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PREVALENCE OF EARLY OPIOID PRESCRIBING FOR NON-SPECIFIC LOW BACK PAIN AND DISABILITY DURATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

BY

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ABSTRACT

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Title: Prevalence of Early Opioid Prescribing for Non-Specific Low Back Pain and Disability Duration: A Systematic Review and Meta-Analysis

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Background: Low back pain (LBP) is a major public health issue, which affects most people at some point in their lives. LBP poses huge burden on the society in terms of economic burden because of workdays lost due to disabilities, loss of productivity, permanents disability, and increased risk of mental health conditions. Length of disability (LOD) due to occupational LBP or non-specific LBP (NSLBP) is related to several factors including individual factors, work related factors and healthcare related factors that are not abided by the clinical guidelines such as early magnetic resonance imaging (eMRI) scanning and early prescription of opioid (within first 15 days of seeking medical care), which were found to be significant predictors of increased LOD.

Aim: The aim of this thesis was to systematically review and summarize the findings of epidemiologic studies assessing the prevalence of early opioid prescribing for LBP and the relationship between early opioid prescribing for LBP and LOD.

Methods: Electronic bibliographic databases were searched from inception to June 2020 (Medline, EMBASE, Psych INFO, and CINAHL). These databases were searched using Medical Subject Headings (MeSH) or Emtree terms and free-text terms. The Web of Science citation index, Google scholar and ResearchGate were also searched using relevant key terms to identify any additional eligible studies for

inclusion in the review. Two reviewers independently selected eligible studies, extracted data, and assessed the methodological quality of included studies using the Newcastle-Ottawa Scale (NOS). Due to high degree of heterogeneity between studies, random effects model (REM) was used to pool the results. Sensitivity analysis was also performed for assessing the causes of heterogeneity.

Results: A total of seven cohort studies were included in this meta-analysis. The overall methodological quality of included studies was found to be good. The pooled prevalence of early opioid prescribing for acute LBP was 20% (95% CI: 10.8-32.1%), Q=12071.2, *p-value* <0.001, and Higgin's I^2=100%. Only three studies examined the relationship between early opioid prescribing for LBP and LOD. The three study reported an association between early opioid prescribing for acute LBP and LOD, with an evidence of a dose-response relationship.

Conclusion: The findings of this systematic review show that one in five patients with acute LBP are prescribed opioid early in the medical care. These findings suggest that incompliance with clinical guidelines recommendations, which discourage early opioid prescribing for acute LBP early in the care, is common and is associated with increased work disability duration. Future research on early opioid prescription for LBP and the relationship with prolonging disability should account for all-important factors associated with LOD in this population to better estimate the effect of early opioid prescription on length of disability. Further research aiming at uncovering the reasons for incompliance with current guidelines is needed. In addition, Developing and testing healthcare quality improvement interventions to enhance compliance with

clinical guidelines about early opioid prescribing for LBP may help in preventing prolonged disability and its associated negative impacts in patients with acute LBP.

LIST of ABBREVIATION

Key words: Low back pain, Opioid, Length of disability

LBP: Low Back Pain

NSLBP: Non-Specific Low Back Pain

DALY: Disability Adjusted Life Year

LOD: Length of Disability

eMRI: Early Magnetic Resonance Imaging

NICE: The National Institute for Health and Care Excellence

NHS: National Health Institute

WHO: World Health Organization

LRP: Lumbar Radicular Pain

BMI: Body Mass Index

OR: Odds Ratio

HR*:* Hazard Ratio

RTW: Return to work

WMSD: Work-related Musculoskeletal Disorders

WC: Workers' Compensation

MEA: Morphine Equivalent Amount

RMDQ: Roland Disability Questionnaire

PRISMA: Preferred reporting items for systematic review and meta-analysis.

MeSH: Medical subject headings

Emtree: Embase subject headings

NOS: Newcastle-Ottawa Scale

FEM: Fixed effect model

REM: Random effect model

$\mathbf{I^2}$: I squared

ICD-9: International Classification of Disease, Ninth revision

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TABLE OF CONTENTS

List of Tables

List of Figures

CHAPTER 1: INTRODUCTION

1.1 Background

Low back pain (LBP) is a major public health issue, which affects most people at some point in their lives. LBP is a non-fatal condition (1). However, LBP poses a huge burden on society in terms of economic burden because of workdays lost due to disabilities, loss of productivity, permanents disability, and increased risk of mental health conditions (2). LBP is defined as "The area on the posterior aspect of the body from the lower margin of the twelfth ribs to the lower gluteal folds" (3). LBP is characterized based on the length of time the person has had the pain; for example, acute LBP is typically persisting for less than 4 weeks, subacute LBP typically lasts for 4 to 12 weeks, and chronic LBP persists greater than 12 weeks (4). The vast variety of LBP cases are of a non-specific cause, however, a cause is identified in around 10% of cases (5). Non-specific low back pain (NSLBP) is defined as "LBP not linked to any specific known pathology" (5). NSLBP can be acute or can be regarded as chronic in nature. Previous research suggests that out of all people who experience LBP, 30% to 40% will continue experiencing symptoms beyond 3 months, then it will be described as chronic, however around 85% of those with chronic LBP will have no diagnosis or underlying pathologies which then will be categorized as chronic nonspecific LBP (6). The lifetime prevalence of LBP is 84% (7). NSLBP accounts for one-third of all occupational musculoskeletal injuries and illnesses causing work disability (8). Moreover, LBP is the second leading cause of sick leaves, and work absence all over the world (1). In 2010, there was a total of 21.8 million disability-adjusted life years (DALYs) attributed to LBP due to ergonomic exposure at work globally (95% confidence intervals (CI) 14.5–30.5 million) (3). Length of work disability (LOD) due

to NSLBP and associated mental health comorbidities account for 93% of total costs of NSLBP (5) where LOD is calculated as ‘the total number of lost workdays from the beginning to the of wage replacement payment’ (9).

LOD due to occupational LBP or NSLBP is related to several factors including individual factors (such as age and gender), work-related factors such as tenure, industry, type, and physical loads required for the occupation (9). Moreover, healthcare-related factors that is not abided by the clinical guidelines such as early magnetic resonance imaging (eMRI) scanning and early prescription of opioid which is defined as" morphine equivalent amount (MEA)” of opioid medications received within 15 days post-onset, and were found to be significant predictors of increased LOD (9). Morphine milligram equivalents (MME) or morphine equivalent doses (MED) is a tool that was established to connect different opioids into one standard value. This standard value is based on morphine and its strength (10)

In the United States, opioid use is considered a major public health issue because drug overdose is a leading cause of accidental death in the US and it caused approximately around 65,000 deaths in 2016 (11). Opioid prescription is an epidemic in the US, where the mortality rate from drug overdose increased tremendously as well as the rate of opioid prescribing (12). Despite representing only 5% of the global population, it was found that Americans make use of 80% of the world’s oxycodone and 90% of the world’s hydrocodone (11). These trends increased with time, wherein 2012, around 259 million opioid prescriptions were written. Consequently, nearly 115 American dies every day from an opioid overdose (13).

Opioids is usually used in treating conditions with severe pain (14). Though opioid prescription for LBP is now common. For example, around 35% and 66% of patients with acute LBP and chronic LBP reported obtaining early opioid

prescriptions(15). However, there are many motives to evade using opioids while dealing with LBP. First, since 1990 there was a growth in the prescription of opioids that was found parallel to a raise in poor conditions such as back pain, and individuals seeking admission for opioid use disorders (commonly called addiction) (11). Second, as any patient who has been prescribed opioids, there are numerous risks of harm including, the progress of opioid use disorders which could lead to misuse (11). Moreover, about 80% of people who used heroin were first exposed to the prescription of opioids (11). Thus, preventing people from exposure to opioid especially in conditions such as NSLBP is important. Opioid has many adverse effects that contain tolerance which means the medication is not as effective as when it was initially started (16). Other side-effects of opioid use include; physical dependence over time, increased sensitivity to pain in some cases, constipation, depression, and many more (16).

Consequently, the rationale for shifting away from opioids due to most acute nonspecific LBP resolve over time without exposure to treatment, and the natural recovery rate is more than 50% -75% at 4 weeks and more than 90% recovery at 6 weeks(17). Thus, if we can shed the light on the opioid issue to shift to nonpharmacological treatments as the first-line medication for NSLBP then, we can potentially avoid some of the damage that has been caused by prescribing opioids.

Accordingly, due to increased risk of dependence, prolonged disability, and sudden death, early opioid prescribing for acute LBP or NSLBP is not recommended by current clinical guidelines. For example, the National Institute for Health and Care Excellence (NICE) guidelines for managing acute LBP recommends that opioid use should be avoided as the first-line medication when treating acute LBP, and can be used in weak doses, only if non-steroidal anti-inflammatory drugs (NSAIDs) is contraindicated (14). In addition, the American College of Physicians Clinical Practice

Guideline does not recommend early opioid prescribing for acute LBP within the first 15 days from seeking medical care (18). Furthermore, the American Society of Regional Anesthesia and Pain Medicine (ASRA), have agreed with previous guidelines that physicians should consider alternative therapy, like non-drug treatments such as physical and behavioral therapies before starting pharmacological intervention (19). Moreover, the use of opioid pain medications should be carefully restricted and limited to the short duration for the treatment of LBP, and NSAIDs are more recommended as the first-line medication for the treatment of LBP (19).

However, there is still inconsistency in compliance with these clinical guidelines. For example, one study assessed the association between early opioid prescription and LBP outcomes among 8443 participants found that 21% of the study populations have received at least one and up to nine opioid prescriptions within 15 days from seeking medical care (20). In that study, those who received more than 450 mg of opioids were disabled for 69 days longer than those who did not receive opioids early in the care (95% CI: 49.2-88.9) (20).

To our knowledge, no systematic reviews have summarized the literature on the prevalence of early opioid prescribing (within the first 15 days of seeking healthcare) for LBP and the relationship between early opioid prescribing for LBP and LOD. This information is useful for identifying and highlighting the incompliance with current clinical guidelines for the management of LBP and related impact on LOD. In addition, such information provides a rationale for future interventions to improve compliance with clinical guidelines on opioid prescribing for non-specific LBP.

1.2 Aim

The aim of this thesis is to systematically review and summarize the findings of epidemiologic studies assessing the prevalence of early opioid prescribing for LBP and the relationship between early opioid prescribing for LBP and LOD.

