care residents received an incident opioid (67,68). In addition, COPD patients have higher prevalence of pain, dyspnoea and mental disorders, hence why opioid use is high (203,204). However, the evidence of safety and efficacy of opioids in dyspnoea is weak (205,206). Some studies recommend that the use of low dose opioids is beneficial for breathlessness and does not increase the risk of adverse respiratory events in COPD patients (207-210). On the other hand, other studies suggested that opioids use in COPD patient increases exacerbations or respiratory depression (68,211,212). These conflicting results may be due to several factors, including the population of choice that is being studied, severity of COPD and outcomes definitions. Moreover, confounding factors may play a role in these mixed findings, including the competing risk of death, the potential confounding by indications when opioids are used for dyspnoea, which is itself a predictor of COPD exacerbation or death (213). Therefore, employing methods to alleviate confounding factors is necessary to generate valid and reliable findings in relation to the use of opioids in older adults (68). Until further research is conducted in this area, prescribers need to cautiously use opioids in old adults with respiratory disorders due to the possible risk of adverse reactions.

*Substance abuse*

Substance abuse was found to be a predictor of persistent opioid use in this study. Substance abuse was reported to be a predictor of persistent opioid use in UK and US studies conducted among general adults (69,89). Since substance abuse is found to be a predictor of persistent opioid use, healthcare providers should refer patients to receive behavioural therapies and medications if necessary. Models of care include re-building support networks, management of other chronic medical conditions, and improving access to medical services.

*Hypertension*

Hypertension was found to be a protective factor in the present study. In literature, conflicting evidence was found in a study conducted by Oh et al., on older adults, where hypertension was a predictor of persistent opioid use in older adults for all opioids (OR=1.44; 95% CI 1.20–1.72) and for strong opioids (OR=1.49; 95% CI 1.21–1.83) (3). Further research is needed to explain association between hypertension and persistent opioid use.

*Osteoarthritis*

Patients diagnosed with osteoarthritis were less likely to be persistent users in the present study. Opioids are not recommended for pain management in osteoarthritis as there is substantial risk of harm and limited evidence of benefit (214). In clinical guidelines, opioids are third-line treatment for the treatment of osteoarthritis, where weak opioids such as tramadol or codeine should be reserved for patients who have not sufficiently improved or have not tolerated or have contradictions to other treatments such as paracetamol, topical treatments or oral NSAIDs. Evidence of using strong opioids is limited, where risks outweigh benefits as strong opioids are associated with adverse effects such as drowsiness, constipation, falls and addiction (215). A potential reason as to why older adults with osteoarthritis were less likely to be on persistent opioid use, as they are already prescribed long-term analgesia such as paracetamol or NSAIDs. This reduces the probability of transitioning from acute to persistent opioid use.

Healthcare utilisation factors

*3+ Outpatient/ED visits*

In this study, older adults who had more than 3 outpatients hospital admissions or ED visits were more likely to be persistent opioid users. A US study investigating risk factors for persistent opioid use among hospitalised patients reported similar results (201,216).

*1-2 inpatient admission*

Inpatient admission once or twice was found to be a protective factor in this study, which is an unexpected finding. However, literature report that patients with hospital admissions related to trauma or surgery (217) and patients with more healthcare visits (71) have been reported as a contributing factor and a driver for persistent opioid use. Further research is needed to clarify the potential relationship between inpatient admissions and the risk of persistent opioid use.

## 5.5 Sensitivity Analyses

In the sensitivity analyses, other variables were found to be predictors of persistent opioids use.

*Seizures*

As previously discussed under antiepileptics, the reason behind higher prevalence of opioid use is unclear, however, possible reasons could be pain prevalence and/or increased psychiatric illness (169). Moreover, opioids can lower seizure threshold (166). Therefore, the development of alternative analgesia strategies is required (169).

*Gout and hyperuricemia medications*

In this study, the use of anti-gout medications and medications for hyperuricemia found to be a predictor of persistent opioid use. It is worth noting that gout is a chronic pain condition, and chronic pain has been reported to be a predictor of persistent opioid use. A study conducted in South Korea reported that persistent opioid use among patients with gout has increased from 2002 to 2015 (218). Another recent US study investigated the use of opioid therapy in acute gout for patients discharged from the emergency department reported that 28.3% of adult patients received opioids, where 80% of them were new patients. Oxycodone was prescribed the most for these patients. These results are concerning, given that there are other effective

therapies for acute gout attacks including colchicine and NSAIDs (219). Opioids have no proven effect in the treatment of gout or gout flares/attacks. Opioids do not have an anti-inflammatory effect and should only be used as an adjunctive treatment. When opioids are used for gout attacks, the lowest possible dose should be prescribed for the shortest duration possible. Moreover, opioids should not substitute effective anti-inflammatory treatments for gout flares (220).

## 5.6 Strengths and Limitations

A key strength of this study is that it is the first NZ study investigating the incidence and prevalence of opioid use, as well as rates and predictors of persistent opioid use. The findings of this population-based study have high generalisability to older population in NZ. Moreover, this study is one of the very few studies conducted worldwide focusing specifically on older adults. Several potential predictors of persistent opioid use were included in this study including sociodemographic factors, opioid-related factors, medication-related factors, co-morbidities, and healthcare utilisation factors. The data for incidence rate and prevalence of opioid use were collected from 2007 to 2018, which is a long period that allows researchers, healthcare professionals and policy makers to observe the trends in the NZ older population for all funded opioids. This will allow them to identify and analyse any concerns regarding opioid prescribing in NZ. Another strength of this study is the clarity of the methods used to determine the rate of persistent opioid use. This study focussed on incident (new) persistent opioid users, and it was clearly stated in our methodology. Most studies and reports in literature did not specify whether they were reporting incident or prevalent persistent use.

The study has some limitations. Firstly, this study might not totally reflect the characteristics of all persistent opioid users in NZ because non-subsidised opioids were not captured in this dataset. This is a limitation as the use of buprenorphine patch in patients has been reported in literature as a predictor of persistent opioids use (1). Secondly, as this was a database study, some predictors in literature, such as patient expectations of persistent opioid use, were not included (99). Thirdly, there is a discrepancy between the number of patients having a specific medical condition and the number of patients taking the medication(s) prescribed for this condition. This discrepancy occurred as electronic medical records from primary healthcare (i.e., from general practice) cannot be accessed in NZ. However, attempts were made to overcome this study limitation by capturing both medical conditions using ICD-10AM codes and medication dispensing data. A fourth limitation is the inability to access the formulations

of opioids used by older adults in this study. Formulations (e.g., patches) has been documented in literature to be a strong predictor (71), and although injections are not used chronically, it is still worth knowing the exact formulation used by the patient in order to properly assess and build conclusions. Another limitation is that prescribing characteristics was not investigated in this study. The prescribed dose and indication for opioid initial prescription were not available, hence this study did not evaluate the adherence of healthcare prescribers to the clinical guidelines and recommendations of opioid prescribing. Lastly, this study did not also investigate other factors as potential predictors, including polypharmacy, urinary incontinence, and nicotine dependence. These factors have been found to be predictors of persistent opioid use in previous studies (1,3).