1.3 Specific Objectives

- To systematically review and summarize the findings of epidemiologic studies assessing the prevalence of early opioid prescribing for LBP.
- To systematically review and summarize the findings of epidemiologic studies examining the relationship between early opioid prescribing for LBP and LOD.

CHAPTER 2: LITERATURE REVIEW

This chapter presents an overview of LBP as a major public health problem and factors associated with LBP.

2.1.1 Low back pain as a public health problem

LBP is an important public health issue because it is an extremely common problem around the world, therefore, imposing a huge burden on societies. Globally, the point prevalence of the adult population experiencing LBP is 12% to 33%, whereas the 1-year prevalence is 22% to 65% (21). The majority of these occurrences are attributed to NSLBP with a lifetime prevalence varying from 11% to 84%, whereas 23% of cases tend to get chronic in nature (22). A systematic review found that the prevalence of LBP varies according to the definition, wherein one study reported the prevalence of LBP to be 8% when LBP was defined as “pain requiring sick leave”. On the other hand, it reached up to 45% when the definition was "pain that lasts at least a day “ (7). Around 90% of LBP cases are attributed to non-specific cause, however, the cause is identified in around 10% of cases (5). Additionally, the lifetime prevalence of LBP is 84%, which is regarded as relatively high (5).

In the middle east region, the problem of LBP is considered prevalent where the proportion of people reporting LBP in united Arab emirates(UAE) are around 64% and a similar proportion was noticed in Saudi Arabia with 51% (23). Moreover, according to Banner et al (24), it was reported in one of his studies on the prevalence of LBP among adult patients visiting primary health care centers through the state of Qatar, and similiter results to the neighboring countries were found. The prevalence of LBP in the included study population was 56% (95% CI, 54.2–58.8) and these findings were considered higher than the prevalence of other developed countries such as Canada(28%), the United Kingdom (36%), and Sweden (39.2%) (24). As a result, these

findings work in alignment with other findings to show that LBP is still considered to be an important clinical, social, and economic burden to the entire world and a major public health issue.

2.1.2 LBP and Quality of life (QOL)

LBP is a very common condition associated with more global disability than any other conditions, and the associated disability is shown to be increasing over time from 1990 to 2017 an increase from 42.5M DALYs to 64.9M DALYs respectively (25). Out of the 359 conditions that have been studied in the global burden of disease (GBD), LBP was the highest in term of years lived with disability (YLDs) in 13 out of 21 regions, and the 6th in term of the overall burden of disability (DALYs) (25). Patients with LBP does not just deal with physical discomfort and pain but also functional limitations that interferes with their QOL. One study aimed to predict health-related quality of life (HRQOL) in Taiwanese people suffering from LBP by using a set of questionnaire including the Taiwan version of the brief questionnaire of the world health organization on QOL (WHO QOL-BREF) moreover, they used Morris Disability Questionnaire the modified version, results showed there was a significant correlation between HRQOL and pain severity, disability days, and disability scale (26). A similar study was conducted in Japan to estimate the HRQOL in people suffering from LBP. Out of 5060 of study sample, around 13.5 % of patients reported LBP as their primary pain. Disability with absence from social activity and > 7 pain sites were clearly correlated with low HRQOL (27).

2.1.3 Economic burden

The economic burden of LBP in the Australian population using the "cost of illness study" reported the cost from various aspects concerning low back pain (28). In the financial year 1999 to 2000, the direct cost such as the cost of hospital care was

estimated in public hospitals to be around $89,386,095 and in private hospitals, it was $75,388,045(28). In terms of provider care costs such as, chiropractor cost, physiotherapy, general practice, massage therapy, psychology, occupational therapy, social worker, the total cost of individual provider care was reported to be US$ 835,458,813 (28). Other services cost coming from imaging diagnostic procedures such as plain radiographs, computed tomography, magnetic resonance imaging (MRI) are very costly with the total cost reaching up to US$ 66,545,865 (28). On the other hand, the indirect cost of LBP which is expressed by the time loss due to LBP was found to be around 62,441,052 days for all the population in 2001. The direct cost unquestionably poses a major economic effect, however, the indirect cost (time loss due to LBP) affects the most and is described as the main economic burden caused by Australian adults suffering from LBP (28). Based on the national health survey of 2017 (NHS 2017), another study evaluated the economic burden of LBP among a representative population sample in Spain from a direct and indirect perspective (29). It was found that most of the economic burden is coming from the indirect cost related to absenteeism and presenteeism; where the total cost attributed to LBP was 8945.6 million euros, and around 74.5% was categorized as indirect cost (29). Additionally, a study was done in the United Kingdom (UK) to assess the economic burden of LBP using the "cost-of-illness" study (29). The approximation of direct health care cost of back pain was £1632 million whereas 35% of the cost was associated with services from the private sector. Moreover, the distribution of cost based on the provider was found out to be around 37% which is accredited to the physiotherapist and allied health specialists. In contrast, the indirect cost was found to be causing much more problems and economic loss compared to the direct cost reaching up to £10668 million. This in turn, indicates LBP being a costly condition that needs to be investigated further to find

a cost-effective alternative treatment option to lessen the burden on the economy (30).

2.2 Risk factors of LBP

Acute non-specific LBP is associated with multiple risk factors that increase the likelihood of suffering from LBP. This is in line with the National Institute of Health (NIH) reporting risk factors of LBP such as aging, poor physical fitness, work-type, and BMI, as experiencing a weak core muscle can be a problem if the body mass index is high, therefore, putting a lot of burden on the lower back and make it more susceptible for injuries (31). Furthermore, some people with genetic conditions such as lupus, arthritis, disc degeneration, or a family history of LBP may be at higher risk of experiencing some form of LBP (31). Moreover, smoking can cause damage to the vascular structure of the discs and joints as well, as it restricts blood flow to spinal discs and vertebral bones, which as a result decreases bone healing (31). Finally, work-related MSD (injuries caused by strenuous or repetitive manual tasks) are among the most frequently reported cause of lost or restricted work time around the world(32). As the population labor force grows older in age, the incidence of work-related MSDs are also likely to increase(32).

2.2.1 Age and gender

A study was conducted in 2001 that was intended to study the different risk factors that might impact LBP (33). In terms of age, people were divided into two age groups (n=450) above 40 years and (n=448) 40 years or less being the reference. It was found that people with older age have a significantly higher prevalence rate of LBP compared to the reference group LBP-25.8% as compared to 17.0% (OR1.70; 95% CI 1.21–2.38) (33). Furthermore, the study also proposed to understand the gender difference when it comes to LBP therefore, dividing 297 women and 601 men. Interestingly, it was found that there was a strong relationship between back disorders

and gender. In other words, women have a higher prevalence rate of LBP compared to men, however, the results were not statistically significant (OR1.08; 95% CI 0.93-3.03) (33). Additionally, available data on the global prevalence of LBP have shown that females of all ages have a higher risk of suffering from LBP compared to males. Using pairwise correlation for continuous variables and t-test for binary variables, the overall mean prevalence (T) of females compared to males was 4.1 (*p-value* <0.001). Both point prevalence, 1-month, and 1 year prevalence were higher in females compared to males, however, the 1 year and lifetime prevalence were not significantly different between both genders (34). Moreover, based on the world health organization (WHO), people of all ages are affected by LBP at some point in their lives (35). Nonetheless, children and teenagers have a lower rate of LBP compared to adults but it is increasing compared to previous years, and the prevalence usually seems to peak at the age of 35 to 55 years (35).

Another study was conducted in Germany to investigate gender-specific risk factors for acute LBP, and the findings indicated that women complain significantly more often about acute LBP compared to men with 28.5% and 18% , respectively (*p-value* <0.001) (36).

2.2.2 Genetics

In terms of genetics, it is suggested that LBP and disc degeneration have a genetic element (37). Therefore, the study estimated the heritability of LBP in men and whether the genes that influence LBP are mediated by the genetic influence on disc degeneration. Consequently, they included 600 twin subjects of which 147 monozygotic twins and 153 dizygotic twins. All subjects were tested by lumbar magnetic resonance imaging, moreover, they underwent detailed interviews that include back pain history and associated risk factors. The results of the study showed a

significant positive correlation between disc height narrowing and the various definitions of LBP. LBP in the study (37) was, however defined as "duration of the worst back pain episode" ($r_g = 0.46$), another definition is “hospitalization due to back pain problems” ($r_g = 0.49$), and finally “disability in the past years due to LBP” ($r_g = 0.33$). There was a range of 30% to 46% heritability estimates for these back-pain variables, concluding that the disc degeneration is a link mediating the genes influencing LBP (37). Another prospective study investigated the potential association of persistent back pain with genetic variability, among 296 patients with LBP or lumbar radicular pain (LRP) (38). It was evident from its findings that at 5 years follow up, the rare allele of MMP9 rs17576 was associated with poor pain recovery. On the other hand, the rare allele of OPRM1 rs1799971 was found to be associated with a better pain recovery (38).

2.2.3 Body mass index (BMI)

With regard to BMI, a meta-analysis was conducted to understand the association between overweight and LBP risk (39). Subgroup analysis was performed on all 10 studies as part of the meta-analysis, to identify any correlation between LBP and BMI. The results showed that the higher the BMI, the higher the risk of LBP in both men and women. For men who were overweight: the pooled estimate was OR=1.16 (95% CI: 1.04–1.31); the pooled estimate for obesity was OR=1.36 (95% CI: 1.15–1.61). In women, the pooled estimate for overweight was OR=1.24 (95% CI: 1.04–1.50), and for obesity, the pooled estimate was OR=1.40 (95% CI: 1.08–1.82). Both of the estimates (overweight and obesity) were found to be higher among women as compared to men (39).

In addition, a cross-sectional study conducted on a sample of 29,424 twin subjects studied the association between BMI and LBP. The findings indicated

a positive relationship between BMI and NSLBP (40). This association was also described as modest and it increased with the duration of LBP. In subjects who were classified as underweight, around 37% of individuals reported LBP in the preceding year. Furthermore, subjects who were classified as normal, overweight, and heavy overweight reported 50%, 56%, and 52% of LBP, respectively. A positive dose-response relationship was established where the corresponding ORs in relation to normal weight was as follows: underweight (OR 0.6, 99% CI: 0.5-0.6), overweight (OR1.3, 99% CI:1.2-1.4) and finally, heavyweight subjects (OR 1.1, 99% CI: 0.9-1.3) (40).

2.2.4 Smoking

A prospective cohort study was conducted among high school students living in Montreal Canada, which was performed to assess whether smoking is a risk factor for LBP and musculoskeletal pain (41). Thus, 502 students in grades 7-9 from 3 schools were chosen. The study consisted of three stages where data was collected at the baseline, at 6 months, and at 12 months. Data was collected through a questionnaire that included questions regarding LBP and lifestyle factors which contained smoking. The findings showed smokers had a higher odd of experiencing LBP compared to non-smokers (OR 2.4, 95% CI: 1.3–6.0). Furthermore, the study has shown a dose-response relationship between the number of cigarettes smoked and the risk of LBP (42).

A population-based study of 29,424 twin individuals aged 12 to 41 years, was performed to examine whether smoking is associated with LBP (43). Dose-response was tested for smoking (frequency of smoking per day, duration of smoking- number of years, total cigarette uses during the years of smoking) in relation with LBP that lasted from one to 7 days, 8 to 30 days, or more than 30 days in the previous year. The effect modification factors were also studied in terms of age, gender, and BMI. The findings indicated a positive association between smoking and duration of LBP as it

was found that 57% of habitual smoker had suffered from LBP in the previous year and it was 40% among people who never smoked (OR 2.95%, CI:1.9-2.1). In addition, the association was also found to get stronger with the length of duration. Consequently, LBP occurring from one to 7 days had an OR of 1.4 (95% CI %: 1.3-1.6) and the OR increased with 8-30 days (OR 2.1, 95% CI: 2.0-2.2). Moreover, in patients among whom LBP lasted for more than 30 days, the OR increased up to 3 (95% CI; 2.8-3.3). It was concluded that there is an established link between smoking and LBP that gets stronger with the frequency and duration of LBP (43).

2.2.5 Work related physical and psychosocial factors

The two main types of work-related risk factors for LBP are physical and psychosocial (44-46). In the past, many researchers have conducted a job strain framework, which is a framework that proposes an interaction between job demands and job control (47). Specifically, the job demands can be expressed in terms of psychosocial demands that may include; stress, time, work pace, competition(48, 49). On the other hand, job control means job autonomy and freedom. Thus, job strain and job demands were shown to be associated with LBP as well (50, 51). Lately, more focus was given towards identifying psychosocial risk factors within the organization which can include; tough work environment, work-family conflict, long working hours, job insecurity, and overtime work (47). Two studies conducted in the USA have exhibited a relationship between LBP and several psychosocial variables such as job satisfaction, mandatory overtime work, supervisor support, and job freedom (45, 46). Similarly, another two occupational based studies conducted in the USA have shown evidence on worsening musculoskeletal pain with tough work environment and conflict between work-family or colleagues (52, 53). One more cross-sectional study conducted in Qatar to investigate the relationship between sedentary behavior and back pain among

employee at Qatar University (QU), found the most frequently reported pain among QU employee is LBP, which is positively associated with sedentary behavior (sitting too much) with an OR of 1.29 (95% CI: 0.87-1.91). Furthermore, LBP due to sedentary behavior has shown a significant association with increased depressed mood among the employee with an OR of 1.41 (95% CI: 0.77-2.63; *p-value* = 0.056). (54)

2.3 Length of Disability

NSLBP accounts for one-third of all occupational musculoskeletal injuries and illnesses causing work disability (55). Moreover, LBP is the second leading cause of sick leaves, and work absence all over the world (3). In 2010, there were 21.8 million DALYs that were attributed to LBP due to ergonomic exposure at work globally (95% CI; 14.5–30.5 million) (3). LOD due to NSLBP and associated mental health comorbidities account for 93% of the total costs of NSLBP (5).

LOD due to occupational LBP is related to several factors including individual factors such as age and gender, work-related factors such as tenure, industry, type, and physical loads required for the occupation (9). Moreover, health-related factors that are not abided by the clinical guidelines such as early magnetic resonance imaging (eMRI) scanning and early prescription of opioids (within the first 15 days of seeking medical care) were found to be significant predictors of increased LOD (9). A systematic review with 22 studies evaluated the association between patients reporting episodes of LBP and a sick leave that lasted for more than six weeks found that the impact of pain, functional status, and radiating pain was modified with the duration of work disability (56). Recovery expectations of workers also held importance after 6 weeks. In a similar fashion, workplace physical factors and age seemed to be important in later phases (56).

2.4 Risk Factors of LOD

2.4.1 Individual factors

2.4.1.1Age and Gender

One study intended to evaluate prognostic factors associated with length of disability after 1-year follow-up among workers who were on sick leave for 2 to 6 weeks due to musculoskeletal disorders (57). A self-administered questionnaire was used to gather information regarding factors associated with work, pain, disability, and general health questions. Cox proportional hazard regression was used for analyzing the factors of interest, and the key factors associated with sick leave and absenteeism included older age and gender. Individuals aged more than 45 years had a higher risk of absence due to LBP (HR 1.17, 95% CI: 0.74-1.86). Moreover, the female gender had obtained similar results compared to males, with modest and nonsignificant association with longer sickness absence (HR1.09, 95% CI; 0.72-1.64) (57). Another population-based cohort study aimed to detect factors related to the length of disability in new worker compensation claims (58). Hence, people who suffered from work injury during work that caused some form of work disability were included. The disability in the study was defined as "any disability that lasted 4 or more days". A total of 81,077 workers were followed for six years. The strongest predictor for cumulatively lost workdays resulting from the multivariate logistic regression model was older age over 45 years as compared to workers with 30 years (OR 2.1, 95% CI: 1.97–2.20) (58).

2.4.2 Workplace related factors

A retrospective cohort study of 433 LBP workers compensation claimants have been followed for four years, to understand the relationship between the psychosocial job factors on length of disability (59). Heavy physical work accounted for 22% reduction in RTW, high job demands accounted for 26% reduction in the RTW, as well

as low job control and high job strain both independently have reduced RTW by one third. All these factors were significantly associated with reduced RTW rates, and the results were persistent even after adjusting for potential confounders such as age, gender, the severity of injury (59). Similarly, another study by Oranye *et al.* in the year 2016, compared the risks of work-related musculoskeletal disorders (WMSD) among health care workers, including the type of physical tasks and the amount of time spent on doing such tasks (60). The findings of the study indicated that workers who worked longer on a physical task were more prone to WMSD as compared to those who spent less time doing the same physical task. Further, the risk of WMSD was found to be twice as high among workers who sit less than 2 hours a day (OR 2.3, 95% CI; 0.9-5.9), compared to those who sit longer than 2 hours a day (60).

2.4.3 Healthcare related factors

2.4.3.1 Magnetic Resonance Imaging (MRI)

Currently, one in four patients presents to primary care with LBP and receives imaging such as x- rays or MRI (61), which is considered to be a high number keeping in mind that around 1% of LBP has a serious underlying pathology (61). Most clinical guidelines advise against imaging in routine care for LBP (14). This high number can be attributed to the fact that most patients consider imaging necessary according to a survey of Jenkins *et al* in the year 2015 that was aimed to understand patient beliefs regarding MRI (62).

Another prospective study indicated that early use of imaging in LBP might be associated with higher medical costs, increased health utilization, persistent pain, and more absence from work (63). MRI is important when used to confirm the diagnosis in the presence of red flags, however, MRI seems to be overused. Consequently, this can cause harm in three possible ways as Darlow and colleagues mentioned, i.e.,

misinterpretation of clinical findings by clinicians, misinterpretation of the findings by the patient, and finally exposure to unnecessary radiation (64).

A study by Herzog et al in the year 2017 had 10 different radiologists take and interpret the MRI of 63 old women. The results showed that 49 different pathological findings were described among all the MRI reports (65). Sixteen pathological findings were found to be unique but none of these were reported consistently in the 10 reports. Only one finding namely anterior spondylolisthesis was reported in 9 out of 10 reports which showed a poor agreement of findings and a higher risk of interpretation error (65).

A retrospective cohort study was performed to test the effect of early exposure to eMRI (eMRI ≤30-day post-onset) on length of disability among 555 patients with acute LBP (66). It was found that around 79.8% of the sample had received eMRI. The study showed that those who received eMRI had a significantly longer length of disability compared to those who were not exposed to eMRI (66).

An additional population-based prospective cohort study was also done to assess the presence of any association between early MRI and disability status after 1 year from injury with acute LBP (67). A total of 1226 participants were included in the study where 18% of them had received early MRI. Workers with mild/major sprain had a 2-fold increase in the likelihood of work disability benefits at 1 year (adjusted relative risk: 2.03; 95% CI: 1.33–3.11). The conclusion of the study indicates that early MRI is associated with worse outcomes after 1-year period and a higher likelihood of disability duration (67).

2.4.3.2 Opioids

Opioid medications such as Morphine, oxycodone, heroin, and fentanyl are strong classes of pain killers. Another type of opioid is weak opioid which includes

codeine dihydrocodeine and tramadol (68). The strong opioids can be a lot effective than weak opioids in cases of severe pain (69). These painkillers can be classified as opiates which are drugs derived from the opium poppy, (morphine, codeine) semisynthetic opioid that is made of chemically modified opiate (heroin, oxycodone) and fully synthetic opioids (fentanyl, methadone); all these drugs work in the same way with slight variation between them (68, 69). These drugs mimic the effect of a small painkilling peptide that the body naturally produces called endogenous opioids (68, 69). These drugs bind to opioid receptors that scatter around the nervous system, four receptors exist with similar structures and a little different effect. One of these receptors is the MU opioid receptors, which are the key receptors that cause pain relief by producing physiological effects (68). The speed and intensity of the drug effect rely on how the drug was administered (70), if taken orally, the effects are usually steady and felt in about 10 to 20 minutes, If injected into a vein, the effects are more strong and felt within one minute (70).

When opioids is taken to relieve the pain, the length of its effect differs depending on the type of opioid taken, and history of opioid use (70). Usually, a single dose can provide pain relief for 4 to 5 hours while a single dose for chronic pain relief is about 200 Mg/day (70). The adverse effect of opioids occurs with increasing dosing or dosage above 300Mg/day (70). Opioids are usually used in treating conditions with severe pain, however in the late 1980 and 2000, a shift in opioid use was introduced and it was increased from 8% to 16% in the number of patients receiving opioids for chronic musculoskeletal pain, and from 8 to 11% in acute musculoskeletal pain (71). Opioid prescription for LBP is now common, where opioid is the most regularly prescribed drug class. For example, little more than half of the opioid users have reported LBP as the reason in the US (15). For people seeking primary care for

treatment, around 21-35% with acute occupational LBP obtain early opioids and around 66% of chronic LBP reported use of opioids early in the care (15). Early prescription of opioid is defined as" morphine equivalent amount (MEA)" of opioid medications received within 15 days post-onset (71). And this is considered against evidence-based clinical guidelines because of its association with adverse outcomes such as prolonged disability, dependence, addiction, and sudden death (15).