## 5.7 Implication for clinical practice and policy

CNCP treatment requires individualisation and is complex, especially in older adults. Given the rising incidence, prevalence and trends of opioid use in older adults, it is crucial to monitor patients during the entire treatment period, as well as to assess the need of opioids periodically. Having a clear, detailed treatment plan with the goals of therapy for the patient (101). In spite of uncertainty about the benefits of long-term opioids use in CNCP treatment in older adults, there is strong evidence of significant harms. In order to reduce harms associated with persistent opioid use, it is crucial to understand who is at a greater risk of persistent use (1). Prescribers need to be fully aware of characteristics of older patients who are most likely to transition from acute to persistent opioid use. Moreover, awareness and knowledge of prescribers that risks of persistent opioid use in older adults increase with every additional day supply, might help them evaluate their initial opioid prescribing decisions, which can potentially reduce the risk of persistent opioid use (97). Not only does prescribers have a significant role in reducing persistent opioid use rate in older adults, but also pharmacists. In NZ, pharmacists have a great role in counselling older patients on opioid risks. Educating older patients on proper opioid use, adverse effects and risks of opioid stockpiling can help patients safely manage opioids (221). Through consulting patients, pharmacists can identify risks (e.g., contraindications, interactions, high dosage) and can report directly to prescribers to avoid the incidence of adverse reactions. Pharmacists can also recommend alternative therapies to prescribers in order to decrease the incidence rate and prevalence of persistent opioid use. The opioid epidemic drivers in the US included false beliefs that opioids can be used safely for CNCP and that developing addiction is uncommon. This happened through public

advertisements of opioid analgesics, which lead to increasing pressure on prescribers to prescribe them (222-224). Although NZ is highly unlikely to experience an opioid epidemic like the US, it is prudent to consider investments or preparations which are proactive, including expanding monitoring/surveillance and early warning systems and improving treatment resources and systems for problematic opioid use. Moreover, NZ could potentially join the ongoing quest of other wealthy jurisdiction to proactively search for and place effective means to decrease the possibility of having an adverse toll from opioids on the public health, especially older adults, that has been serious and extensive in other countries such as the US (225).

## 5.8 Directions for further research

The use of opioids remains unclear in the older population, including initiating, monitoring and de-prescribing of opioids. Prescribers can be reluctant to shift established and fixed patterns of prescribing. Future research focusing on the long-term use of opioids in the older population is needed to establish evidence-based recommendations (8). The need for more information on efficacy and safety of opioids in older adults is needed to optimise pain relieving treatment in this population. Further research should also investigate the time to dose escalation and progression from a weak to a strong opioid amongst older adults who are persistent users (1). for developing screening tools to assess potential risks associated with persistent opioid use based on patient characteristics, as more validation and prospective outcome studies are required to investigate how these screening tools accurately predict and affect clinical outcomes (49). My passion for research has been growing and I am planning to continue my research journey through PhD and post-doctoral research in opioids as it is a vast topic with many research gaps and opportunities.

# 6. CONCLUSIONS

The present study found the overall incidence rate of opioid use in NZ older adults ranged between 74.3 per 1000 persons in 2008 and 86.3 per 1000 persons in 2018. As for the overall prevalence of opioid use, it ranged from 153.4 per 1000 persons in 2007 to 181.5 per 1000 persons in 2018. Moreover, 2.2% of opioid-naïve older adults without a cancer diagnosis became persistent opioid users. The use of fentanyl, slow-release preparations, presence of three or more comorbidities, the use of anti-epileptics, non-opioid analgesics and strong opioids were the strongest predictors of persistent opioid use. Overall, understanding the characteristics predicting persistent opioid use will enable prescribers to target early intervention efforts and monitoring to prevent future opioid-related adverse events. Prescribers should only consider long-term opioid therapy for older patients when potential benefits are likely to outweigh risks, where there is no alternative therapy that is likely to pose as favourable balance of benefits to harms. Certain factors should be assessed before prescribing opioids long-term, such as the absence of significant psychiatric co-morbidities, no personal or family history of addiction or drug abuse, or major medical co-morbidities. Long-term opioids can then be prescribed with extensive monitoring and regular assessments to determine the need for continuation. Future research should focus on providing evidence-based guidelines for the use of opioid in the older population.

# LIST OF APPENDICES

# Appendix A: Literature review MeSH terms

| Keyword | MeSH Terms |
|---|---|
| **Incidence**<br><br>**Prevalence** | Proportion, rate*, epidemiolog*, pattern*, percentage*, extent, frequenc*, trend* |
| **Old** | Old*, elder*, geriatric*, aged |
| **Persistent** | Chronic, constant, continuous, regular, long-term, long term, prolonged |
| **Predictors** | Predictor*, factor*, risk factor*, determinant* |
| **Opioid** | Opioid*, opiate*, fentanyl, morphine, buprenorphine, pethidine, meperidine, oxycodone, dihydrocodeine, tramadol, codeine, hydrocodone, hydromorphone, oliceridine, oxymorphone, tapentadol, butorphanol, levorphanol, (methadone not opioid substitution) |

# Appendix B: Potential Predictors/Variables for Study 2

**Table 1: Baseline sociodemographic variables**

| Variable | Data Source | Definitions |
|---|---|---|
| eNHI | NHI | Unique identifier per person (encrypted NHI) |
| Index date | Multiple | The index date for all individuals is defined as the date of the first opioid dispensing between Jan 1, 2013 and June 30, 2018. |
| Cohort Year | NHI | Year of index date. The year MUST be between Jan 1, 2013 and June 30, 2018 |
| Date of Birth | NHI | Date of birth in DD/MM/YYYY date format |
| Sex | NHI | Sex |
| Ethnicity | NH | Ethnicity at the time of cohort entry |
| Prioritised Ethnicity | NHI | Prioritised ethnicity at time of cohort entry: Māori, NZ European, Pacific people, Asian, Other, or Unknown |
| Deprivation Index | NHI | NZDep Score recorded on NHI database at the time of cohort entry: 1 to 10 deprivation scores |
| Death (No/Yes) | MORT | Create a flag indicating death from any cause within 6 months after the index date |
| Death date | MORT | Date of death from any cause within 6 months after the index date |
| Prior opioid exposure365 (No/Yes) | Pharms | Flag if patients have any dispensing for any opioid 365 days prior to the index date. |
| Prior opioid exposure180 (No/Yes) | | Flag if patients have any dispensing for any opioid 180 days prior to the index date.<br><br>This variable needed for sensitivity analysis |
| Prior opioid exposure90 (No/Yes) | | Flag if patients have any dispensing for any opioid 90 days prior to the index date.<br><br>This variable needed for sensitivity analysis |
| Number of outpatient/ED visits | NNPAC | Number of outpatient/Emergency department visits within 365 days prior to the index date |
| Number of hospitalisations | NMDS | Number of hospital visits (inpatient) within 365 days prior to the index date |
| End Date | Multiple | **Observation end date (or cohort exit date).**<br>Opioid users should be censored if they discontinued opioid use (as defined by the absence of a new prescription by the end of the 45-day period from the last identified index medication fill), died or reached the end of the study period (31st December 2018), whichever occurred first. The study period starts on 1st January 1, 2013, with enrolment to the end of June 30, 2018, and follow-up to the end of December 31, 2018. |

| | | |
|---|---|---|
| | | **Note: An individual can only enter the cohort once, if they have multiple opioid dispensings at different years of the study period, only their first period should be included.** |