The Agency for Health Care Policy and research recommended clinical practice guidelines for the use of opioids in cases with acute LBP to be time-limited course, because of the adverse side effects that might occur (71). Moreover, current clinically accepted guidelines state that there should be no early prescription of opioids within 15 days from seeking medical care (72). Furthermore, the clinical practice guideline was evaluated in 15 clinical guidelines that focus on LBP management and containing the current clinical practice recommendations.

2.4.3.3 Diagnosis, management, and treatment of LBP

NSLBP diagnosis mainly based on the omission of underlying pathomorphological changes (73). This means that there is no serious pathology that can hinder the recovery of the patient (73). On the other hand, if LBP was linked to any specific pathology such as systemic disease, infection, structural deformity. then it will be diagnosed as specific LBP (73). The management and treatment options for nonspecific LBP that is recommended by the American College of Physicians (ACP) and many other guidelines are; for acute and subacute LBP minimal or no medical intervention is recommended, reassurance, advice to return to normal activity as soon as possible, and to avoid bed rest is the recommended (4, 14, 19, 74, 75). The nonpharmacological treatment options are superficial heat, messages, and spinal manipulation. The first line of medication should be nonsteroidal anti-inflammatory

drug (NSAIDs) such as ibuprofen (400 to 600 mg) four times per day and naproxen (250 to 500 mg twice daily) followed by Muscle relaxants. These muscle relaxants are defined as a group of drugs that cause physiological effects such as analgesia and muscle relaxation. Examples of these drugs include; benzodiazepines, cyclobenzaprine methocarbamol, baclofen, and tizanidine (4). If muscle relaxants were found to be not tolerated or contraindicated, a combination of NSAIDs and acetaminophen can be given as an option. Furthermore, opioid use should be restricted in acute and subacute low back pain to lessen chronic opioid use, surgery, and length of disability. If opioids were to be used, it should be used just for a short amount of time (4, 14, 19, 74, 75). In cases of chronic LBP, the treatment option may be different where the first-line medication is still NSAIDs. However, if the majority of patient with chronic pain have already used NSAIDs, a second line medication could be added such as duloxetine and tramadol. The latter is less favorable as it contains opiate, therefore, it carries a risk of misuse and dependence. Physicians should only consider the choice of opioids in patients who have unsuccessfully used the previously mentioned treatments and only if the potential benefits outweigh the harm (4, 14, 19, 75). Having said that, there is still inconsistency in compliance with the proper practice in prescribing opioids for LBP. In a study aiming to assess the association between early opioid prescription and LBP outcomes among 8443 participants, researchers found that 21% of the study populations have received at least 1 and up to 9 opioid prescriptions within 15 days from seeking medical care. In the same study, those who received more than 450 mg opioids were disabled for 69 days longer as compared to those who did not receive opioids early in the care (95% CI, 49.2-88.9) (76). Another study showed that around 50% of the sample received an opioid prescription at the first medical visit (58). Moreover, 14% of the sample got disability compensation at 1 year, which indicates that early prescription of opioid for

workers with LBP is a risk factor for long term disability (77). Additionally, a prospective cohort study of LBP patients in primary care reported that patients who were prescribed opioids at baseline had greater self-reported disability on Roland and Morris Disability Questionnaire RMDQ, higher anxiety and depression scores, worse self-efficacy, and greater anxiety with movement at six months follow-up as compared to patients with no opioid prescription (78).

As shown in the previous literature, there is an association between early opioid prescribing and LOD, however the current gap in the literature is that most of the data are coming from worker compensation databases and in most studies, they didn't account for potential confounders such as, mental health issues, pain severity, job accommodation. Moreover, this topic has not been systematically reviewed before. Synthesizing the evidence base on the relationship between early opioid prescribing for acute LBP has important implications for practitioners, policymakers, LBP patients, and raising awareness about the negative effect of early opioid prescribing on disability outcomes among acute LBP patients.

CHAPTER 3: METHODS

This chapter presents the methods used in conducting the current systematic review following the recommendation of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement checklist (79). The checklist consists of 27 items and several charts (79). The tool can be found in Appendix 1.

3.1 Eligibility criteria

3.1.1 Type of studies

This systematic review considered observational epidemiologic studies (cross-sectional, case-control, and cohort studies) published in peer-reviewed journals.

3.1.2 Type of participants

Patients with occupational or NSLBP and aged 18 years and older. Occupational LBP was operationally defined as "reported pain in the lumbar region as the primary reason for a medical visit and registered as such (occupational origin) in medical records" (80). NSLBP was operationally defined as "low back pain not linked to any specifically known pathology" (5).

3.1.3 Exclusion criteria

We excluded studies with chronic LBP or complicated LBP caused by specific pathologies such as vertebral spinal stenosis, ankylosing spondylitis, scoliosis, and coccydynia, cancer, infection, post-partum LBP, or pelvic pain due to pregnancy. This is because such patients' management and disability duration differ from those patients with acute occupational or NSLBP (75, 81).

3.1.4 Types of exposure

The exposure was early opioid prescribing defined as any opioid prescribing within the first 15 days of seeking healthcare for acute occupational or NSLBP.

3.1.5 Type of outcomes measures

The outcome measures were:

(1) The prevalence of early opioid prescribing for acute occupational or NSLBP.

(2) The LOD was defined as the number of days away from work or sick leave associated with early opioid prescribing for occupational or NSLBP (9, 82).

3.1.6 Search strategy

To identify relevant studies, the following electronic bibliographic databases were searched from inception to June 2020: (Medline, EMBASE, PsychINFO, and CINAHL). These databases were searched using Medical Subject Headings (MeSH) or Emtree terms and free-text terms covering the following concepts in "any field" (title, abstract, and full-text): opioid (exp analgesics, opioid/, opioid, opiate, opium, "opioid prescribing", "opioid prescription", "opioid use"), LBP (exp low back pain/, sciatica/, sciatica, "Low back pain", "Lower back pain", "Low back injury", "Low back injuries", Lumbago , "lumbosacral pain"), and work disability (Exp return to Work/, Workers' Compensation/, Insurance, Disability/, Sick leave/, Absenteeism/, "return to Work", "work disability", "length of disability" , "work incapacity", "back to work", "work resumption", absenteeism, "duration of disability", "sick leave", "sick days"). To avoid excluding any relevant studies reporting on the prevalence of early opioid prescribing for LBP without examining the relationship between early opioid and LOD, the search concepts were combined using two ways: (a) records identified using the full search strategy as shown above, (b) the full search strategy excluding records identified using the concept of (work disability). All records identified in the two ways were then combined and duplicates were removed. Appendix 2 presents the full search strategy and Appendix 3 represents the number of records identified from each database. The references list of all relevant papers was searched to identify studies for potential

inclusion in the review. The Web of Science citation index was also used to trace citations of included studies to identify any additional relevant papers. Furthermore, Google scholar and ResearchGate were searched using relevant key terms such as opioid prescribing, low back pain, disability duration, prevalence to identify any additional eligible studies for inclusion in the review, however, the search was not conducted in a systematic way.

Table 1: PICO Criteria used in the Current Systematic Review

Concept	P (population)		I (Intervention or exposure)	C (comparison)		O (outcome)
Prevalence	Patients with occupational or NSLBP and aged 18 years and older		early opioid prescribing within the first 15 days of seeking healthcare			The prevalence of early opioid prescribing for acute occupational or NSLBP
LOD	Patients with occupational or NSLBP and aged 18 years and older		early opioid prescribing within the first 15 days of seeking healthcare	No early opioid prescribing		The LOD associated with early opioid prescribing for occupational or NSLBP
Search terms	low back pain* OR sciatica OR Lumbago	AND	Opioid* OR opioid prescription OR opioid prescribing OR opioid use		AND	return to Work* OR Workers' Compensation OR Sick leave OR absenteeism OR length of disability

3.1.7 Study selection

All retrieved records were exported to Rayyan Web Application (https://rayyan.qcri.org/) for initial screening of titles and abstracts (83). Two reviewers (HA) and (AS) screened titles and abstract independently to identify potentially relevant studies. Then, the full text articles were reviewed in depth, when a decision could not be made based on the title and abstract. Any disagreement was resolved by consensus discussions, and when necessary a third reviewer was involved (thesis supervisor).

3.1.8 Data extraction

Data extraction was performed independently by the two reviewers using a standardized form, that was developed and piloted with two papers to extract the following information from each included study: first author, publication year, country, study design, setting, sample size, socio-demographic characteristics of participants (age, sex), definition of LBP, prevalence of early opioid prescribing for LBP, and the measure and magnitude of association with confidence intervals (CI) between early opioid prescribing for LBP and LOD at the longest follow-up reported, corresponding author contact details, source of funding, and any declared conflict of interest (see Table 1).

3.1.9 Risk of bias assessment

The methodological quality of included cohort studies was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) (84). This tool is developed specially to assess the methodological quality of nonrandomized studies, such as case-control and cohort studies (85). Assessment of the quality of such studies is essential for a proper understanding of nonrandomized studies. The Newcastle-Ottawa Scale (NOS) is a continual partnership between the Universities of Newcastle, Australia and Ottawa, Canada (84). It is created to evaluate the quality of nonrandomised studies in

terms of the design, content, and ease of use. Its primary purpose is to assess the quality of included studies in the meta-analytic results (85). This NOS contains eight items with three subscales (selection, comparability, and outcome) (84). The *selection* domain includes representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. The *comparability* domain evaluates if the study controlled for possible confounders. The *outcome* domain contains three items assessing if follow up was long enough for outcome to occur and adequacy of follow up of cohorts (84). The quality of the studies was apprised, by adding a star in each domains of the scale (See Table 2).

The score for each item differs as follows, the studies are rated as good, fair, and poor. A "good" quality score requires at least 3 to 4 stars in the selection domain, 1 to 2 in the comparability, and 2 to 3 in the outcome. A "fair "quality score requires 2 stars in the selection, 1 to 2 stars in the comparability, and 2 to 3 stars in the outcome. A "poor" quality score requires score 0 or 1 starts in the selection, 0 stars in the comparability, and 0 or 1 star in the outcomes. The total score from the three subscales is 9. Studies with scores higher than or equal to 7 are considered good, quality score of less than 5 are considered low quality study, a score of 5-7 are considered fair or moderate quality. The scoring systems was adapted from previous published studies as no formal cut-off points is used yet (86-88) (Appendix 4). The quality assessment of the included studies was assessed by the two reviewers (HA and AS) independently. Any disagreements were resolved by discussion from the thesis supervisor.

3.1.10 Statistical analysis

For statistical analysis, MetaXL tool version 5.3 was used to pool the overall prevalence of opioid prescribing using the fixed effect (FE) and random effect (RE)

models (50). The I-squared (I^2) and the Cochran Q statistics were used to examine statistical heterogeneity of results across studies. I-squared (I^2) illustrates the percentage of heterogeneity not due to sampling error across studies (89). In addition, fixed effect model was used to pool the prevalence estimates of early opioid prescribing from included studies assuming all the effect sizes of included studies are similar and any difference between the effect sizes is purely due to chance (random error) (90). When a significant heterogeneity was present i.e. I^2 more than 75% and Cochran Q *p-value <0.001*, a random-effects model was performed assuming the included studies are assessing different prevalence estimates. The random effect (RE) model takes both sampling error (within-study error, and between studies error) into account and control for the potential heterogeneity by adjusting the pooled effect size (90). We investigated the cause of heterogeneity by preforming sensitivity analysis, which is defined as a repeated analysis of the primary meta-analysis in which alternative judgments or ranges of values are replaced for decisions that were arbitrary or ambiguous (91).

3.2 Ethical Considerations

This thesis will only review prior studies and therefore does not require an ethical approval.

3.3 Source of Funding

This project was funded by Qatar University (student grant QUST-2-CHS-2020- 19). The funder had no role in conducting this thesis.

3.4 Conflict of interest:

The author has no conflict of interest to declare

3.5 Registration

The protocol for the current systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number:

CRD42020177799; available from

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=177799).

CHAPTER 5: RESULTS

This chapter presents the results of the systematic review and meta-analysis. The first section describes the results of search strategy and the characteristics of the included studies. The second section presents the methodological quality of included studies. The final section summarizes the prevalence of early opioid prescription for LBP and the relationship between early opioid prescribing for LBP and associated LOD.

4.1 Study selection

The electronic search of bibliographic databases yielded 8802 records along with 10 records identified to be eligible for full text review from Google Scholar and references lists (figure 1). A total of 8748 articles were excluded after screening the titles and abstracts leaving 64 articles for full-text review. Seven studies met the inclusion criteria, and the remaining 57 articles were excluded. The main reasons of exclusion were as follows: 34 articles did not meet the definition of early opioid prescribing; 22 articles did not meet the inclusion criteria for LBP, and one more study was excluded because it was published in German language.

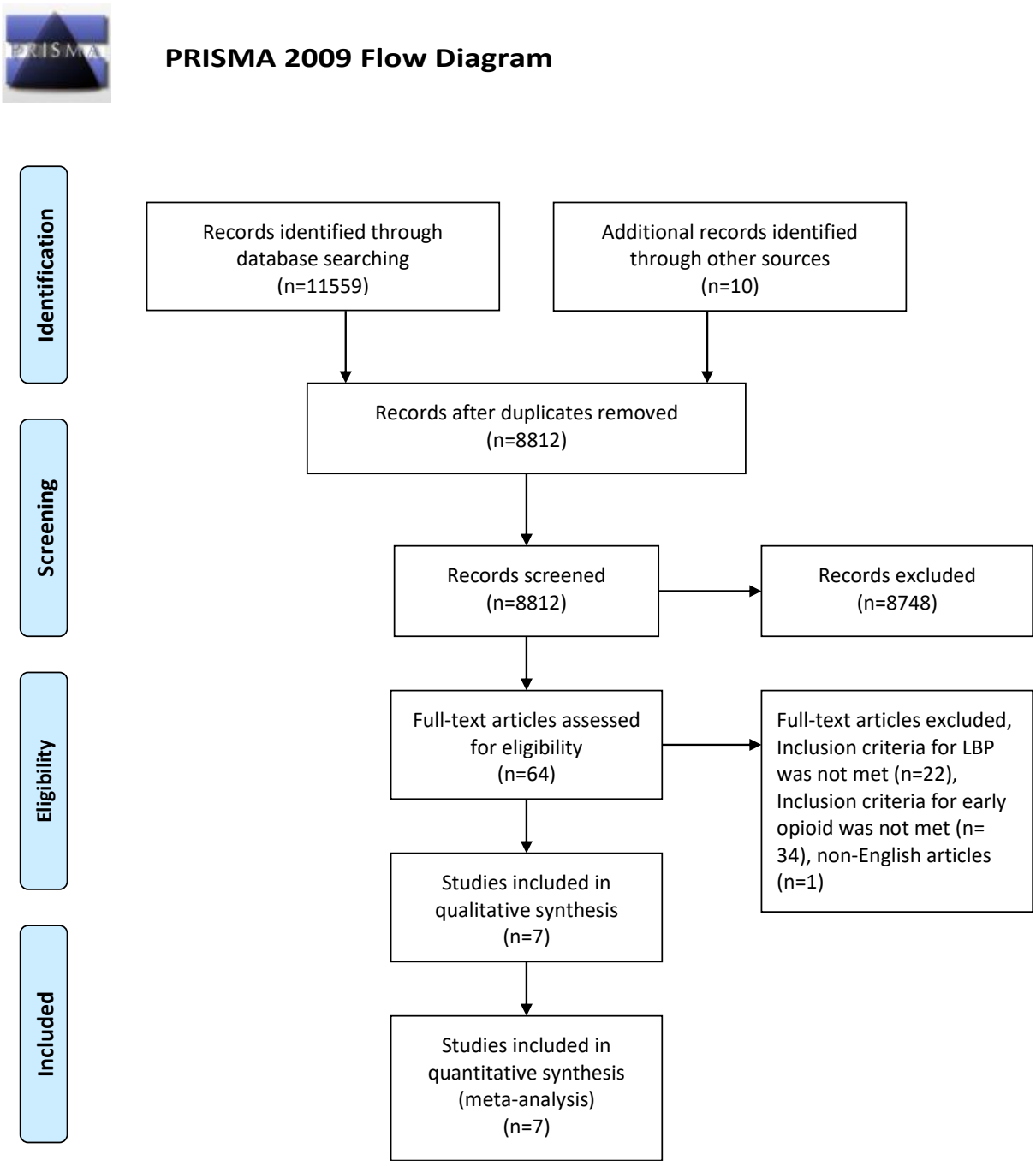

Figure 1: PRISMA flowchart of articles in the review

4.2 Study characteristics

A total of seven studies were included. All the studies were retrospective cohort studies. Six studies were conducted in the USA (9, 20, 63, 92-94) and one study was conducted in Canada (95). Five of the studies were based on nationally representative United States workers' compensation (WC) administrative databases. One study used Medical and pharmacy claim data of employees from a single payer (94). The remaining Canadian study used data from the Workers' Compensation Board of Alberta (95). Table 1 presents the characteristics of included studies. The sample sizes ranged from 2627 to 59360 participants. The age of participants in included studies ranged between 18 to 65 years, with overall proportion of males of % 69 (n= 91717).

Table 2: Characteristics of the Included Studies

Author year	Country	Sample size	Setting and source of data	Demographic characteristics	Follow-up period (years)
Fritz et al., 2018 (94)	USA	2627	Medical and pharmacy claim data of enrollee from a single payer	Mean age (yr.) = 38.1 Sex (%) = Female (67.8)	1
Gross et al., 2009 (95)	Canada	47,813	Workers' Compensation Board of Alberta (WCB-Alberta) administrative database	Mean age (yr.) =37.4 Sex (%) = Male (70)	1
Shraim et al., 2019 (9)	USA	59360	WC database that represents approximately 10% of the private U.S private WC market.	Mean age (SD) = 39.4 (10.8) Sex (%) = Male (69.1)	1
Webster et al., 2007 (20)	USA	8443	WC database that represents approximately 10% of the private U.S. private WC market.	Mean age (SD) =40.3 (10.4) Sex (%) = Female (28.2)	2
Webster et al., 2009 (93)	USA	8262	WC database that represents approximately 10% of the private U.S. private WC market.	Mean age (yr.) =40.3 Sex% = Male (71.8)	2
Webster et al., 2010 (96)	USA	3264	WC database that represents approximately 10% of the private U.S. private WC market.	Mean age (yr)= 41.4 Sex (%) = Male (69.7)	1
Webster et al., 2014(92)	USA	3022	WC database that represents approximately 10% of the private U.S. private WC market.	Mean age (yr.) =41.6 Sex (%) = Female (30)	1

4.3 Risk of bias

4.3.1 Newcastle-Ottawa scale (NOS)

All included studies are retrospective cohort, and the tool was used using the coding manual of cohort studies design which is specially formed to complement the design (Appendix 4). All included studies were of good methodological quality (9, 20, 63, 92-94).

4.3.1.A Selection domain

In all includes studies, representative samples of LBP cases were used. The exposed and unexposed cohorts were identified from the same WC administrative data. The exposure to opioid was ascertained using medical bills, and the outcome (LOD) was measured longitudinally from the first medical visit to end of follow-up period.

4.3.1.B Comparability domain

Comparability of Cohorts based on the Design or Analysis, where in all included studies the cohorts were comparable based on the study design or analyses. Adjustment for all important characteristics and potential confounders included in the studies were adjusted for, using multivariable analysis models.

4.3.1.C Outcome domain

In all included studies, the outcomes were assessed based on medical bills and record linkage of administrative data for wage replacement. Participants were followed up for at least one year, and all subjects were accounted for.