**Table 2: Information on opioid use**

<table>
<tr><td>Opioid type at cohort entry</td><td></td><td>Flag indicating the initial opioid dispensing record as “morphine”, “Oxycodone”, “Fentanyl”, “Pethidine”, “dihydrocodeine”, “Codeine”, “Tramadol” or “Multiple opioids”.<br><br><table><tr><td>Opioid name</td><td>Chem ID</td></tr><tr><td>Fentanyl</td><td>3801</td></tr><tr><td>Oxycodone</td><td>3822</td></tr><tr><td>Morphine</td><td>1830, 1831</td></tr><tr><td>Pethidine</td><td>1953</td></tr><tr><td>Codeine</td><td>1332</td></tr><tr><td>Dihydrocodeine</td><td>2427</td></tr><tr><td>Tramadol</td><td>3906</td></tr></table><br>Note: If patients received more than one opioid prescription at cohort entry – it should be recorded as “multiple opioid”</td></tr>
<tr><td>Opioid strength (week opioid/Strong Opioid)</td><td>Pharms</td><td>Flag indicating whether the initial opioid prescription is for strong (any of the following: morphine, oxycodone, fentanyl, or pethidine) OR weak opioid (any of these: dihydrocodeine, codeine, or tramadol).<br><br><table><tr><td>Opioid type and name</td><td>Chem ID</td></tr><tr><td>Strong opioids</td><td></td></tr><tr><td>Fentanyl</td><td>3801</td></tr><tr><td>Oxycodone</td><td>3822</td></tr><tr><td>Morphine</td><td>1830, 1831</td></tr><tr><td>Pethidine</td><td>1953</td></tr><tr><td>Weak Opioids</td><td></td></tr><tr><td>Codeine</td><td>1332</td></tr><tr><td>Dihydrocodeine</td><td>2427</td></tr></table></td></tr>
</table>

| | | |
|---|---|---|
| | | <table><tr><td>Tramadol</td><td>3906</td></tr></table><br><br>If the person received both weak and strong opioids at cohort entry, it should be recorded as strong opioid. |
| Opioid load (OME) initial prescription | Pharms | Total oral morphine equivalence of the initial prescription via converting all the different opioid types to the equivalence of morphine as per conversion factors below and adding together the OME for the total load:<br><br>Opioid dosing will be standardised via conversion OME_mg via the formula:<br><br>OME = Pack Strength × OME conversion factor × Quantity dispensed<br><br>The total quantity dispensed per opioid will be used irrespective of duration or instructions used on the prescription.<br><br>**OME conversion factors:**<br>Morphine- 1<br>Oxycodone- 1.5<br>Fentanyl Patch- 7.2<br>Pethidine- 0.4<br>Dihydrocodeine- 0.1<br>Codeine- 0.1<br>Tramadol- 0.1 |
| Injectable preparation (Yes/No) | PHARMs | Flag indicating if any of the following injectable opioid preparation was dispensed on the initial prescription:<br><br>Morphine sulphate (Form ID): 183108, 183110, 183107<br>Morphine tartrate (Form ID): 238301, 238302<br>Oxycodone HCL (Form ID): 382234, 382235, 382236<br>Fentanyl (Form ID): 380116, 380115<br>Pethidine (Form ID): 195303, 195305 |
| Slow-release preparation (Yes/No) | Pharms | Flag indicating if any of the following slow-release opioid preparation was dispensed on the initial prescription: |

| | | |
|---|---|---|
| | | Morphine:<br>Long- acting oral: Formulation ID: 183122, 183119, 183126, 183127, 183101, 183104, 183102, 183103<br><br>Oxycodone:<br>Long-acting oral: Formulation ID: 382228, 382229, 382230, 382232, 382231<br><br>Fentanyl:<br>Formulation ID: Topical patch: 380137, 380133, 380134, 380135, 380136, 380132<br><br>Tramadol:<br>Long-acting oral: Formulation ID: 390626, 390627, 390628<br><br>Dihydrocodeine:<br>Long-acting oral: Formulation ID: 242701 |
| Opioid type switch (Yes/No) | Pharms | Create a flag that shows that the patient switched from initially prescribed opioid(s) to other opioid(s) during any subsequent prescriptions from the index date |
| Opioid switch date | Pharms | Record the date of treatment switch (only the first time a switch occur will be recorded if multiple switches occur from the index date to end date). |
| Opioid discontinuation date | Pharms | Record the date if the patient censored due to 45-day gap in opioid dispensing during follow-up |
| Outcome_1 (non-persistent opioid user/Persistent Opioid user) | Pharms | Create a flag indicating whether the person is a "persistent opioid user" or "non-persistent opioid user" as per the following definitions.<br><br>**Persistent opioid user**<br>Persistent opioid users are patients who had an opioid dispensing at index date and who had at least one additional opioid dispensing between 91 and 180 days after the index date.<br><br>**Non-persistent opioid user**<br>Patients who do not have dispensing of opioid beyond 90 days after the index date and does not meet any of the persistent opioid user definitions above will be considered as non-persistent opioid users. |
| Outcome_2 (non-persistent opioid user/Persistent Opioid user) | Pharms | Alternative definition for persistent use/non-persistent use (for sensitivity analysis)<br><br>Create a flag indicating whether the person is a "persistent opioid user" or "non-persistent opioid user" as per the following definitions. |

| | | |
|---|---|---|
| | | **Persistent opioid user**<br>Persistent opioid users are patients who had an opioid dispensing at index date and who had continuous opioid dispensing for at least 120 days within 6 months following the index date.<br><br>**Non-persistent opioid user**<br>Patients who do not have dispensing of opioid beyond 119 days after the index date and does not meet any of the persistent opioid user definitions above will be considered as non-persistent opioid users. |

**Table 3: Baseline comorbidities**

| **Comorbidity** | **Data Source** | **Definition-** note all specified comorbidities have a look back period of 3 years. |
|---|---|---|
| Hypertension (Yes/No) | NMDS/PHARMS | ≥ 1 inpatient claim with ICD-10AM diagnoses (any position) of hypertension within 3 years prior to the index date: I10-I15, I674 |
| Heart Failure (Yes/No) | NMDS/PHARMS | ≥ 1 inpatient claim with ICD-10AM diagnoses (any position) of heart failure within 3 years prior to the index date Any of the following diagnosis within 3 years prior to the index date: I110, I130, I132, I50 |
| COPD (Yes/No) | NMDS/PHARMs | ≥ 1 inpatient claim with ICD-10AM diagnoses (any position) of COPD within 3 years prior to the index date: J40-J44 |
| Asthma (Yes/No) | NMDS/PHARMS | ≥ 1 inpatient claim with ICD-10AM diagnoses (any position) of asthma within 3 years prior to the index date: J45, J46 |
| Sleep Apnoea (Yes/No) | NMDS | ≥ 1 inpatient claim with ICD-10AM diagnoses of sleep apnoea (any position) within 3 years prior to the index date: G47 |
| Diabetes mellitus (Yes/No) | NMDS/PHARMS | ≥ 1 inpatient claim with ICD-10AM diagnoses of diabetes (any position) within 3 years prior to the index date: E10 - E14. |
| Psychotic disorder (Yes/No) | NMDS/Pharms | ≥ 1 inpatient claim with ICD-10AM diagnoses of psychiatric disorder (any position) within 3 years prior to the index date: F20 – F29 |
| Bipolar disorder (Yes/No) | NMDS/Pharms | ≥ 1 inpatient claim with ICD-10AM diagnoses of bipolar disorder (any position) within 3 years prior to the index date: F30-F31 |
| Anxiety (Yes/No) | NMDS/Pharms | ≥ 1 inpatient claim with ICD-10AM diagnoses of anxiety disorder (any position) within 3 years prior to the index date: F40-F48 |
| Depression (Yes/No) | NMDS/Pharms | ≥ 1 inpatient claim with ICD-10AM diagnoses of depression (any position) within 3 years prior to the index date: F32–F34, F38–F39 |
| Seizures (Yes/No) | | ≥1 inpatient claim with a diagnosis code of seizures (ICD 10AM: G40–G41, R56) in any position within 3 years prior to the index date. |

| | | |
|---|---|---|
| Dementia/Alzheimer (Yes/No) | NMDS/Pharms | ≥1 inpatient claim with a diagnosis code of Dementia/Alzheimer (ICD-10AM diagnosis code of F00 – F03, G30, G31) in any position within 3 years prior to the index date. |
| Parkinson disease (Yes/No) | NMDS/ Pharms | ≥1 inpatient claim with a diagnosis code of Parkinson disease (ICD-10AM diagnosis code of G20, G21) in any position within 3 years prior to the index date. |
| Suicide and self-harm (Yes/No) | NMDS | ≥1 inpatient claim with a diagnosis code of intentional self-harm (ICD-10AM diagnosis code of X60 to X84; Y10-Y34) in any position within 3 years prior to the index date. |
| Alcohol-related condition (chronic high use) (Yes/No) | NMDS | Any of the following within 3 years prior to the index date:<br>Alcohol-induced pseudo-Cushing syndrome: E244<br>Degeneration of nervous system due to alcohol: G312<br>Alcoholic polyneuropathy: G621<br>Alcoholic myopathy: G721<br>Alcoholic cardiomyopathy: I426<br>Alcoholic gastritis: K292.2<br>Alcoholic liver disease: K70<br>Alcohol-induced chronic pancreatitis: K860<br>Mental and behavioural disorders due to use of alcohol: F10<br>History of alcohol use disorder: Z8641<br>Alcohol counselling, detoxification, or rehabilitation: Z502, Z714, 9201000, 9200200, 9200300, 9200400, 9200800, 9200900<br>**OR**<br>≥1 pharmacy claim for disulfiram within 1 year prior to index date (Chem ID: 1432) |
| Chronic Pain (Yes/No) | NMDS | Any of the following within 3 years prior to the index date:<br><br>ICD-10AM code: R52.1, R52.2<br>**OR**<br>Common chronic pain related diagnosis (ICD-10 codes incl. relevant subcodes):<br>Fibromyalgia (M79.7)<br>Irritable bowel syndrome (K58)<br>Interstitial cystitis/bladder pain syndrome (N30.10, N30.30)<br>Chronic prostatitis (N41.1)<br>Vulvodynia (N94.8)<br>Migraine (G43)<br>Chronic tension-type headache (G44.2)<br>Temporomandibular disorder (K07.6, S01.4)<br>Chronic low back pain (M54.4, M54.5, M54.89) |

| | | |
|---|---|---|
| | | Chronic fatigue syndrome (R53.82) |
| Rheumatoid arthritis (Yes/No) | NMDS | ≥1 inpatient claim with a diagnosis code of rheumatoid arthritis (ICD-10AM diagnosis code of M05-M06) in any position within 3 years prior to the index date |
| Systemic lupus erythematosus, | NMDS | ≥1 inpatient claim with a diagnosis code of lupus (ICD-10AM: M32) in any position within 3 years prior to the index date |
| Soft tissue disorders (Yes/No) | NMDS | ≥1 inpatient claim with a diagnosis code of any soft tissue disorder (ICD-10AM: M60 – M79) in any position within 3 years prior to the index date |
| Gout (Yes/No) | NMDS | ≥1 inpatient claim with a diagnosis code of gout (ICD-10AM: M10) in any position within 3 years prior to the index date |
| Osteoarthritis (Yes/No) | NMDS | ≥1 inpatient claim with a diagnosis code of osteoarthritis (ICD-10AM: M15-M19) in any position within 3 years prior to the index date |
| Obesity (Yes/No) | NMDS | A diagnosis of obesity 3 years before the index date (ICD 10AM: E66) |
| Substance Abuse (Yes/No) | NMDS/ Pharms | Any of the followings:<br>(a)≥1 inpatient claim with a diagnosis code of substance abuse (ICD-10-AM diagnosis code of F11-F19, F55) in any position within 3 years prior to the index date.<br><br>**OR**<br>(b) ≥1 pharmacy claim for one of the following medications used to treat substance dependence within 1 year prior to the index date:<br>**Methadone** (Chem ID: 1795)<br>**Buprenorphine with naloxone** (Chem ID= 3950)<br>**Bupropion hydrochloride** (Chem ID= 3892)<br>**Naltrexone hydrochloride** (Chem ID= 3793)<br>**Nicotine** (Chem ID= 3722)<br>**Varenicline tartrate** (Chem ID= 3920)<br>Disulfiram (Chem ID: 1432) |
| Chronic kidney disease (Yes/No) | NMDS/PHARMS | ≥1 inpatient claim with a discharge diagnosis code of chronic kidney disease (ICD 10AM: E10.2, E11.2, E12.2, E13.2, E14.2, I12.0, I13.0, I13.1, I13.2, N08, N18, N19, N25.0, Z49.0, Z49.1, Z49.2, Z99.2) in any discharge position within 3 years prior to the index date. |
| Chronic liver disease (Yes/No) | NMDS/PHARMS | A diagnosis of chronic liver disease 3 years before the index date:<br><br>ICD 10 AM codes:<br>Chronic hepatic failure: K721<br>Varices (gastric or oesophageal): I850, I859, I864 |

| | | |
|---|---|---|
| | | Alcoholic liver disease: K702, K703, K704<br>Biliary cirrhosis: K743, K744, K745<br>Other chronic liver disease: K717, K746, K766, K767 |
| CCI | NMDS | Charlson Comorbidity Index (score of 1 to 24)– see Table 6 for algorithm. |