Table 3: Risk of Bias Assessment (Newcastle–Ottawa Quality Assessment Scale Criteria)

Study	Selection (max4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)	SCORE	Quality of the study
Fritz et al., 2018 (94)	****	**	***	9	Good
Gross et al., 2009 (95)	****	**	***	9	Good
Shraim et al., 2019 (9)	****	**	***	9	Good
Webster et al., 2007 (20)	****	**	***	9	Good
Webster et al., 2009 (93)	****	**	***	9	Good
Webster et al., 2010 (96)	****	**	***	9	Good
Webster et al., 2014 (92)	****	**	***	9	Good

4.4.1 Prevalence of early opioid prescribing

In all included studies, information about early opioid prescription prevalence was obtained from medical bills. The pooled prevalence of early opioid prescribing for LBP using the fixed-effects (FE) model was 17% (95% CI 17.2-18.8%). However, there was a high-level of heterogeneity (Cochran Q=12071.2, *p-value <0.001,* and I^2=100%) (see figure2). We conducted a sensitivity analysis to explore the potential reason for observed heterogeneity. The included studies were relatively similar in characteristics of participants and methodological quality. One potential cause was the geographical area of study as six of the included studies were from the USA (9, 20, 63, 92-94) and the remaining study was conducted in Canada (95) which reported a low prevalence of early opioid prescribing for LBP (6%) as compared to those from the USA (prevalence ranging from 21% to 28%). Therefore, we eliminated the Canadian study and re-analysed the data using the FE model. The overall pooled estimate was 26% (95% CI 25.7-26.3%) after eliminating the Canadian study, with statistically significant heterogeneity, (Cochran Q=329.73, *p-value <0.001* and I^2=98%) (See figure 3). We could not think of any reasons for potential clinical heterogeneity, thereby assuming that this could be explained by the small number of included studies. We further pooled the results using the RE model to incorporate the observed heterogeneity. The random-effects model (RE) showed a pooled prevalence of 20% (95% CI 10.8-32.1%); Q=12071.2, *p-value <0.001,* and I^2=100%) (Figure 4). We did not use the Funnel plot to assess for the potential of missing results due to the small number of included studies. According to the Cochran handbook, tests for funnel plot asymmetry should be conducted only when there are at least 10 studies in the meta-analysis, because in case of fewer studies, the power of the tests inevitably tends to get low (97).

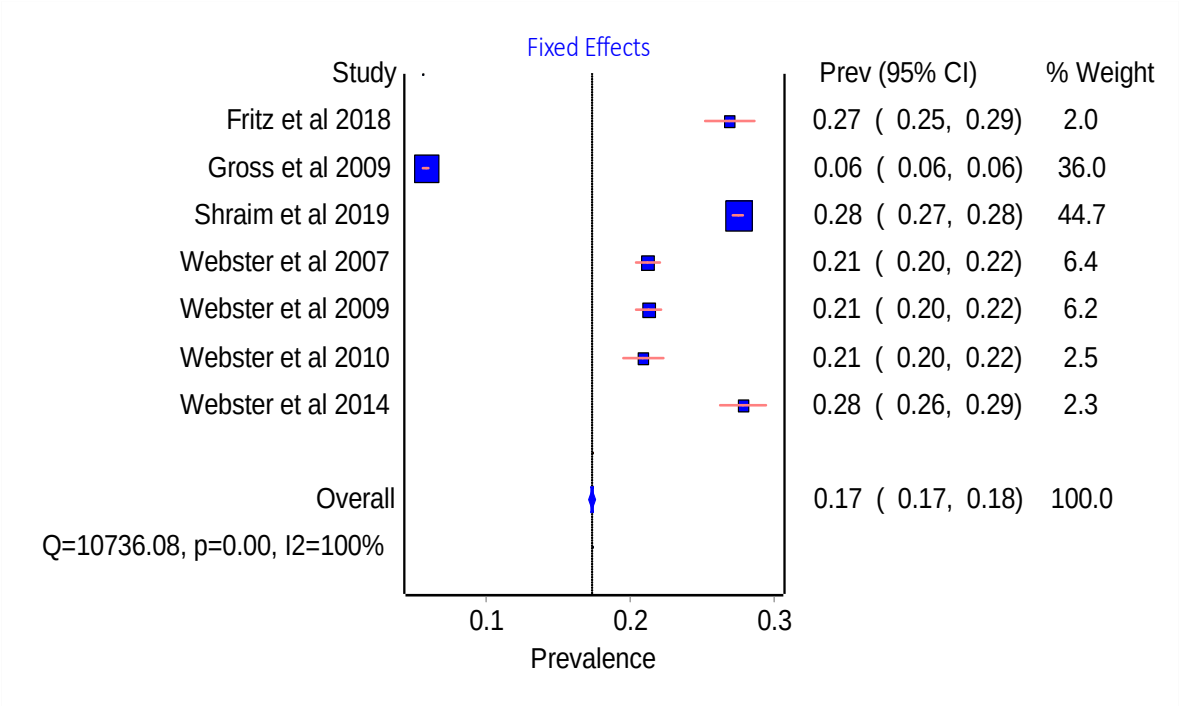

Figure 2: Prevalence of early opioid prescribing for low back pain (fixed effects).

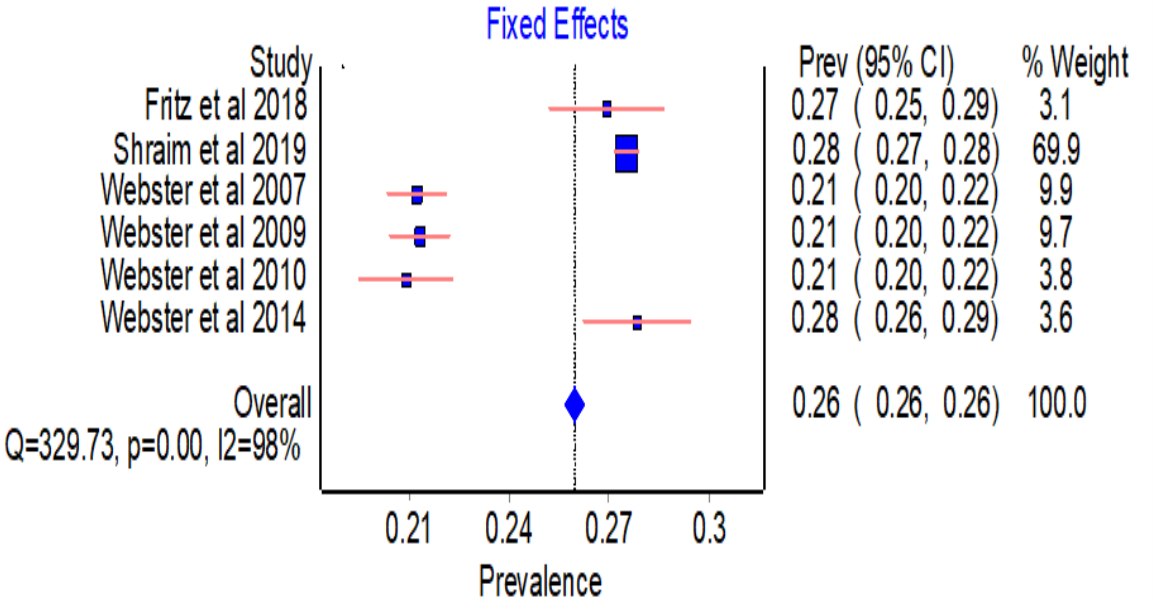

Figure 3: FE model to get the Prevalence of early opioid prescribing for low back pain (fixed effect) after excluding Gross et al., 2009 study (95) *for Sensitivity analysis.*

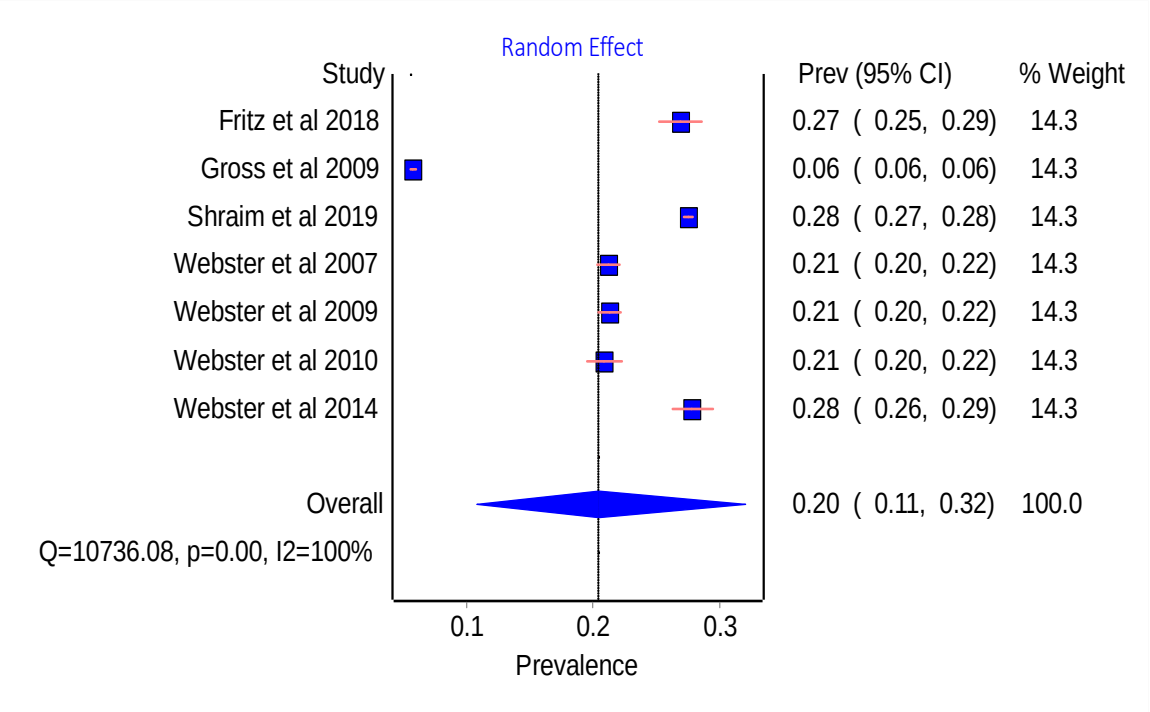

Figure 4: Pooled prevalence of early opioid prescribing for low back pain (Random-effects model).

4.4.2 The relationship between early opioid prescribing for LBP and LOD

Only three (9, 20, 95)of the included studies reported an association between early opioid prescribing for LBP and LOD. Due to differences in measures of association reported in these three studies, formal pooling of the overall association between early opioid prescribing and LOD was not feasible. One Canadian study (95) showed that subjects who were not prescribed early opioid had a higher likelihood of returning to work (hazard ratio 1.96, 95% CI;1.88–2.04) than subjects who received early opioid prescriptions (95). The second study (20)was conducted in the USA and showed that an increase in early opioid by 100 mg Morphine equivalent amount (MEA) was associated with an increase in the geometric mean of LOD by 0.4 day (95% CI; 0.3-0.5) (9). The third study (9)was also conducted in the USA reported that those who were prescribed 1-140 mg MEA had higher LOD by 5 days (95% CI; 14.6 to 25.0) as compared to those who were not prescribed early opioids for LBP (20). In addition, LBP cases who were prescribed early opioid of 141-225 mg, 226-450 mg, and more than 450 mg of MEA had increased LOD by 21 days (95% CI; 3.2-40.6), 43.8 days (95% CI; 23.7-63.9), and 69 days (95% CI; 49.3-89.0) than cases who were not prescribed early opioid for LBP, respectively (20).

Table 4: Prevalence of Early Opioid Prescription and the Associated LOD in LBP

Author, year	Cohort location	Sample size	LBP diagnostic criteria	Prevalence of early opioid prescription	Length of disability
Fritz et al., 2018 (94)	USA	2627	ICD-9 code	707/2627=26.9%	-
Gross et al., 2009 (95)	Canada	47813	ICD-9 codes	2770/47,813=5.8 %	Subjects not prescribed early opioid had a higher likelihood of returning to work (hazard ratio 1.96, 95% CI 1.88–2.04) than subjects who received early opioid prescription
Shraim et al., 2019 (9)	USA	59360	ICD-9 codes	16324/59360=27.5 %	Each 100 mg of early opioid (MEA) was associated with increase in geometric mean of LOD by 0.4 (95% CI: 0.3-0.5) days
Webster et al.,2007 (20)	USA	8443	ICD-9 codes	1792/8443=21.2%	Total cumulative MEA increased LOD increased Those who received more than 450 mg MEA were, on average, disabled 69 days longer.

Table 4: Prevalence of Early Opioid Prescription and the Associated LOD in LBP (cont'd)

Webster et al.,2009 (93)	USA	8262	ICD-9 codes	1760/8262=21.3%	-
Webster et al., 2010 (96)	USA	3264	ICD-9 codes	682/3264=20.9%	-
Webster et al., 2014 (92)	USA	3022	ICD-9) codes	841/3022=27.8%	-

CHAPTER 5: DISCUSSION

This systematic review has identified seven studies reporting on the prevalence of early opioid prescribing for LBP and only three of them examined the relationship between early opioid prescribing for LBP and LOD. The overall pooled prevalence of early opioid prescribing for LBP was 20% (95% CI 0.8, 32.1%). Findings from the three studies which examined the relationship between early opioid prescribing for LBP and LOD showed consistent findings. Early opioid prescribing for LBP was associated with increased LOD with evidence of dose-response relationship from one study (20).

The results of the current systematic review showed that, on average, one out of five patients with acute occupational LBP or NSLBP is prescribed early opioid against the recommendations of current clinical guidelines. Additionally, the systematic review showed that early prescribing of opioids for acute LBP cases is associated with a significant prolonged disability with evidence of a dose-response relationship. One study also reported that early opioid prescribing was associated with an increased risk of surgery and poor outcomes after 2 years of LBP onset (20). The findings of a systematic review showed that the prescription of opioid was significantly associated with long-term continued use of opioids (OR 1.57 95% CI, 1.06-2.33) (98). The long-term use of opioids was associated with an increased dose of opioids over time (99). Moreover, it also causes opioid receptors in the body to become tolerant to opioids (100). As a result, people have to take larger doses with the cycle leading to physical dependence, addiction, and more disability, which can be hard to reverse due to withdrawal symptoms (100). The findings of the current systematic review have important implications for healthcare quality improvement initiatives and policymakers for better management of patients with acute LBP, and highlight the negative impact associated with incompliance with the recommendations of clinical guidelines.

In our meta-analysis, heterogeneity was significant using both FE model and RE model, (RE:Cochran Q=12071.2, *p-value <0.001,* I^2=100%). Study heterogeneity can occur because of clinical heterogeneity or statistical heterogeneity. That being said, clinical heterogeneity is usually caused by clinical differences between studies arising from variation in the study population or the process of selection of participants (101). However, in this review, study populations were relatively similar in terms of their characteristics (age between 18 -65, most of the sample were males, data were extracted from worker compensation database, diagnosis of LBP based on ICD 9 codes). Moreover, the majority of the studies were from the USA, and the selection of cases was based on medical billing records. It was evident that all the included studies had adjusted for potential confounders in the analysis such as age, sex, severity, job tenure, income. Thus, it can be assumed that heterogeneity is not resulting from the clinical aspect. One point was noticed in the study of Canada, which had a lower prevalence and a higher weight compared to other studies in the USA, where the prevalence of prescription has decreased within 5 years to reach 5%. This was explained in the study to be likely caused due to the under-representation of opioid prescriptions in the Alberta database among claimants with short disability duration. Moreover, another assumption was culture where there are existing differences between people reporting pain and the rules and regulations of the country authority also play a significant role (95). This difference raised the question if there is a variation in the prescription pattern-based on the geographical area. This point was investigated through conducting a sensitivity analysis by geographical area, where the Canadian study was removed from the analysis, and the heterogeneity changed by a considerable amount using FE and RE model (Cochran Q=329.7; *p-value* <0.001; I^2=98%) however, it was found to be still high. Furthermore, locally in the USA, it was proven that there is between states

variability in the prescription pattern of opioids and the states with the highest proportion of early opioid prescribing were South Carolina (52.9%) and Oklahoma (49.3%). On the other hand, Massachusetts (5.7%) and Vermont (6.2%) had the lowest prevalence of early opioid prescription. Some of the reasons that were showing significant association with the state-level variables are the number of physicians at each area, household income level, and the state workers compensation cost containment score variables. All these factors were found to be associated with state-level opioid prescription patterns (93), and this might also be the case between countries. Therefore, adding to the small number of the included studies and the fairly big difference in sample size between studies, geographical variation is showing changes in heterogeneity which can be a potential reason for the heterogeneity observed.

5.2 Strengths and limitations

This review has several strengths. Relevant and key bibliographic databases were searched using a comprehensive list of key terms. Additionally, the references list of relevant studies was searched, and their citations were tracked to identify any relevant articles. Also, some sources of grey literature (Google Scholar and ResearchGate) were searched. In addition, two reviewers independently screened studies for inclusion, extracted data using a standardized form, and assessed the risk of bias in included studies. Any disagreements were resolved by discussion or recourse to the thesis supervisor. Another important strength is that the included studies were of good methodological quality. Moreover, the studies included highly comparable samples of LBP in terms of characteristics of participants, used medical billing data to ascertain opioid prescribing, wage replacement data to ascertain LOD, with adjustment key confounding factors, and used adequate follow-up for at least one year. One more

important strength is that five of the included studies are based on a large national sample of occupational LBP cases which are representative of private industry workers. This sample has a parallel distribution of demographic characteristics reported in prior studies investigating occupational LBP (9, 102). Therefore, it is considered representative sample of the USA population.

The current systematic review also has several limitations. The evidence provided by this review was based on the findings of a relatively small number of relevant studies from two countries and using WC administrative databases. Although identification of LBP cases was on ICD-9 diagnostic codes, there is a possibility that the findings have been affected by the coding behavior of practitioners and potential coding bias associated with any changes in hospital record keeping behavior in relation to case mix and reimbursement issues (103). Moreover, some of the studies have not adjusted for potential confounders such as pain intensity, psychosocial factors, workplace factors. Moreover, measurement of LOD using wage replacement data could underestimate the LOD. Additionally, all the studies were done in the US, and only one study was done in Canada which restricted the ability of the findings to be generalized and results may be the only representative to the US population. plus, the used databases are based on worker compensation insurance, which can restrict the generalizability to non-workers, However, all workers by law must be insured with worker compensation that covers their health care therefore, any type of injury would be covered by the insurance. also, some of the studies are using a sample from the same time such as webster 2009 and 2007, and Webster 2010 and 2014 that could potentially cause an overlap in the sample included however the studies have different sample sizes, follow up period, prevalence, and outcome thus, overlapping is probable but not definite and there is no clear evidence of overlapping. Finally, all the included studies were

published in English. However, only one potentially relevant study was published in German and it was excluded at the full-text stage of study selection because of lack of access to professional translation service for this review.

5.3 Implications for future research

Future research needs to control for potential confounding factors that might affect the size of the relationship between early opioid prescribing and associated LOD in LBPs. Additionally, qualitative interviews with medical practitioners that were conducted on LBP patients about their perceived impact of the early opioid on LOD, may provide more information about the potential reasons for the lack of compliance with current clinical guidelines. In addition, future interventions to improve compliance with opioid prescribing guidelines using objective measures of LOD (not only compensation claims) for longer period are also needed. The current findings of the study serve as a basis for policymakers and governments to take steps in investigating ways to better improve the compliance with the clinical guidelines and work as a motive for physicians to take any action against early opioid prescribing for acute LBP.

5.4 Conclusion

The findings of this systematic review show that one in five patients with acute LBP are prescribed opioids early in medical care against the current clinical guidelines. The review also showed that early opioid prescribing is associated with prolonged disability. Future research on early opioid prescription for LBP and the relationship with prolonging disability should account for diverse factors associated with LOD in this population. In addition, developing and testing healthcare quality improvement interventions to enhance compliance with clinical guidelines about early opioid prescribing for LBP may help in preventing prolonged disability and its associated negative impact among patients with acute LBP.

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APPENDEX

APPENDIX1 PRISMA CHECK LIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	iii
INTRODUCTION			1
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,21
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	26
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	21
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	22
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	22
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	24
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	24
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	23
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	24

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	26
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	26

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	26
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	26
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	28
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	30
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	32
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	35
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	32
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	38
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	41
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	43
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	45
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	26

Appendix 2 Search strategy

	Opioid	Low Back Pain	Work Disability
MEDLINE	exp analgesics, opioid/ opioid opiate opium "opioid prescribing" "opioid prescription" "opioid use"	exp low back pain/ sciatica/ sciatica "Low back pain" "Lower back pain" "Low back injury" "Low back injuries" Lumbago "lumbosacral pain"	Exp return to Work/ Workers' Compensation/ Insurance, Disability/ Sick leave/ Absenteeism/ "return to Work" "work disability" "length of disability" "work incapacity" "back to work" "work resumption" absenteeism "duration of disability" "sick leave" "sick days"
EMBASE	exp opiate/ exp narcotic agent/ opioid opiate opium "opioid prescribing" "opioid prescription" "opioid use"	exp ISCHIALGIA/ exp low back pain/ sciatica "Low back pain" "Lower back pain" "Low back injury" "Low back injuries" Lumbago "lumbosacral pain"	work disability/ work resumption/ return to work/ absenteeism/ "return to Work" "work disability" "length of disability" "work incapacity" "back to work" "work resumption" absenteeism "duration of disability" "sick leave" "sick days"
CINAHL	exp analgesics, Opioid/ exp narcotics/ opioid opiate opium "opioid prescribing" "opioid prescription" "opioid use"	Exp Low Back Pain/ sciatica "Low back pain" "Lower back pain" "Low back injury" "Low back injuries" Lumbago "lumbosacral pain"	Insurance, Disability/ Absenteeism/ Sick Leave/ Worker's compensation/ Employee, Disabled/ "return to Work" "work disability" "length of disability" "work incapacity" "back to work" "work resumption" absenteeism "duration of disability" "sick leave" "sick days"
PsycINFO	exp opiates/ exp narcotic drugs/ opioid opiate opium "opioid prescribing" "opioid prescription" "opioid use"	back pain/ sciatica "Low back pain" "Lower back pain" "Low back injury" "Low back injuries" Lumbago "lumbosacral pain" backache "back pain" "back ache"	Exp Employee Absenteeism/ Exp return to work/ "return to Work" "work disability" "length of disability" "work incapacity" "back to work" "work resumption" absenteeism "duration of disability" "sick leave" "sick days"