**Table 4: Baseline Medications use in 365 days prior to index date**

| | | |
|---|---|---|
| Antihypertensives (Yes/No) | PHARMS | Any of the following Chem IDs:<br>**Adrenergic alpha antagonists:** 704, 1966, 2031, 2515, 2543<br>**Non-loop diuretics:** 1050, 2176, 4006, 1116, 1282, 1290, 1367, 1643, 1801<br>**Vasodilators:** 1160, 1365, 1604, 1862, 1928, 2451, 2455, 3889, 3890, 3891, 3904, 3975, 6001<br>**Beta blockers:** 1001, 1029, 1094, 1699, 1817, 1818, 1838, 1912, 1991, 2060<br>**Calcium channel blockers:** 1863, 1949, 2317, 2398, 2528, 2771, 2793<br>**Central acting agents:** 1317, 1318, 1805, 1806<br>**ACE inhibitors:** 1031, 2711, 2770, 2772, 2794, 2797, 2806, 2841,<br>**Angiotensin-II receptor antagonists:** 1061, 1254<br>**Thiazide and related diuretics**: 1116, 1290, 1643<br>**Potassium-sparing diuretics:** 1050, 4100, 4006, 2176<br>**ACE inhibitors with diuretics**: 1127, 2708, 2795, 2840, 3749<br>**Angiotensin-II receptor antagonists with diuretics:** 70705<br>**Potassium sparing combination diuretics:** 1051, 1053, 2293 |
| Antidiabetics (Yes/No) | PHARMS | Any of the following Chem IDs:<br>**Oral hypoglycaemic agents**: 1567, 1568, 1569, 1794, 2277, 3800, 4103, 4104,<br>**Acarbose:** 1247<br>**Insulin preparations:** 1192, 1242, 1648, 1649, 1649, 1655, 2276, 2424, 3739, 3783, 3857, 3908, 3982, 6300 |
| Gout medications (Yes/No) | PHARMS | Hyperuricaemia and Antigout: TG2ID: 1913 |
| Antiepileptic drugs (Yes/No) | PHARMS | Antiepileptic drugs: TG2ID: 2207 |
| Non-opioid analgesics (Yes/No) | PHARMS | **Any of the following Form ID/Chem IDs/TG2ID:**<br>Aspirin (Form IDs: 108701, 108705)<br>Paracetamol (1929, 1931) |

| | | |
|---|---|---|
| | | Nefopam (1849)<br>Clonidine (1317, 1318)<br>Gabapentin (1062, 1060)<br>Pregabalin (4097)<br>Amitriptyline (1059)<br>Nortriptyline (1876)<br>Capsaicin (3854)<br>NSAIDs: TG2ID: 1904 |
| Anxiolytics, sedatives and hypnotics | PHARMS | Anxiolytics: TG2ID: 2225<br>CHEM ID: Zopiclone (24801) |
| Antipsychotics (Yes/No) | PHARMS | Antipsychotics: TG2ID: 2222 |
| Mood Stabilisers (Yes/No) | PHARMS | Any of the followings: Chem IDs- Carbamazepine (1217), Lamotrigine (1002), Sodium valproate (2166), Lithium carbonate (2466) |
| Antidepressants (Yes/No) | PHARMS | Antidepressants: TG2ID: 2205 |
| Parkinson medications | PHARMS | Agents for Parkinsonism and Related Disorders: TG2ID: 2201 |
| Dementia medications | PHARMS | Treatments for Dementia: TG2ID: 2232 |

**Table 5: ICD-10 Coding Algorithm for Charlson Comorbidity Index (CCI)** [based on hospital discharge records (inpatient) for 3 years before the index date for each comorbidity of interest]

| **Comorbidities** | **ICD-10** | **Weight assigned to comorbidities** |
|---|---|---|
| Congestive heart failure | I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 – I42.9, I43, I50, P29.0 | 2 |
| Dementia | F00 – F03, F05.1, G30, G31.1l | 2 |
| Chronic pulmonary disease | I27.8, I27.9, J40 - J47, J60 - J67, J68.4, J70.1, J70.3 | 1 |
| Rheumatic disease | M05, M06, M31.5, M32 - M34, M35.1, M35.3, M36.0 | 1 |
| Mild liver disease | B18, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73, K74, K76.0, K76.2 - K76.4, K76.8, K76.9, Z94.4 | 2 |
| Diabetes with chronic complications | E10.2 – E10.5, E10.7, E11.2 – E11.5, E11.7, E12.2 – E12.5, E12.7, E13.2 – E13.5, E13.7, E14.2 – E14.5, El4.7 | 1 |
| Hemiplegia or paraplegia | G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0 - G83.4, G83.9 | 2 |
| Renal disease | I12.0, I13.1, N03.2 - N03.7, N05.2 - N05.7, N18, N19, N25.0, Z49.0 - Z49.2, Z99.2 | 1 |
| Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin | C00 - C26, C30 - C34, C37 - C41, C43, C45 - C58, C60 - C76, C81 - C85, C88, C90 - C97 | 2 |
| Moderate or severe liver disease | I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7 | 4 |
| Metastatic solid tumour | C77 - C80 | 6 |
| AIDS/HIV | B20 - B22, B24 | 4 |
| **Maximum comorbidity score** | | **24** |

# Appendix C: Multivariable Logistic Regression Model examining predictors of persistent opioid use in older population in NZ

**Sensitivity Analysis 1 (n=258,676)**

1) Persistent opioid use is defined as opioid use in 91-180 days
2) 12 months look-back period - i.e., only those with no opioid use history 12 months before cohort entry included

| | B | p-value | Adjusted odds ratio | 95% C.I. | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| **Sociodemographic factors** | | | | | |
| Female | 0.032 | 0.284 | 1.033 | 0.974 | 1.095 |
| **Age Group (Ref=65-74 years)** | | | | | |
| 75-84 years | -0.034 | 0.328 | 0.966 | 0.902 | 1.035 |
| 85+ years | 0.651 | <0.001 | 1.917 | 1.777 | 2.069 |
| **Ethnic Group (Ref=European)** | | | | | |
| Māori | 0.085 | 0.143 | 1.089 | 0.972 | 1.220 |
| Pacific | -0.841 | <0.001 | 0.431 | 0.338 | 0.550 |
| Asian | -0.785 | <0.001 | 0.456 | 0.370 | 0.562 |
| Other | -0.736 | 0.006 | 0.479 | 0.285 | 0.806 |
| **Deprivation Index (Ref=Quintile 1)** | | | | | |
| Quintile 2 | 0.045 | 0.378 | 1.046 | 0.946 | 1.156 |
| Quintile 3 | 0.149 | 0.002 | 1.161 | 1.055 | 1.277 |
| Quintile 4 | 0.305 | <0.001 | 1.357 | 1.239 | 1.486 |
| Quintile 5 | 0.344 | <0.001 | 1.410 | 1.280 | 1.554 |
| **Healthcare utilisation factors** | | | | | |
| **Number of outpatient/ED visits (Ref=No Visit)** | | | | | |
| 1-2 Outpatient/ED visits | -0.072 | 0.095 | 0.930 | 0.855 | 1.013 |
| 3+ Outpatient/ED visits | 0.117 | 0.005 | 1.124 | 1.036 | 1.221 |
| **Number of inpatient admissions (Ref= No inpatient admission)** | | | | | |
| 1-2 Inpatient admissions | -0.199 | <0.001 | 0.819 | 0.764 | 0.879 |
| 3+ Inpatient admissions | -0.100 | 0.059 | 0.905 | 0.815 | 1.004 |
| **Opioid-related factors** | | | | | |
| **Opioid type (Ref = Codeine)** | | | | | |
| Oxycodone | -0.149 | 0.321 | 0.862 | 0.642 | 1.156 |
| Fentanyl | 1.309 | <0.001 | 3.702 | 2.687 | 5.101 |
| Morphine | 0.237 | 0.106 | 1.267 | 0.951 | 1.687 |
| Dihydrocodeine | -0.003 | 0.976 | 0.997 | 0.837 | 1.188 |
| Tramadol | -0.299 | <0.001 | 0.742 | 0.681 | 0.807 |
| Multiple | -0.321 | 0.002 | 0.726 | 0.591 | 0.891 |
| **Opioid strength (Ref=Weak opioid)** | | | | | |
| Strong Opioid | 0.675 | <0.001 | 1.965 | 1.497 | 2.579 |
| **Oral Morphine Milligram Equivalent (Ref = ≤50 MME/day)** | | | | | |
| 51-90 MME/day | -0.167 | 0.002 | 0.846 | 0.761 | 0.941 |

| | | | | | |
|---|---|---|---|---|---|
| 91-120 MME/day | 0.020 | 0.765 | 1.020 | .895 | 1.163 |
| 121-200 MME/day | 0.174 | 0.001 | 1.190 | 1.073 | 1.319 |
| >200 MME/day | 0.603 | <0.001 | 1.828 | 1.645 | 2.030 |
| **Injectable preparation** | -0.992 | <0.001 | 0.371 | 0.277 | 0.496 |
| **Slow-release preparation** | 1.103 | <0.001 | 3.014 | 2.768 | 3.283 |
| **Co-morbidities** | | | | | |
| CCI (Ref = CCI 0) | | | | | |
| CCI 1 | 0.434 | <0.001 | 1.544 | 1.364 | 1.747 |
| CCI 2 | 0.574 | <0.001 | 1.775 | 1.590 | 1.982 |
| CCI ≥3 | 0.775 | <0.001 | 2.171 | 1.843 | 2.557 |
| Hypertension | -0.166 | <0.001 | 0.847 | 0.774 | 0.927 |
| Heart failure | -0.132 | 0.066 | 0.876 | 0.761 | 1.009 |
| Diabetes | -0.080 | 0.232 | 0.923 | 0.809 | 1.053 |
| Respiratory disorder | 0.128 | 0.045 | 1.136 | 1.003 | 1.287 |
| Mental disorder | -0.003 | 0.971 | 0.997 | 0.861 | 1.155 |
| Dementia/Alzheimer | 0.003 | 0.967 | 1.003 | 0.865 | 1.163 |
| Parkinson Disease | -0.106 | 0.470 | 0.900 | 0.676 | 1.198 |
| Seizures | 0.234 | 0.052 | 1.263 | 0.998 | 1.599 |
| Chronic pain | 0.324 | <0.001 | 1.383 | 1.167 | 1.639 |
| Soft tissue disorders | 0.105 | 0.136 | 1.111 | 0.967 | 1.276 |
| Gout | 0.334 | 0.008 | 1.397 | 1.093 | 1.786 |
| Osteoarthritis | -0.128 | 0.044 | 0.880 | 0.776 | 0.997 |
| Alcohol related condition | 0.129 | 0.278 | 1.138 | 0.901 | 1.436 |
| Substance abuse | 0.413 | <0.001 | 1.512 | 1.334 | 1.712 |
| Obesity | 0.109 | 0.319 | 1.115 | 0.900 | 1.383 |
| CKD | -0.070 | 0.300 | 0.932 | 0.816 | 1.065 |
| **Other Medications used** | | | | | |
| Antihypertensives | -0.026 | 0.417 | 0.974 | 0.914 | 1.038 |
| Antidiabetics | -0.009 | 0.863 | 0.991 | 0.891 | 1.101 |
| Gout medications | -0.071 | 0.155 | 0.932 | 0.845 | 1.027 |
| Antiepileptics | 0.748 | <0.001 | 2.114 | 1.927 | 2.318 |
| Non-opioid analgesics | 0.727 | <0.001 | 2.068 | 1.909 | 2.240 |
| Benzodiazepines/Zopiclone | 0.178 | <0.001 | 1.195 | 1.110 | 1.287 |
| Antipsychotics | 0.656 | <0.001 | 1.927 | 1.740 | 2.134 |
| Mood stabilisers | -0.371 | <0.001 | 0.690 | 0.589 | 0.808 |
| Antidepressants | 0.405 | <0.001 | 1.499 | 1.410 | 1.593 |
| Anxiolytics | 0.247 | <0.001 | 1.280 | 1.160 | 1.413 |
| Parkinson medications | 0.375 | <0.001 | 1.455 | 1.221 | 1.733 |
| Dementia medications | 0.275 | 0.003 | 1.317 | 1.095 | 1.583 |

**Sensitivity Analysis 2 (n=258,676)**

1) Persistent opioid use is defined as opioid use in 91-180 days
2) 3 months look-back period - i.e., only those with no opioid use history 3 months before cohort entry included

| | B | p-value | Adjusted odds ratio | 95% C.I | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| **Sociodemographic factors** | | | | | |
| Female | 0.028 | 0.337 | 1.029 | 0.971 | 1.089 |
| **Age Group (Ref=65-74 years)** | | | | | |
| 75-84 years | -0.019 | 0.577 | 0.981 | 0.917 | 1.049 |
| 85+ years | 0.680 | <0.001 | 1.974 | 1.833 | 2.125 |
| **Ethnic Group (Ref=European)** | | | | | |
| Māori | 0.095 | 0.094 | 1.100 | 0.984 | 1.230 |
| Pacific | -0.788 | <0.001 | 0.455 | 0.360 | 0.574 |
| Asian | -0.795 | <0.001 | 0.452 | 0.368 | 0.555 |
| Other | -0.682 | 0.006 | 0.506 | 0.310 | 0.826 |
| **Deprivation Index (Ref=Quintile 1)** | | | | | |
| Quintile 2 | 0.048 | 0.336 | 1.049 | 0.951 | 1.157 |
| Quintile 3 | 0.154 | 0.001 | 1.166 | 1.062 | 1.280 |
| Quintile 4 | 0.301 | <0.001 | 1.351 | 1.236 | 1.477 |
| Quintile 5 | 0.330 | <0.001 | 1.391 | 1.265 | 1.530 |
| **Healthcare utilisation factors** | | | | | |
| **Number of outpatient/ED visits (Ref=No Visit)** | | | | | |
| 1-2 Outpatient/ED visits | -0.079 | 0.063 | 0.924 | 0.850 | 1.004 |
| 3+ Outpatient/ED visits | 0.092 | 0.026 | 1.096 | 1.011 | 1.188 |
| **Number of inpatient admissions (Ref= No inpatient admission)** | | | | | |
| 1-2 Inpatient admissions | -0.199 | <0.001 | 0.819 | 0.765 | 0.877 |
| 3+ Inpatient admissions | -0.079 | 0.123 | 0.924 | 0.835 | 1.022 |
| **Opioid-related factors** | | | | | |
| **Opioid type (Ref = Codeine)** | | | | | |
| Oxycodone | -0.193 | 0.190 | 0.824 | 0.618 | 1.100 |
| Fentanyl | 1.249 | <0.001 | 3.485 | 2.546 | 4.772 |
| Morphine | 0.199 | 0.165 | 1.221 | 0.921 | 1.617 |
| Dihydrocodeine | -0.061 | 0.486 | 0.941 | 0.793 | 1.117 |
| Tramadol | -0.290 | <0.001 | 0.748 | 0.689 | 0.813 |
| Multiple | -0.331 | 0.001 | 0.718 | 0.586 | 0.881 |
| **Opioid strength (Ref=Weak opioid)** | | | | | |
| Strong Opioid | 0.732 | <0.001 | 2.080 | 1.592 | 2.717 |
| **Oral Morphine Milligram Equivalent (Ref = ≤50 MME/day)** | | | | | |
| 51-90 MME/day | -0.173 | 0.001 | 0.841 | 0.758 | 0.932 |
| 91-120 MME/day | -0.009 | 0.890 | 0.991 | 0.871 | 1.127 |
| 121-200 MME/day | 0.149 | 0.004 | 1.160 | 1.049 | 1.284 |
| >200 MME/day | 0.561 | <0.001 | 1.752 | 1.581 | 1.941 |
| **Injectable preparation** | -0.978 | <0.001 | 0.376 | 0.283 | 0.499 |
| **Slow-release preparation** | 1.109 | <0.001 | 3.032 | 2.790 | 3.296 |
| **Co-morbidities** | | | | | |
| CCI (Ref = CCI 0) | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| CCI 1 | 0.419 | <0.001 | 1.520 | 1.348 | 1.714 |
| CCI 2 | 0.557 | <0.001 | 1.746 | 1.568 | 1.944 |
| CCI ≥3 | 0.753 | <0.001 | 2.122 | 1.811 | 2.488 |
| Hypertension | -0.186 | <0.001 | 0.831 | 0.761 | 0.906 |
| Heart failure | -0.129 | 0.065 | 0.879 | 0.767 | 1.008 |
| Diabetes | -0.070 | 0.283 | 0.932 | 0.820 | 1.060 |
| Respiratory disorder | 0.131 | 0.034 | 1.140 | 1.010 | 1.286 |
| Mental disorder | -0.009 | 0.904 | 0.991 | 0.860 | 1.142 |
| Dementia/Alzheimer | 0.031 | 0.675 | 1.031 | 0.894 | 1.190 |
| Parkinson Disease | -0.091 | 0.522 | 0.913 | 0.691 | 1.206 |
| Seizures | 0.235 | 0.043 | 1.265 | 1.007 | 1.590 |
| Chronic pain | 0.310 | <0.001 | 1.363 | 1.160 | 1.601 |
| Soft tissue disorders | 0.072 | 0.286 | 1.075 | 0.941 | 1.227 |
| Gout | 0.266 | 0.028 | 1.305 | 1.029 | 1.656 |
| Osteoarthritis | -0.153 | 0.012 | 0.858 | 0.762 | 0.967 |
| Alcohol related condition | 0.118 | 0.305 | 1.126 | 0.898 | 1.412 |
| Substance abuse | 0.398 | <0.001 | 1.489 | 1.319 | 1.681 |
| Obesity | 0.109 | 0.302 | 1.115 | 0.907 | 1.373 |
| CKD | -0.064 | 0.335 | 0.938 | 0.825 | 1.068 |
| **Other Medications used** | | | | | |
| Antihypertensives | -0.030 | 0.341 | 0.970 | 0.912 | 1.032 |
| Antidiabetics | -0.013 | 0.801 | 0.987 | 0.890 | 1.094 |
| Gout medications | -0.075 | 0.123 | 0.928 | 0.843 | 1.020 |
| Antiepileptics | 0.725 | <0.001 | 2.064 | 1.887 | 2.259 |
| Non-opioid analgesics | 0.707 | <0.001 | 2.027 | 1.873 | 2.194 |
| Benzodiazepines/Zopiclone | 0.181 | <0.001 | 1.199 | 1.116 | 1.288 |
| Antipsychotics | 0.648 | <0.001 | 1.911 | 1.730 | 2.111 |
| Mood stabilisers | -0.315 | <0.001 | 0.730 | 0.627 | 0.850 |
| Antidepressants | 0.387 | <0.001 | 1.473 | 1.388 | 1.563 |
| Anxiolytics | 0.219 | <0.001 | 1.245 | 1.131 | 1.370 |
| Parkinson medications | 0.364 | <0.001 | 1.439 | 1.212 | 1.708 |
| Dementia medications | 0.271 | 0.003 | 1.311 | 1.094 | 1.570 |

**Sensitivity Analysis 3 (n=258,676)**

1) Persistent opioid use is defined as >120 days of opioid supply during the 6 months period
2) 6 months look-back period - i.e., only those with no opioid use history 6 months before cohort entry included

| | B | p-value | Adjusted Odds ratio | 95% C.I. | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| **Sociodemographic factors** | | | | | |
| Female | 0.023 | 0.469 | 1.023 | 0.962 | 1.087 |
| **Age Group (Ref=65-74 years)** | | | | | |
| 75-84 years | -0.033 | 0.370 | 0.968 | 0.900 | 1.040 |
| 85+ years | 0.696 | <0.001 | 2.006 | 1.855 | 2.170 |
| **Ethnic Group (Ref=European)** | | | | | |
| Māori | 0.113 | 0.060 | 1.120 | 0.995 | 1.259 |
| Pacific | -0.830 | <0.001 | 0.436 | 0.338 | 0.562 |
| Asian | -0.813 | <0.001 | 0.444 | 0.355 | 0.554 |
| Other | -0.666 | 0.013 | 0.514 | 0.305 | 0.867 |
| **Deprivation Index (Ref=Quintile 1)** | | | | | |
| Quintile 2 | 0.052 | 0.331 | 1.053 | 0.949 | 1.169 |
| Quintile 3 | 0.162 | 0.001 | 1.176 | 1.065 | 1.300 |
| Quintile 4 | 0.322 | <0.001 | 1.380 | 1.255 | 1.518 |
| Quintile 5 | 0.365 | <0.001 | 1.440 | 1.302 | 1.593 |
| **Healthcare utilisation factors** | | | | | |
| Number of outpatient/ED visits (Ref=No Visit) | | | | | |
| 1-2 Outpatient/ED visits | -0.076 | 0.094 | 0.927 | 0.848 | 1.013 |
| 3+ Outpatient/ED visits | 0.107 | 0.015 | 1.113 | 1.021 | 1.213 |
| **Number of inpatient admissions (Ref= No inpatient admission)** | | | | | |
| 1-2 Inpatient admissions | -0.208 | 0.000 | 0.812 | 0.755 | 0.873 |
| 3+ Inpatient admissions | -0.097 | 0.074 | 0.908 | 0.816 | 1.010 |
| **Opioid-related factors** | | | | | |
| **Opioid type (Reference = Codeine)** | | | | | |
| Oxycodone | -0.276 | 0.080 | 0.759 | 0.558 | 1.033 |
| Fentanyl | 1.201 | <0.001 | 3.322 | 2.381 | 4.635 |
| Morphine | 0.150 | 0.328 | 1.162 | 0.860 | 1.569 |
| Dihydrocodeine | -0.073 | 0.427 | 0.930 | 0.776 | 1.113 |
| Tramadol | -0.348 | <0.001 | 0.706 | 0.645 | 0.772 |
| Multiple | -0.416 | <0.001 | 0.660 | 0.529 | 0.822 |
| **Opioid strength (Ref=Weak opioid)** | | | | | |
| Strong Opioid | 0.764 | <0.001 | 2.148 | 1.614 | 2.858 |
| **Oral Morphine Milligram Equivalent (Ref = ≤50 MME/day)** | | | | | |
| 51-90 MME/day | -0.196 | <0.001 | 0.822 | 0.737 | 0.917 |
| 91-120 MME/day | -0.019 | 0.790 | 0.982 | 0.856 | 1.125 |
| 121-200 MME/day | 0.135 | 0.014 | 1.145 | 1.028 | 1.274 |
| >200 MME/day | 0.583 | <0.001 | 1.792 | 1.607 | 1.997 |
| **Injectable preparation** | -0.935 | <0.001 | 0.393 | 0.294 | 0.525 |
| **Slow-release preparation** | 1.180 | <0.001 | 3.255 | 2.981 | 3.555 |
| **Co-morbidities** | | | | | |
| CCI (Ref = CCI 0) | | | | | |
| CCI 1 | 0.450 | <0.001 | 1.569 | 1.383 | 1.780 |

| | | | | | |
|---|---|---|---|---|---|
| CCI 2 | 0.590 | <0.001 | 1.804 | 1.611 | 2.019 |
| CCI ≥3 | 0.805 | <0.001 | 2.236 | 1.893 | 2.640 |
| Hypertension | -0.182 | <0.001 | 0.834 | 0.761 | 0.914 |
| Heart failure | -0.105 | 0.150 | 0.901 | 0.781 | 1.039 |
| Diabetes | -0.090 | 0.195 | 0.914 | 0.798 | 1.047 |
| Respiratory disorder | 0.150 | 0.020 | 1.162 | 1.024 | 1.319 |
| Mental disorder | 0.005 | 0.945 | 1.005 | 0.868 | 1.164 |
| Dementia/Alzheimer | 0.011 | 0.889 | 1.011 | 0.870 | 1.174 |
| Parkinson Disease | -0.060 | 0.685 | 0.942 | 0.707 | 1.256 |
| Seizures | 0.214 | 0.079 | 1.239 | 0.976 | 1.572 |
| Chronic pain | 0.321 | <0.001 | 1.379 | 1.164 | 1.633 |
| Soft tissue disorders | 0.108 | 0.131 | 1.114 | 0.969 | 1.280 |
| Gout | 0.306 | 0.016 | 1.358 | 1.058 | 1.744 |
| Osteoarthritis | -0.130 | 0.044 | 0.878 | 0.774 | 0.997 |
| Alcohol related condition | 0.184 | 0.120 | 1.202 | 0.953 | 1.515 |
| Substance abuse | 0.431 | <0.001 | 1.539 | 1.356 | 1.746 |
| Obesity | 0.137 | 0.217 | 1.147 | 0.923 | 1.426 |
| CKD | -0.050 | 0.467 | 0.951 | 0.831 | 1.089 |
| **Other Medications used** | | | | | |
| Antihypertensives | -0.035 | 0.298 | 0.966 | 0.904 | 1.031 |
| Antidiabetics | -0.014 | 0.801 | 0.986 | 0.883 | 1.101 |
| Gout medications | -0.104 | 0.046 | 0.901 | 0.814 | 0.998 |
| Antiepileptics | 0.766 | <0.001 | 2.151 | 1.959 | 2.362 |
| Non-opioid analgesics | 0.766 | <0.001 | 2.151 | 1.974 | 2.344 |
| Benzodiazepines/Zopiclone | 0.195 | <0.001 | 1.215 | 1.126 | 1.311 |
| Antipsychotics | 0.676 | <0.001 | 1.966 | 1.773 | 2.180 |
| Mood stabilisers | -0.323 | <0.001 | 0.724 | 0.619 | 0.848 |
| Antidepressants | 0.424 | <0.001 | 1.528 | 1.435 | 1.628 |
| Anxiolytics | 0.241 | <0.001 | 1.272 | 1.150 | 1.407 |
| Parkinson medications | 0.364 | <0.001 | 1.440 | 1.202 | 1.724 |
| Dementia medications | 0.248 | 0.010 | 1.282 | 1.060 | 1.549 |

The following patients were excluded from analysis:

1- Patients with opioid exposure within 6 months before the index date
2- Those who died within 6 months of follow-up period
3- Patients with cancer diagnosis before or after index date
4- Pethidine users (n=317)
5- Methadone users

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