Appendix 3 Number of records identified from each database

	Database	Search Term	Number of records
1	Medline	exp ANALGESICS, OPIOID/	139,386
2	Medline	(opioid).ti,ab,af	110,087
3	Medline	(opiate).ti,ab,af	21,942
4	Medline	(opium).ti,ab,af	3,677
5	Medline	("opioid prescribing").ti,ab,af	1,601
6	Medline	("opioid prescription").ti,ab,af	1,167
7	Medline	("opioid use").ti,ab,af	8,147
8	Medline	exp LOW BACK PAIN/	21,537
9	Medline	SCIATICA/	4,979
10	Medline	(sciatica).ti,ab	4,191
11	Medline	("Low back pain").ti,ab	26,552
12	Medline	("Lower back pain").ti,ab	2,466
13	Medline	("Low back injury").ti,ab	272
14	Medline	("Low back injuries").ti,ab	195
15	Medline	(Lumbago).ti,ab	1,354
16	Medline	("lumbosacral pain").ti,ab	223
17	Medline	exp RETURN TO WORK/	2,440
18	Medline	WORKERS' COMPENSATION/	7,452
19	Medline	INSURANCE, DISABILITY/	1,487
20	Medline	SICK LEAVE/	5,770
21	Medline	ABSENTEEISM/	9,019
22	Medline	("return to Work").ti,ab,af	9,913
23	Medline	("work disability").ti,ab,af	2,029
24	Medline	("length of disability").ti,ab,af	66
25	Medline	("work incapacity").ti,ab,af	336
26	Medline	("back to work").ti,ab,af	562
27	Medline	("work resumption").ti,ab,af	157
28	Medline	(absenteeism).ti,ab,af	12,092
29	Medline	("duration of disability").ti,ab,af	170
30	Medline	("sick leave").ti,ab,af	8,544
31	Medline	("sick days").ti,ab,af	390
32	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7)	185,862
33	Medline	(8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16)	41,528
34	Medline	(17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31)	37,224
35	Medline	(32 AND 33 AND 34)	66
36	Medline	(32 AND 33)	1,084
37	Medline	(32 AND 34)	289
38	Medline	(33 AND 34)	1,846

	Database(s)	Search Term	
32	EMBASE	exp OPIATE/	84,895
33	EMBASE	exp NARCOTIC AGENT/	268,039
2	EMBASE	(opioid).ti,ab,af	105,122
3	EMBASE	(opiate).ti,ab,af	151,868
4	EMBASE	(opium).ti,ab,af	2,914
5	EMBASE	("opioid prescribing").ti,ab,af	2,435
6	EMBASE	("opioid prescription").ti,ab,af	1,979
7	EMBASE	("opioid use").ti,ab,af	12,603
8	EMBASE	exp LOW BACK PAIN/	57,129
34	EMBASE	exp ISCHIALGIA/	4,747
10	EMBASE	(sciatica).ti,ab	4,463
11	EMBASE	("Low back pain").ti,ab	35,602
12	EMBASE	("Lower back pain").ti,ab	3,875
13	EMBASE	("Low back injury").ti,ab	308
14	EMBASE	("Low back injuries").ti,ab	210
15	EMBASE	(Lumbago).ti,ab	1,592
16	EMBASE	("lumbosacral pain").ti,ab	265
35	EMBASE	*"RETURN TO WORK"/	1,637
36	EMBASE	*"WORK RESUMPTION"/	1,050
37	EMBASE	*"WORK DISABILITY"/	1,960
38	EMBASE	*ABSENTEEISM/	5,256
22	EMBASE	("return to Work").ti,ab,af	13,815
23	EMBASE	("work disability").ti,ab,af	6,285
24	EMBASE	("length of disability").ti,ab,af	84
25	EMBASE	("work incapacity").ti,ab,af	332
26	EMBASE	("back to work").ti,ab,af	1,097
27	EMBASE	("work resumption").ti,ab,af	3,573
28	EMBASE	(absenteeism).ti,ab,af	19,544
29	EMBASE	("duration of disability").ti,ab,af	635
30	EMBASE	("sick leave").ti,ab,af	6,629
31	EMBASE	("sick days").ti,ab,af	558
39	EMBASE	(32 OR 33 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7)	368,973
40	EMBASE	(8 OR 34 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16)	69,112
41	EMBASE	(35 OR 36 OR 37 OR 38 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31)	44,124
42	EMBASE	(39 AND 40 AND 41)	156
43	EMBASE	(39 AND 40)	4,333
44	EMBASE	(39 AND 41)	833
45	EMBASE	(40 AND 41)	2,663
46	EMBASE	(39 AND 40) [DT 1900-2000]	353
47	EMBASE	(39 AND 40) [DT 2001-2020]	3,978
	Database(s)	Search term	

1	CINAHL	exp ANALGESICS, OPIOID/	37,827
32	CINAHL	*NARCOTICS/	6,990
2	CINAHL	(opioid).ti,ab,af	42,287
3	CINAHL	(opiate).ti,ab,af	4,902
4	CINAHL	(opium).ti,ab,af	889
5	CINAHL	("opioid prescribing").ti,ab,af	1,316
6	CINAHL	("opioid prescription").ti,ab,af	817
7	CINAHL	("opioid use").ti,ab,af	5,804
8	CINAHL	exp LOW BACK PAIN/	20,937
10	CINAHL	(sciatica).ti,ab	1,288
11	CINAHL	("Low back pain").ti,ab	18,056
12	CINAHL	("Lower back pain").ti,ab	1,328
13	CINAHL	("Low back injury").ti,ab	202
14	CINAHL	("Low back injuries").ti,ab	126
15	CINAHL	(Lumbago).ti,ab	134
16	CINAHL	("lumbosacral pain").ti,ab	48
18	CINAHL	WORKER'S COMPENSATION/	4,062
19	CINAHL	INSURANCE, DISABILITY/	1,945
20	CINAHL	SICK LEAVE/	5,377
21	CINAHL	ABSENTEEISM/	5,094
35	CINAHL	*"EMPLOYEE, DISABLED"/	384
22	CINAHL	("return to Work").ti,ab,af	5,572
23	CINAHL	("work disability").ti,ab,af	1,037
24	CINAHL	("length of disability").ti,ab,af	35
25	CINAHL	("work incapacity").ti,ab,af	53
26	CINAHL	("back to work").ti,ab,af	802
27	CINAHL	("work resumption").ti,ab,af	53
28	CINAHL	(absenteeism).ti,ab,af	6,898
29	CINAHL	("duration of disability").ti,ab,af	138
30	CINAHL	("sick leave").ti,ab,af	6,981
31	CINAHL	("sick days").ti,ab,af	451
36	CINAHL	(1 OR 32 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7)	60,895
37	CINAHL	(8 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16)	27,221
38	CINAHL	(18 OR 19 OR 20 OR 21 OR 35 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31)	24,628
39	CINAHL	(36 AND 37 AND 38)	49
40	CINAHL	(36 AND 37)	852
41	CINAHL	(36 AND 38)	288
42	CINAHL	(37 AND 38)	1,255
	Database(s)	Search term	
1	PsycINFO	exp OPIATES/	25,575
2	PsycINFO	(opioid).ti,ab,af	25,916
3	PsycINFO	(opiate).ti,ab,af	8,727

4	PsycINFO	(opium).ti,ab,af	775
5	PsycINFO	("opioid prescribing").ti,ab,af	365
6	PsycINFO	("opioid prescription").ti,ab,af	244
7	PsycINFO	("opioid use").ti,ab,af	3,223
8	PsycINFO	BACK PAIN/	4,319
32	PsycINFO	(backache).ti,ab	134
34	PsycINFO	("back ache").ti,ab	8
33	PsycINFO	("back pain").ti,ab	5,343
10	PsycINFO	(sciatica).ti,ab	155
11	PsycINFO	("Low back pain").ti,ab	3,398
12	PsycINFO	("Lower back pain").ti,ab	297
13	PsycINFO	("Low back injury").ti,ab	60
14	PsycINFO	("Low back injuries").ti,ab	36
15	PsycINFO	(Lumbago).ti,ab	36
16	PsycINFO	("lumbosacral pain").ti,ab	11
22	PsycINFO	("return to Work").ti,ab,af	2,685
23	PsycINFO	("work disability").ti,ab,af	658
24	PsycINFO	("length of disability").ti,ab,af	26
25	PsycINFO	("work incapacity").ti,ab,af	37
26	PsycINFO	("back to work").ti,ab,af	188
27	PsycINFO	("work resumption").ti,ab,af	51
28	PsycINFO	(absenteeism).ti,ab,af	5,686
29	PsycINFO	("duration of disability").ti,ab,af	42
30	PsycINFO	("sick leave").ti,ab,af	2,134
31	PsycINFO	("sick days").ti,ab,af	173
35	PsycINFO	*"EMPLOYEE ABSENTEEISM"/	1,834
36	PsycINFO	*REEMPLOYMENT/	1,219
37	PsycINFO	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7)	37,580
38	PsycINFO	(8 OR 32 OR 34 OR 33 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16)	6,260
39	PsycINFO	(22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 35 OR 36)	10,330
40	PsycINFO	(37 AND 38 AND 39)	3
41	PsycINFO	(37 AND 38)	266
42	PsycINFO	(37 AND 39)	51
43	PsycINFO	(38 AND 39)	432

Appendix 4. Newcastle Ottawa scale NOS

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✵
   b) somewhat representative of the average _____ in the community ✵
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort ✵
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview ✵
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✵
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✵
   b) record linkage ✵
   c) self-report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✵
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✵
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✵
   c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement