Influences of Pain, Insomnia, and Depression on Health Care Utilization in Older Adults with Osteoarthritis

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**Abstract**

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**Background**: Osteoarthritis (OA), the most common type of arthritis, is prevalent and costly. Pain is the principle reason patients with OA seek treatment. Older adults with OA often report co-existing insomnia and depression. OA pain, insomnia, and depression are prevalent and greatly increase health care utilization (HCU) in this population.

**Purpose**: a) Describe the prevalence of pain, insomnia, and depression in older adults with OA, and b) Examine individual and combined effects of pain, insomnia, and depression on HCU.

**Methods**: A total of 8,057 participants aged 60+ with an electronic medical record diagnosis of OA were mailed a screening survey that asked about their pain, insomnia, and depressive symptoms. Pain was assessed by the Graded Chronic Pain Scale (GCPS); Grades 2 - 4 were moderate to severe pain. Insomnia severity was measured by the Insomnia Severity Index (ISI); a score of 7 or greater indicates at least sub-threshold insomnia. Depression was measured by the Patient Health Questionnaire depression scale (PHQ-8), with a score greater than 5 representing at least sub-clinical depression. All participants were members of Group Health Cooperative

(GHC), a Seattle-based health maintenance organization. HCU variables from 1 year before and 3 years after the index date were extracted from GHC medical records. Variables included medication use (opioids, sedatives, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs)), total number of office visits, length of stay (LOS) (days), inpatient and outpatient costs, and hip/knee replacement. Patient demographics (age, sex, race, marital status, employment status, and educational levels), days of enrollment in GHC, and Charlson Comorbidity Index scores were also recorded. Negative binominal, generalized linear, and logistical models were used for the data analysis.

**Results**: A total of 2,976 participants were included in the data analysis. About half the participants reported moderate to severe level pain (47.1%), at least sub-threshold insomnia (55.05%), or at least sub-clinical depression (45.2%). About one third of participants presented moderate to severe pain and at least sub-threshold insomnia (33.9%), or moderate to severe pain and at least sub-clinical depression (28.8%). Pain individually contributed to opioids and TCAs use. Depression individually contributed to use of sedatives, TCAs, and SSRIs. Insomnia individually contributed to opioid, sedative, and SSRI use. Generally, combined effects of these symptoms on opioid, sedative, and TCA use increased with symptom severity. Combined effects on SSRI use did not change significantly regardless of insomnia and depression severity. Individual effects of pain were statistically significant across all types of the examined HCU. Insomnia and depression individually contributed only to office visits and outpatient costs. Combined effects of pain/insomnia, and pain/depression were significant across all types of HCU except for hip/knee replacement and increased with insomnia/depression severity.

**Conclusions**: OA pain, insomnia, and depression are prevalent in older adults. Individual and combined effects of pain, insomnia, and depression on medication use are significant. Effects of

pain on health care utilization in OA are significant and cost-effective strategies are needed for better pain management to reduce OA-related health care burden. Significant combined effects of pain/insomnia and pain/depression suggest the importance of inquiring about insomnia and depression as part of the routine assessment for OA and working collaboratively across specialists for improved symptom management in clinical practice in order to reduce OA-associated health care burden.

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# Chapter 1. Introduction

## SIGNIFICANCE OF THE PROBLEM

Osteoarthritis (OA) is a clinical syndrome of joint pain accompanied by various degrees of physical function limitation and reduced quality of life. It is by far the most common form of arthritis and one of the leading causes of pain and disability worldwide.[1] Overall, in the United States, OA affected 13.9% of adults age 25 years and older and 33.6% (12.4 million) of those over 65 years old in 2005.[2] The prevalence of symptomatic knee OA is approximately 10% in men and 13% in women among adults of 60 years age or older.[1] The most prevalent locations affected by OA include the knee (23%), hand (43.3%), and hip (10.9%).[3] Pain, as the dominant clinical symptom of OA, is accompanied by functional impairment that includes joint stiffness and dysfunction and a vastly reduced quality of life.[4] Currently, there is no cure for OA and it is associated with increased mortality.[5] Deaths from all causes, cardiovascular deaths, and dementia deaths among adults with OA were 1.6, 1.7, and 2.0 times higher, respectively, compared to the general population.[6] OA is also associated with a high health care burden. The direct health care costs of OA patients were over two times higher than those of similar patients without OA. The primary drivers of cost differences were comorbidities and inpatient costs.[7] Given the high prevalence and huge health care burden on patients with OA, it is important to understand how health care utilization is influenced by this condition and its comorbidities.

Patients with OA are more likely to have comorbidities, including musculoskeletal and neuropathic pain conditions, depression, and sleep disorders compared to patients without OA.[8] Depression and insomnia are the two most common comorbidities in OA.[9] The prevalence of insomnia symptoms and sleep problems in persons with arthritis has been reported to be 24.8% and 11.9%, respectively.[10] Symptomatic OA in the hip or knee was reported to be associated with increased odds of any sleep problem (OR = 1.25), insomnia (OR = 1.29), and insufficient

sleep (OR = 1.35) in a large community-based sample.[11] High rates of clinical depressive disorders are often seen in patients seeking treatment for chronic pain associated with OA.[12] The link between depression and insomnia is also suggested in other epidemiological studies and the relationship is bidirectional. For example, about 20% of patients with insomnia manifest some depressive symptoms, while depression has been demonstrated to be the largest and most consistent risk factor for insomnia.[13] However, the associations among pain, insomnia, and depression in persons with OA are not clear. Parmelee and colleagues[14] found that depression appeared to mediate the relationship between sleep and pain, particularly when pain was severe. They also stated that sleep was independently associated with pain and depression. In contrast, another study showed that pain in OA is a predictor of sleep disturbance and mediates a large amount of the relationship between arthritis and sleep problems.[15] Varied results have been reported in previous studies, because the studies varied in study design, population observed, and variables examined. Therefore, studies using both cross-sectional and longitudinal data on all three symptoms are needed to better understand the complex linkages and interactions in this population.

The health care burden is substantial for patients with OA, who have significantly greater use of pain-related and adjunctive medications and higher direct medical costs. For instance, patients with OA are more likely than those without OA to receive pain-related medications, including opioids (40.7% vs. 17.1%), nonsteroidal anti-inflammatory drugs (37.1% vs. 11.5%), tramadol (9.8% vs. 1.8%), and adjunctive medications for treating depression, anxiety, and insomnia.[8] Patients with OA tend to experience a mean total direct medical cost that is more than two times higher than patients without OA ($12,905 vs. $5,099).[16] Some evidence suggests that various long-acting opioid analgesics simultaneously improve sleep and pain symptoms;

however, the complex interaction between sleep and reduced pain is not clear and needs further study. In addition to greater use of psychoactive medication and high health care costs, OA results in a high frequency of general practitioner visits, which in turn is related to depressive and pain symptoms.[17] Compared to patients with other chronic conditions, patients with sleep problems such as insomnia also have more health professional contacts (81% vs. 60%) and prescription medication usage (57% vs. 31%, respectively).[18] Similarly, patients with OA and comorbid depression had 38.8% higher health care utilization compared to those without depression.[19] Given these associations, it is important to understand how pain, insomnia, and depression influence health care utilization (HCU) in this population.

## CONCEPTUAL FRAMEWORK

The importance of understanding the effects of comorbid symptoms on HCU can be illustrated using Andersen's conceptual model for individual determinants of HCU.[20] This model proposes a sequence of conditions contributing to the amount of health services a person uses. The model has been adapted for this study (see Figure 1). The individual use depends on three factors: (a) characteristics of the individual that may predispose him/her to use services, such as age, sex, race, ethnicity, education level, and employment status; (b) ability to secure services, which is influenced by enabling factors such as income level and access to the health insurance; and (c) illness level, including OA pain, insomnia, depression, and other chronic illness conditions or symptoms. Among these three factors, illness level represents the most immediate factor determining likelihood of HCU. In addition, the illness level is "high" in relative importance for all three factors, and is the greater determinant of HCU, compared to the predisposing and enabling factors, which are of "medium" importance. Considering the strong association between pain, insomnia, and depression in OA, it is important to explore their

individual and combined effects on HCU, while controlling for predisposing characteristics and enabling factors.

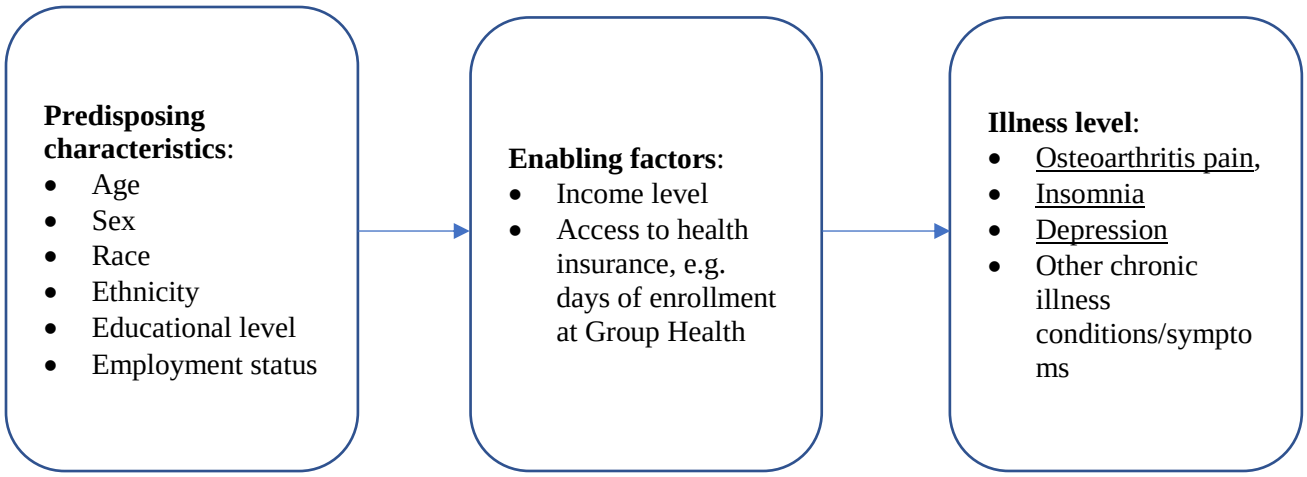


Figure 1. Individual determinants of health care utilization for patients with osteoarthritis (adapted from Andersen's conceptual model for individual determinants of health care utilization)

## STUDY PURPOSE

Different clinical trials have been developed for patients with pain or sleep problems, but few of them have addressed the OA population or examined several comorbidities simultaneously. In the Lifestyles randomized controlled trial for older adults with severe OA pain and insomnia symptoms, Vitiello and colleagues [21] showed sustained improvements in multiple measures of sleep, chronic pain, and fatigue among persons whose insomnia symptoms had been successfully reduced in the trial. No improvements were observed in depressive symptoms, but the study sample had been relatively non-depressed at baseline. The current study will build upon these results by using electronic medical records available for participants who have been screened and were invited to participate in the Lifestyles study to examine how each comorbidity individually and jointly influences HCU (health care visits, length of hospital stay,

medication usage, surgical procedures, and health care costs), controlling for other characteristics among older adults with OA.

## CONTENT OF THE DISSERTATION

The dissertation consists of two papers. The purpose of the first paper is to examine the individual and combined effects of pain, insomnia, and depression on medication use (opioids, sedatives, tricyclic antidepressants, and selective serotonin reuptake inhibitors) in older adults with OA. The purpose of the second paper is to investigate the individual and combined effects of pain, insomnia, and depression on HCU (office visits, hospital length of stay, health care costs, and hip/knee replacement) in older adults with OA.

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# Chapter 2. Influences of Osteoarthritis Pain, Insomnia, and Depression on Medication Use in Older Adults with Osteoarthritis

**ABSTRACT**

**Background** Medication use represents a major health care expenditure, but the influence of osteoarthritis (OA) pain, insomnia, and depression on its use has not been well investigated.

**Objective** To examine individual and combined effects of pain, insomnia, and depression on medication use in older adults with OA.

**Research Design** Secondary data analysis using cross-sectional screening data and medical records to examine effects of symptoms on medication use in four categories (opioids, sedatives, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs)) in a 4-year period.

**Subjects** Group Health Cooperative patients with a primary diagnosis of OA (N = 2,976)

**Measures** We used survey data on pain (Graded Chronic Pain Scale), insomnia (Insomnia Severity Index), depression (Patient Health Questionnaire-8), and medication use extracted from medical records. Negative binomial models were performed for data analysis.

**Results** About half the participants reported moderate to severe level pain (47.07%), at least sub-threshold insomnia (54.95%), or sub-clinical depression (45.23%). Pain individually contributed to opioid and TCA use. Depression individually contributed to use of sedatives, TCAs, and SSRIs. Insomnia individually contributed to opioid, sedatives, and SSRIs use. Generally, combined effects of these symptoms on opioids, sedatives, and TCA use increased with symptom severity. Combined effects on SSRI use did not change regardless of insomnia and depression severity.

**Conclusion** OA pain, insomnia, and depression should be viewed jointly and adequately evaluated when prescribing medications in clinical practice. Prescription of opioids and TCAs

should be monitored due to either insufficient evidence on long-term efficacy or substantial side effects.

## INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis and a debilitating disease. It is among the leading causes of disability for adults in the United States, affecting 52.5 million adults and 49.7% of adults aged ≥ 65 years.[1] The combined economic burden of all forms of arthritis is significant. The cost attributable to arthritis and other rheumatic conditions in the United States was estimated at $128 billion in 2003 ($169 in 2017 dollars).[2] Diagnosis of symptomatic OA most often occurs early to mid-life (median age 55 years), meaning that OA will impact health care utilization and costs for a given patient over many years.[3,4] Multiple studies have evaluated the economic burden of OA, which is substantial and significant.[5–7] Mean total costs of health care were more than two times higher in patients with OA compared to those without the condition ($12,905 vs. $5,099).[8] A recent review estimated that the weighted average annual costs per patient with knee and hip OA were $11,802 in total costs, $10,101 in direct costs, and $4,678 in indirect costs.[9]

With this increasing health care burden, it is important to understand medication use, as it represents a major health care expenditure for people with OA in the United States.[10] Significant increases in polypharmacy have been observed, especially in older adults with comorbid conditions.[11] Pain is the principal reason for OA patients to seek medication, but OA patients often report living with other comorbidities, most notably insomnia and depression.[12,13] A few studies have examined patterns of medication use in OA and non-cancer pain conditions. Patients with OA or non-cancer pain were significantly more likely to use opioids and adjunctive medications for treating depression and insomnia.[14–16] Wright and colleagues[17] reported an increase in likelihood of getting an opioid prescription by patients with OA and a history of depression, and similar findings were reported in patients with non-cancer pain and depression.[18]

However, existing studies have neither presented an overview of depression, pain, and insomnia in OA nor examined the medication use specific to the level of symptom severity. In addition, given that the complicated associations between OA pain and insomnia have been well-established,[19–22] it is important to understand how each of these three symptoms may predict use of commonly prescribed medications in this population.

Therefore, the purpose of this study was to (a) describe pain, insomnia, and depressive symptom severity in older adults with OA, and (b) examine the individual and combined effects of pain, insomnia, and depression on utilization of four types of commonly prescribed medications (opioids, sedatives, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs)) for treating the three conditions.

## METHODS

### *Participants*

The dataset used in this study was from part of a National Institutes of Health (NIH)-funded clinical trial that compared the efficacy of three group interventions for people with comorbid OA and insomnia to help them manage their pain and insomnia symptoms.[23] The study was carried out collaboratively between the University of Washington (UW) and Group Health Cooperative (GHC) (recently changed to Kaiser Permanente Washington), a Seattle-area integrated health care plan with over 600,000 enrollees. Prior to the clinical trial, from 2008 to 2010, a screening survey questionnaire was mailed to 8,057 GHC members age 60+ who had an electronic medical record OA diagnosis associated with a health care visit in the prior 3 years. The questionnaire asked respondents about the frequency and interference level of their OA pain over the previous 3 months, and the frequency and nature of their sleep problems. A total of

3,041 participants completed the screening questionnaire and gave permission to access their medical records. This study used data from the screening survey and participants' GHC electronic medical records. The clinical trial was approved by the UW Human Subjects Division and the GHC Institutional Review Board. This secondary data analysis was reviewed by the UW Human Subjects Division and qualified for an exemption.

Inclusion criteria for receiving the screening survey were: age 60+, continuously enrolled in GHC 1 year prior to screening, receiving primary care services at one of six regional participating clinics, not in the "No Contact for Research File," and at least one visit noted in medical record for OA in the prior 3 years. Participants were excluded if the medical record information indicated a diagnosis of: (a) rheumatoid arthritis, (b) obstructive sleep apnea, (c) periodic leg movement disorder, (d) restless leg syndrome, (e) sleep-wake cycle disturbance, (f) rapid eye movement (REM) behavior disorder, (g) dementia or receiving cholinesterase inhibitors, (h) Parkinson's disease or another neurodegenerative disease known to directly impact sleep, (i) cancer in the past year and receiving chemotherapy or radiation therapy in the past year, and/or (j) inpatient treatment for congestive heart failure within the previous 6 months.

*Dataset Elements*

Symptom measures

*Pain*. The Graded Chronic Pain Scale (GCPS) assesses two dimensions of overall chronic pain severity: pain intensity and pain-related disability.[24] Subscale scores for pain intensity and disability are combined to calculate a chronic pain grade with five hierarchical categories, with grade 0 meaning no pain and grade IV meaning high disability-severely limiting pain.[25] Internal consistency of the GCPS has been reported to be 0.74 (Cronbach's alpha) for patients with chronic back pain.[24] The GCPS also has a high test-retest reliability and construct

validity.[26,27] For this study, pain was coded as a binary variable: no to mild pain (GCPS = 1) and moderate to severe pain (2 to 4).

*Insomnia*. The Insomnia Severity Index (ISI) was designed to assess the nature, severity, and impact of insomnia and monitor treatment response in adults.[28] The ISI is a seven-item measure with scores ranging from 0 to 28, with a higher score indicating more severe insomnia and a score ≥ 15 indicating moderate to severe clinical insomnia. ISI internal consistency is excellent for both the community and clinical samples (Cronbach's alpha of 0.90 and 0.91, respectively).[29] Convergent validity is supported by significant correlations between total ISI score and measures of fatigue, quality of life, anxiety, and depression.[29] Research indicates that the ISI is a reliable and valid instrument to detect cases of insomnia and is sensitive to treatment response in clinical patients.[30] For this study, the insomnia variable was coded according to validated cut-points for this scale which were: no insomnia (≤ 7), sub-threshold insomnia (8 to 14) and clinical insomnia (15 to 28).[31]

*Depression*. The eight-item Patient Health Questionnaire depression scale (PHQ-8) has been shown to be a valid diagnostic and severity measure for depressive disorders in large clinical trials. PHQ-8 total scores range from 0 to 24, with higher scores representing more severe depression. The PHQ-8 is a reliable measure for depression in population-based studies, and a cut point ≥ 10 can be used for determining current depression.[32] The depression variable was coded according to validated cut-points for this scale as follows: no depression (≤ 4), sub-clinical depression (5 to 9) and current depression (10 to 24).[33]

Medication use

A programmer at GHC used the First Databank licensed by GHC, which uses the American Hospital Formulary Service (AHFS) code to classify drugs from the electronic medical

records.[34] For the analysis of screening survey data, the index date was defined as the date when the screening questionnaire was mailed to the participant. Medical records of one year before (Year 1) and three years after (Year 2 – 4) were used. Medication use was measured as days of supply for the following medication categories: a) opioids; b) sedatives; and c) anti-depressants, including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).

Participant characteristics

Demographics were collected from the screening survey, including age, sex, race, marital status, employment status and educational levels. Variables of age and sex were verified from the medical records and replaced if participants did not report their age or sex. Months of enrollment in GHC for each of the four years and Charlson Comorbidity Index scores calculated from participants' medical records were also calculated.

*Data Analysis*

Participants with no enrollment in GHC after the index date were excluded (N = 6) which left a sample of 3,035. Participants with missing data on more than two of the following variables were excluded: pain (39 (1.3%)), insomnia (20 (0.7%)), depression (107 (3.5%)), education (62 (2.0%)), marital status (67 (2.2%)), race (110 (3.6%)) and employment (122 (4.0%)) with a final sample of 2,976 participants included in the final analysis. Multiple imputation technique was used with five imputations to accommodate the remaining missing information in the statistical analyses.[35] Demographics, symptoms of pain, insomnia and depression, months of enrollment, Charlson Comorbidity Index, and medication use variables were used in the imputation models.

Data analyses investigated the individual effects of pain, insomnia, and depression, and combined effects of (a) pain and insomnia and (b) pain and depression. Combined effects

focused on pairing the other two symptoms with pain, given that pain is the main complaint in older adults with OA. The combined effects of insomnia and depression were not examined because of the high correlation between the two symptoms in this sample (Pearson correlation coefficient was 0.73). Two categorical patient variables were created based on the combination of symptom severities, with one variable representing the severity of pain and insomnia, and the other representing the severity of pain and depression. Although insomnia and depression are highly correlated, few studies have examined pain, insomnia, and depression all together in OA populations. A third categorical variable was created based on the combination of the severities of the three symptoms. Categories with fewer than 20 participants were combined with other categories based on clinical justification. For example, the category "No to mild pain & clinical insomnia & no depression" (N = 6) was combined with the category "No to mild pain & sub-threshold to clinical insomnia & no depression" (N = 240).

All data analyses were performed using Stata version 14.0.[36] Due to the skewed distribution of the outcome variables, analyses using negative binomial models were conducted to examine the individual and combined effects of pain, insomnia, and depression on days of supply for medications after the index date. The negative binomial model was appropriate, because the count data were over-dispersed, with the conditional variance exceeding the condition mean. Months of enrollment in GHC was included as an exposure variable because the length of enrollment varied in participants. All models were adjusted for demographics and the Charlson Comorbidity Index. The magnitude of individual and combined effects was compared before and after adjusting the medication use before the index date.

Three models were examined for each medication category (a pain/insomnia model, a pain/depression model, and a pain/insomnia/depression model). In the pain/insomnia models, the

no to mild pain/no insomnia category was treated as reference. Individual effects of pain were determined by comparing the category with pain but not insomnia symptoms (moderate to severe pain & no insomnia) to the reference category, and individual effects of insomnia were determined by comparing the categories with insomnia but no pain (no to mild pain & sub-threshold to clinical insomnia) to the reference category. In the pain/depression models, the no to mild pain/no depression category was treated as reference. Individual effects of pain were determined by comparing the category with pain but no depression (moderate to severe pain & no depression) to the reference category, and individual effects of depression were determined by comparing the categories with depression but no pain (no to mild pain & sub-clinical to current depression) to the reference category.

In the combination pain/insomnia/depression models, the no to mild pain/no insomnia/no depression category was treated as reference. Individual effects of pain were determined by comparing the category with "pain but no insomnia and depression symptoms" (moderate to severe pain & no insomnia & no depression) to the reference category; individual effects of insomnia were determined by comparing the category with insomnia but no pain and no depression (no to mild pain & sub-threshold to clinical insomnia & no depression) to the reference category, and individual effects of depression were determined by comparing the category with depression but no pain and no insomnia (no to mild pain & no insomnia & sub-clinical to current depression). In this paper, results for the pain/insomnia and pain/depression models are reported in detail, and results for the pain/insomnia/depression are shown in Appendix A. Incidence rate ratios (IRRs) and 95% confidence intervals were reported; a *p* value less than .05 was considered statistically significant.

## RESULTS

Tables 2.1 and 2.2 show participant demographic characteristics and symptom severity, respectively. Participants were, on average, 72 years old (range 60 – 90, SD = 8.93) and largely Caucasian (90.86%), female (66.23%), married (60.67%), and highly educated (57.39% community college or higher). Participants reported moderate to severe pain (47.07%), at least sub-threshold insomnia (54.95%), and sub-clinical to current depression (45.23%). About 34% and 29% of participants presented at least sub-threshold insomnia and at least sub-clinical depression, respectively, in addition to concurrent moderate to severe pain. Table 2.3 describes days of supply for opioids, sedatives, TCAs, and SSRIs from Year 1 to Year 4. Participants had the highest days of supply for SSRIs among the four types of medication during the 4 years (Mean = 51.52, SD = 106.74). Days of supply for opioids and SSRIs increased steadily during the 4 years, whereas TCAs decreased and sedatives remained almost the same.

Table 2.4 and Figure 2.1 show the individual and combined effects of pain/insomnia and pain/depression severity on four types of medication use after adjusting for demographics, Charlson Comorbidity Index, months of enrollment in GHC, and corresponding medication use prior to the index date. Table 2.A1 and Figure 2.A1 in the Appendix A present similar models, but without adjusting corresponding medication use before the index date. In the results section, the analyses of the pain/insomnia models are reported first, followed by the results in the pain/depression models.

*Opioids.* In the pain/insomnia models, individual effects of pain (IRR: 1.90, 95% CI: 1.42 – 2.55) and insomnia (IRR: 1.44, 95% CI: 1.10 – 1.89) on opioid use were significant. Combined effects of pain and insomnia were significant and increased with insomnia severity. Participants

with moderate to severe pain and clinical insomnia were three times more likely to use opioids compared to the reference group (IRR: 2.96, 95% CI: 2.20 – 3.97).

In the pain/depression models, individual effects of pain showed a significant effect on opioid use (IRR: 1.91, 95% CI: 1.45 – 2.53), but depression did not individually show significant effects. Combined effects of pain and depression increased with symptom severity of depression, and participants with moderate to severe pain and current depression were most likely to use opioids (IRR: 2.89, 95% CI: 2.17 – 3.85). Individual effects of depression were significant when the prior opioid use was not adjusted (see Table 2.A1 in the Appendix).

*Sedatives.* In the pain/insomnia models, individual effects on sedative use were not significant for pain (IRR: 1.09, 95% CI: 0.68 – 1.76) but they were significant for insomnia (IRR: 2.08, 95% CI: 1.35 – 3.22). Combined effects of pain and insomnia were significant and increased with insomnia severity. Participants with moderate to severe pain and clinical insomnia were most likely to use sedatives (IRR: 2.61, 95% CI: 1.60 – 4.25).

In pain/depression models, pain did not individually contribute to sedative use (IRR: 1.08, 95% CI: 0.72 – 1.63) but depression did (IRR: 2.34, 95% CI: 1.49 – 3.65). Combined effects of pain and depression were significant only when participants presented moderate to severe pain and current depression, and these participants were most likely to use sedatives (IRR: 3.32, 95% CI: 2.06 – 5.37). Individual effects of pain were significant when the prior sedative use was not adjusted.

*TCAs.* In the pain/insomnia models, neither pain (IRR: 2.05, 95% CI: 0.90 – 4.68) nor insomnia (IRR: 2.07, 95% CI: 0.99 – 4.33) individually contributed to TCA use. However, combined effects of pain and insomnia were significant and greatly increased with severity of insomnia. Participants with moderate to severe pain and clinical insomnia were most likely to

take TCAs (IRR: 7.49, 95% CI: 3.88 – 14.42). Individual effects of pain and insomnia were significant, and their combined effects decreased without adjustment for the prior TCA use.

In the pain/depression models, individual effects were significant on TCA use for both pain (IRR: 2.75, 95% CI: 1.25 – 6.09) and depression (IRR: 2.34, 95% CI: 1.11 – 4.95). Combined effects of pain and depression were significant on TCA use and greatly increased with depression severity. Participants with moderate to severe pain and current depression were most likely to consume TCAs (IRR: 7.03, 95% CI: 3.65 – 13.51). Individual effects of pain and insomnia were non-significant on TCA use, and their combined effects greatly decreased before adjusting the prior TCA use.

*SSRIs.* In the pain/insomnia models, pain did not individually contribute to SSRI use (IRR: 1.55, 95% CI: 0.96 – 2.49) but insomnia did (IRR: 2.30, 95% CI: 1.56 – 3.40). Combined effects of pain and insomnia were smaller than the individual effect of insomnia, but still significant, and they increased with insomnia severity. Participants with moderate to severe pain and clinical insomnia were most likely to take SSRIs (IRR: 2.87, IRR: 1.92 – 4.28). Neither pain nor insomnia individually contributed to SSRI use and their combined effects decreased when the prior SSRI use was not adjusted.

In the pain/depression models, individual effects on SSRI use were significant only for depression (IRR: 3.20, 95% CI: 2.21 – 4.63). Combined effects of pain and depression were smaller than individual effects of depression, but still significant, and increased with insomnia severity. Participants with current depression only were most likely to use SSRIs (IRR: 3.20, 95% CI: 2.21 – 4.63). Individual effects of depression and combined effects of pain and depression on SSRIs use were significant but combined effects slightly increased with depression severity.

## DISCUSSION

This study used survey data and medical records to describe symptom severity of OA pain, insomnia, and depression and also to examine individual and combined effects of these symptoms on medication use in a large sample of older adults with OA. To our knowledge, this is the first attempt to examine effects of comorbid insomnia and depression jointly with pain on medication use in OA condition. About half of the participants presented with at least one of the three symptoms, and around 34% and 29% suffered from insomnia or depression, respectively, in addition to moderate to severe pain. Given the complicated and unclear associations among OA pain, insomnia, and depression, this study provides valuable information on how these variables individually and jointly contribute to medication use in an older adult population.

Our study shows that pain and insomnia individually contribute to significantly greater opioid use. Individual effects of depression on opioid use was not significant; however, depressive symptoms did increase the likelihood of taking opioids (IRR 1.91 vs. 2.89 for sub-clinical depression and current depression, respectively) when patients presented a moderate to severe level pain. Insomnia and depression showed individual effects on sedative use but pain did not. However, effects of insomnia and depression on sedative use increased when moderate to severe pain was present. These findings on combined effects of pain and depression on opioid use corroborate what was found by Edlund and colleages,[37] namely, that prescription of opioids for non-cancer pain was higher and growing faster in patients with mental health disorders than for those without the disorders. The effect magnitude of insomnia on opioids was almost equivalent to depression when patients had a moderate to severe level of pain. These findings call clinicians' attention to OA patients with comorbid insomnia and depression, as they are

more likely to use opioids, for which there is insufficient evidence on long-term efficacy and safety.[38–40]

We further observed that insomnia individually contributed to a concurrent use of opioids and sedatives. This finding is supported by research that opioids have been reported to have non-analgesic effects that could be used for treating minor sleep problems.[40] It is worth mentioning that participants with pain symptom only were two times more likely to use opioids compared to those without symptoms. According to the OA treatment guideline published in 2012, opioids are conditionally recommended in patients who had an inadequate response to initial therapy, such as acetaminophen and oral or topical nonsteroidal anti-inflammatory drugs.[43] Our study revealed the significant numbers of older adults using opioids and suggested that physicians should be sure to follow treatment guidelines due to the risk of adverse events, tolerance and addition associated with opioids.[44,45]

Substantial influences of depression on TCA and SSRI use were found in this study. Although individual effects were found only on TCA use for pain and SSRI use for insomnia, the effects of insomnia and depression on TCA use greatly increased when moderate to severe pain was present. The increased combined effects indicate that pain may interact with insomnia and depressive symptoms multiplicatively, contributing to more TCA use since combined effects were much greater than the addition of individual effects. This interactive effect seemed not to apply to SSRI use, because the combined effects of pain and insomnia or pain and depression did not change much, regardless of insomnia or depression severity, but the slight decrease of combined effects should be noted when moderate to severe pain is present with sub-threshold insomnia or sub-clinical depression. In addition, comparing the use of TCAs and SSRIs across the same symptom categories, we observed that SSRIs were preferred in participants with no to

mild pain and current depression or insomnia, but the preference seemed to switch to TCAs when moderate to severe pain was present and depression or insomnia severity increased. These findings are consistent with current literature to the effect that TCAs and SSRIs are being used to treat some chronic pain conditions, because the analgesic effects of these agents appear to be independent of their antidepressant effects and since TCAs are more efficacious in treating severe depression.[46–48] However, both TCAs and SSRIs should be used with caution as there are no data supporting the use of antidepressants for pain management in OA, especially given our findings that the likelihood of using TCAs increased greatly when pain symptoms were present.[49] It should be noted that participants with moderate to severe pain and clinical insomnia or current depression are about seven times more likely to use TCAs compared to those with no or mild pain symptoms, which could be due to the fact that TCAs are also prescribed for treating insomnia in addition to pain and depression symptoms.[50] The high likelihood of using TCAs suggests a need of monitoring their use as TCAs are associated with significant side effects in older people compared to SSRIs.[43]

This study had several limitations. First, although an experienced and trained programmer helped extract the medical records, errors in coding and recording of the medical records may still exist. Second, overall medication use was underestimated, because the medical records included only prescription medications and not over-the-counter medications or medications filled outside the GHC pharmacy system. Future studies may add a survey section asking their over-the-counter medication use. Third, we were not able to explore the influence of symptoms on use of a specific medication since our dataset did not include this information. Fourth, the dataset did not include information about patient adherence with prescription medications. In future studies we would recommend an inquiry as to adherence to medications.

In summary, our study revealed that the OA pain, comorbid insomnia, and depression are highly prevalent in older adults with OA and reinforced the complexities of medication management for these symptoms. Pain individually contributed to opioids and TCA use. Depression individually contributed to use of sedatives, TCAs, and SSRIs. Insomnia individually contributed to opioid, sedative, and SSRI use. Combined effects of these symptoms on opioid, sedative, and TCA use increased with symptom severity. Combined effects on SSRI use did not change much regardless of insomnia and depression severity. Given the significant individual and combined effects of pain, insomnia, and depression on medication use, these symptoms should be viewed jointly and adequately evaluated when prescribing medications for OA patients in clinical practice. In addition, clinicians should follow current guidelines for opioid prescriptions with OA patients, and monitor the use of opioids and TCAs in light of insufficient evidence on long-term efficacy and substantial side effect risks.

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Table 2.1 Participant demographics (N = 2,911 – 2,976)

| Variable | N | Mean | SD |
|---|---|---|---|
| Age | 2,976 | 72.16 | 8.81 |
| Months of enrollment | | | |
| Y1 | 2,976 | 12 | 0.08 |
| Y2 – Y4 | 2,976 | 34.45 | 5.66 |
| | N | Number | Percentage |
| Gender | 2,976 | | |
| Female | | 1,971 | 66.23% |
| Male | | 1,005 | 33.77% |
| Education | 2,971 | | |
| Lower than college | | 1,266 | 42.61% |
| College | | 721 | 24.27% |
| Graduate or professional | | 984 | 33.12% |
| Marital status | 2,965 | | |
| Married/living as married | | 1,799 | 60.67% |
| Single/never married | | 120 | 4.05% |
| Separated/divorced | | 477 | 16.09% |
| Widowed | | 569 | 19.19% |
| Employment | 2,911 | | |
| Employed | | 678 | 23.29% |
| Unemployed | | 436 | 14.98% |
| Retired | | 1,797 | 61.73% |
| Race | 2,922 | | |
| White | | 2,655 | 90.86% |
| Asian | | 119 | 4.07% |
| African American | | 97 | 3.32% |
| Others | | 51 | 1.75% |
| Charlson Comorbidity Index | 2,976 | | |
| = 0 | | 1,917 | 64.42% |
| ≥ 1 | | 1,059 | 35.58% |
| Months of enrollment | | | |
| Y1 | 2,976 | 12 | 0.08 |
| Y2 – Y4 | 2,976 | 34.45 | 5.66 |

Notes: SD = Standard deviation; Y = year

Table 2.2 Distribution of symptoms and participant categories (N = 2,891 – 2,959)

| Symptom/patient categories | N | Number | Percentage |
|---|---|---|---|
| Pain | 2,940 | | |
| No to mild pain | | 1,556 | 52.93% |
| Moderate to severe pain | | 1,384 | 47.07% |
| Insomnia | 2,959 | | |
| No insomnia | | 1,333 | 45.05% |
| Sub-threshold insomnia | | 1,119 | 37.82% |
| Clinical insomnia | | 507 | 17.13% |
| Depression | 2,927 | | |
| No depression | | 1,603 | 54.77% |
| Sub-clinical depression | | 711 | 24.29% |
| Current depression | | 613 | 20.94% |
| Pain & Insomnia | 2,923 | | |
| No to mild pain & no insomnia | | 931 | 31.85% |
| No to mild pain & sub-threshold insomnia | | 509 | 17.41% |
| No to mild pain & clinical insomnia | | 109 | 3.73% |
| Moderate to severe pain & no insomnia | | 383 | 13.10% |
| Moderate to severe pain & sub-threshold insomnia | | 598 | 20.46% |
| Moderate to severe pain & clinical insomnia | | 393 | 13.45% |
| Pain & Depression | 2,891 | | |
| No to mild pain & no depression | | 1,055 | 36.49% |
| No to mild pain & sub-clinical depression | | 368 | 12.73% |
| No to mild pain & current depression | | 110 | 3.80% |
| Moderate to severe pain & no depression | | 526 | 18.19% |
| Moderate to severe pain & sub-clinical depression | | 442 | 15.29% |
| Moderate to severe pain & current depression | | 390 | 13.49% |

Table 2.3 Descriptive analysis for medication use (N = 2,976)

| Medications | Year | % | Mean | Standard Deviation |
|---|---|---|---|---|
| Opioid supply (days) | 1 | 37.23% | 60.03 | 110.29 |
| | 2 | 37.37% | 63.86 | 109.42 |
| | 3 | 35.85% | 69.30 | 112.61 |
| | 4 | 35.11% | 73.30 | 121.81 |
| Sedative supply (days) | 1 | 20.56% | 78.00 | 108.60 |
| | 2 | 21.88% | 74.57 | 106.85 |
| | 3 | 21.10% | 75.81 | 105.79 |
| | 4 | 18.92% | 78.88 | 107.00 |
| Tricyclic antidepressants supply (days) | 1 | 7.56% | 188.58 | 128.47 |
| | 2 | 7.29% | 193.15 | 124.68 |
| | 3 | 6.89% | 200.14 | 128.67 |
| | 4 | 6.72% | 196.54 | 131.48 |
| Selective serotonin reuptake inhibitors (SSRIs) supply (days) | 1 | 20.50% | 242.72 | 119.91 |
| | 2 | 21.67% | 237.48 | 121.00 |
| | 3 | 21.64% | 239.57 | 119.05 |
| | 4 | 21.98% | 241.22 | 119.51 |

Table 2.4 Individual and combined effects of pain/insomnia and pain/depression on medication use (days of supply) adjusted for the use prior to the index date

| Category | Opioids<br>IRR (95% CI) | Sedatives<br>IRR (95% CI) | Tricyclic antidepressants<br>IRR (95% CI) | SSRIs<br>IRR (95% CI) |
|---|---|---|---|---|
| Pain & Insomnia [a] | | | | |
| No to mild pain & sub-threshold to clinical insomnia [b] | **1.44 (1.10 – 1.89)** | **2.08 (1.35 – 3.22)** | 2.07 (0.99 – 4.33) | **2.30 (1.56 – 3.40)** |
| Moderate to severe pain & no insomnia [c] | **1.90 (1.42 – 2.55)** | 1.09 (0.68 – 1.76) | 2.05 (0.90 – 4.68) | 1.55 (0.96 – 2.49) |
| Moderate to severe pain & sub-threshold insomnia | **2.28 (1.73 – 2.99)** | **1.89 (1.21 – 2.94)** | **3.29 (1.76 – 6.14)** | **1.61 (1.11 – 2.34)** |
| Moderate to severe pain & clinical insomnia | **2.96 (2.20 – 3.97)** | **2.61 (1.60 – 4.25)** | **7.49 (3.88 – 14.42)** | **2.87 (1.92 – 4.28)** |
| Pain & Depression [d] | | | | |
| No to mild pain & sub-clinical to current depression [e] | 1.31 (1.00 – 1.73) | **2.34 (1.49 – 3.65)** | **2.75 (1.25 – 6.09)** | **3.20 (2.21 – 4.63)** |
| Moderate to severe pain & no depression [f] | **1.91 (1.45 – 2.53)** | 1.08 (0.72 – 1.63) | **2.34 (1.11 – 4.95)** | 1.28 (0.86 – 1.90) |
| Moderate to severe pain & sub-clinical depression | **1.98 (1.49 – 2.64)** | 1.49 (0.98 – 2.27) | **5.66 (2.96 – 10.82)** | **2.70 (1.82 – 4.00)** |
| Moderate to severe pain & current depression | **2.89 (2.17 – 3.85)** | **3.32 (2.06 – 5.37)** | **7.03 (3.65 – 13.51)** | **3.05 (2.07 – 4.49)** |

a. Reference group is “No pain & no insomnia”.

b. Individual effects of insomnia;

c. individual effects of pain in pain/insomnia model.

d. Reference group is “No pain & no depression”.

e. Individual effects of depression;

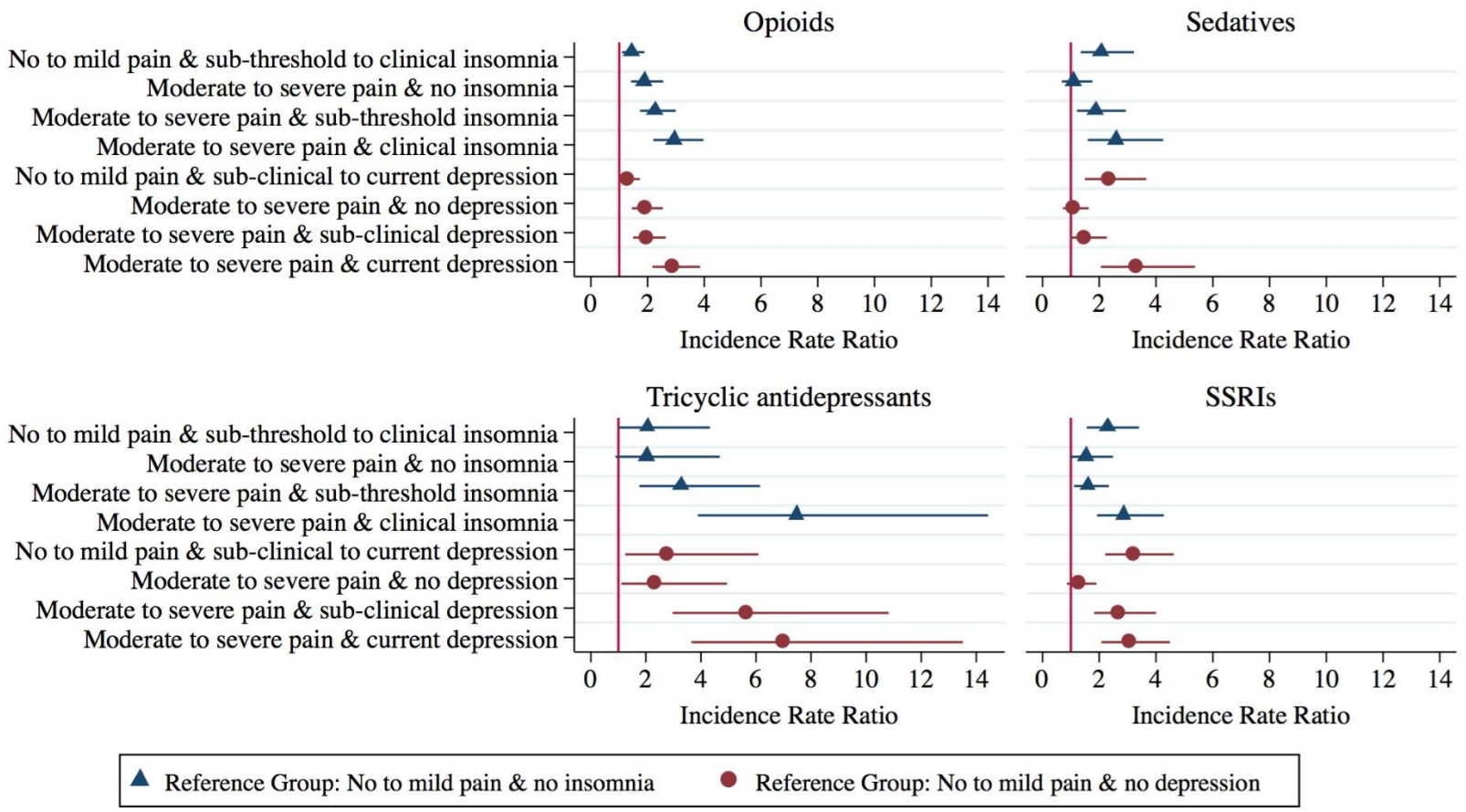
f. individual effects of pain in pain/depression model.

IRR: incidence rate ratio; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors.

Incidence rate ratios and confidence intervals that are significant are in bold.

Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 2.1 Individual and combined effects of pain/insomnia and pain/depression on medication use (days of supply) adjusted for the use prior to the index date*




*Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health. SSRIs: selective serotonin reuptake inhibitors.

# APPENDIX A

Table 2.A1 Individual and combined effects of pain/insomnia and pain/depression on medication use (days of supply) without adjustment for the use prior to the index date

| Category | Opioids<br>IRR (95% CI) | Sedatives<br>IRR (95% CI) | Tricyclic antidepressants<br>IRR (95% CI) | SSRIs<br>IRR (95% CI) |
|---|---|---|---|---|
| Pain & Insomnia [a] | | | | |
| No to mild pain & sub-threshold to clinical insomnia [b] | **1.96 (1.43 – 2.71)** | **3.18 (2.14 – 4.72)** | **2.05 (1.16 – 3.61)** | 1.08 (0.83 – 1.41) |
| Moderate to severe pain & no insomnia [c] | **3.47 (2.46 – 4.88)** | 1.70 (1.00 – 2.91) | **2.05 (1.11 – 3.81)** | 1.08 (0.81 – 1.45) |
| Moderate to severe pain & sub-threshold insomnia | **5.02 (3.70 – 6.83)** | **2.95 (1.94 – 4.50)** | **2.48 (1.48 – 4.17)** | **1.37 (1.07 – 1.75)** |
| Moderate to severe pain & clinical insomnia | **6.62 (4.86 – 9.03)** | **4.23 (2.75 – 6.52)** | **4.69 (2.71 – 8.12)** | **1.80 (1.39 – 2.32)** |
| Pain & Depression [d] | | | | |
| No to mild pain & sub-clinical to current depression [e] | **1.55 (1.10 – 2.18)** | **3.05 (2.09 – 4.43)** | 1.08 (0.62 – 1.90) | **2.18 (1.68 – 2.82)** |
| Moderate to severe pain & no depression [f] | **2.81 (2.05 – 3.84)** | **1.68 (1.10 – 2.59)** | 1.43 (0.80 – 2.57) | 0.99 (0.73 – 1.34) |
| Moderate to severe pain & sub-clinical depression | **3.45 (2.47 – 4.82)** | **2.24 (1.49 – 3.37)** | **1.82 (1.01 – 3.26)** | **2.29 (1.78 – 2.95)** |
| Moderate to severe pain & current depression | **7.52 (5.58 – 10.13)** | **4.16 (2.83 – 6.12)** | **3.88 (2.43 – 6.21)** | **2.72 (2.12 – 3.49)** |

a. Reference group is "No pain & no insomnia".

b. Individual effects of insomnia; c. individual effects of pain in pain/insomnia model.

d. Reference group is "No pain & no depression".

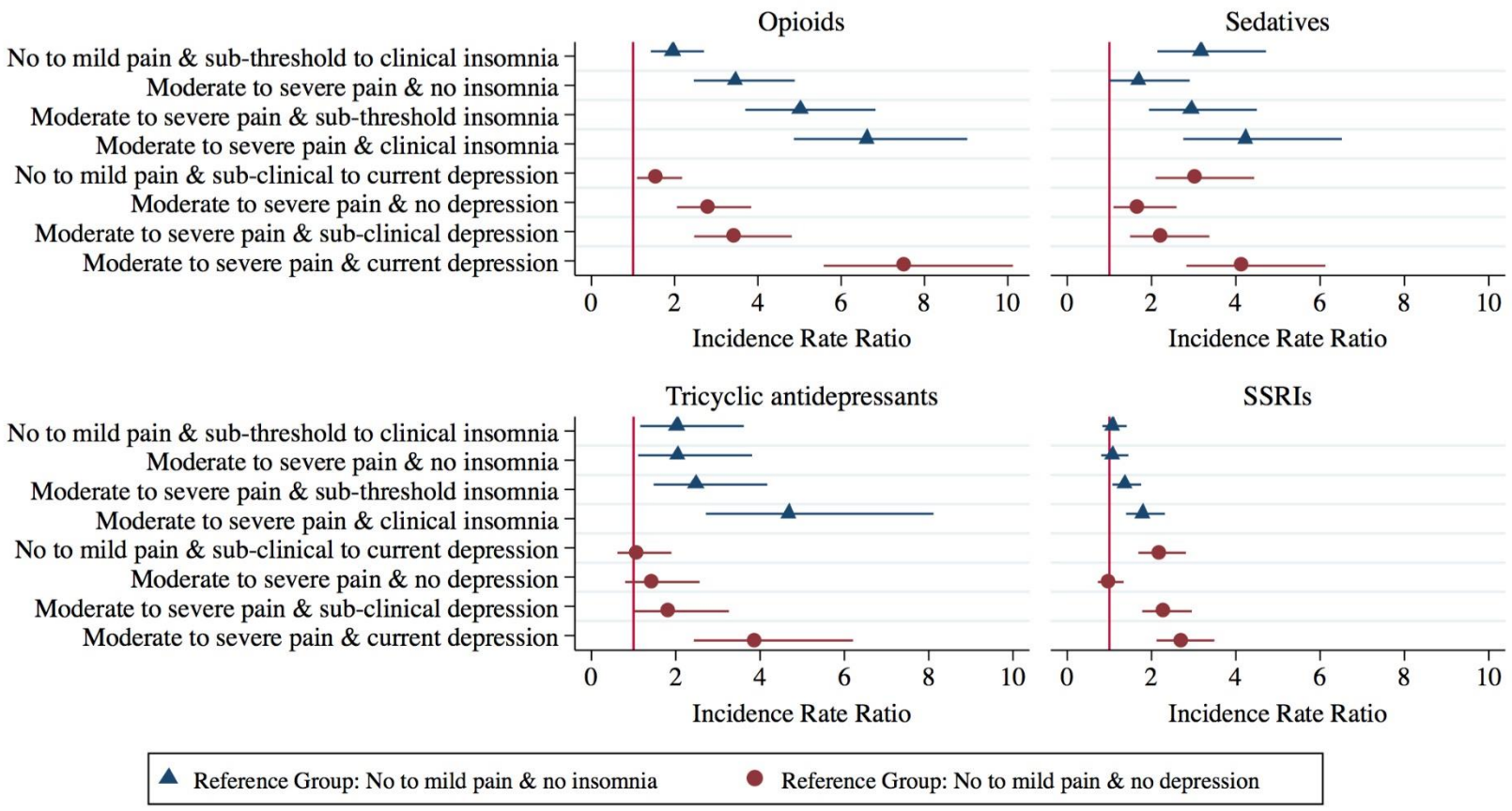
e. Individual effects of depression; f. individual effects of pain in pain/depression model.

IRR: incidence rate ratio; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors.

Incidence rate ratios and confidence intervals that are significant are in bold.

Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 2.A1 Individual and combined effects of pain/insomnia and pain/depression on medication use (days of supply) without adjustment for the use prior to the index date*




*Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health. SSRIs: selective serotonin reuptake inhibitors.

Table 2.A2 Distribution of participant categories by three symptoms (N = 2,883)

| Participant category | Number | Percentage |
|---|---|---|
| No to mild pain & no insomnia & no depression | 805 | 27.92% |
| No to mild pain & sub-threshold to clinical insomnia & no depression | 246 | 8.53% |
| No to mild pain & no insomnia & sub-clinical to current depression | 113 | 3.92% |
| Moderate to severe pain & no insomnia & no depression | 297 | 10.30% |
| No to mild pain & sub-threshold insomnia & sub-clinical depression | 211 | 7.32% |
| No to mild pain & clinical insomnia & sub-clinical depression | 53 | 1.84% |
| No to mild pain & sub-threshold insomnia & current depression | 53 | 1.84% |
| No to mild pain & clinical insomnia & current depression | 47 | 1.63% |
| Moderate to severe pain & sub-threshold to clinical insomnia & no depression | 227 | 7.87% |
| Moderate to severe pain & no insomnia & sub-clinical depression | 70 | 2.43% |
| Moderate to severe pain & sub-threshold insomnia & sub-clinical depression | 250 | 8.67% |
| Moderate to severe pain & clinical insomnia & sub-clinical depression | 122 | 4.23% |
| Moderate to severe pain & no insomnia to sub-threshold insomnia & current depression | 147 | 5.10% |
| Moderate to severe pain & clinical insomnia & current depression | 242 | 8.39% |

Table 2.A3 Individual and combined effects of pain, insomnia and depression on medication use (days of supply) adjusted for the use prior to the index date

| Category [a] | Opioids IRR (95% CI) | Sedatives IRR (95% CI) | Tricyclic antidepressants IRR (95% CI) | SSRIs IRR (95% CI) |
|---|---|---|---|---|
| No to mild pain & sub-threshold to clinical insomnia & no depression | 1.24 (0.82 – 1.87) | 1.75 (1.00 – 3.07) | 1.22 (0.50 – 2.95) | **1.95 (1.02 – 3.75)** |
| No to mild pain & no insomnia & sub-clinical to current depression | 0.84 (0.54 – 1.32) | 2.41 (0.93 – 6.28) | 2.30 (0.77 – 6.88) | **3.77 (1.96 – 7.23)** |
| Moderate to severe pain & no insomnia & no depression | **1.84 (1.32 – 2.57)** | 1.20 (0.58 – 2.49) | 1.51 (0.60 – 3.82) | 1.33 (0.74 – 2.37) |
| No to mild pain & sub-threshold insomnia & sub-clinical depression | **1.61 (1.12 – 2.32)** | **2.26 (1.17 – 4.36)** | **4.36 (1.46 – 13.02)** | **2.81 (1.59 – 4.96)** |
| No to mild pain & clinical insomnia & sub-clinical depression | 1.26 (0.57 – 2.76) | **3.85 (1.45 – 10.18)** | 0.71 (0.16 – 3.07) | **2.95 (1.36 – 6.37)** |
| No to mild pain & sub-threshold insomnia & current depression | 1.78 (0.96 – 3.31) | 2.03 (0.80 – 5.20) | 4.46 (0.83 – 23.99) | **5.16 (2.11 – 12.64)** |
| No to mild pain & clinical insomnia & current depression | 1.43 (0.58 – 3.57) | **3.10 (1.38 – 6.98)** | 0.35 (0.09 – 1.44) | **6.60 (3.05 – 14.26)** |
| Moderate to severe pain & sub-threshold to clinical insomnia & no depression | **2.18 (1.46 – 3.25)** | 1.38 (0.74 – 2.58) | **3.14 (1.14 – 8.67)** | 1.41 (0.84 – 2.37) |
| Moderate to severe pain & no insomnia & sub-clinical depression | **1.95 (1.18 – 3.20)** | 0.90 (0.30 – 2.70) | 0.72 (0.18 – 2.94) | **3.62 (1.54 – 8.51)** |
| Moderate to severe pain & sub-threshold insomnia & sub-clinical depression | **2.10 (1.45 – 3.05)** | **1.73 (1.01 – 2.95)** | **4.84 (2.10 – 11.17)** | **2.52 (1.49 – 4.25)** |
| Moderate to severe pain & clinical insomnia & sub-clinical depression | **2.14 (1.27 – 3.60)** | **2.02 (1.00 – 4.07)** | **12.59 (4.70 – 33.70)** | **3.95 (2.11 – 7.37)** |
| Moderate to severe pain & no insomnia to sub-threshold insomnia & current depression | **2.61 (1.77 – 3.84)** | **4.41 (2.15 – 9.06)** | **6.55 (2.23 – 19.24)** | **2.72 (1.45 – 5.09)** |
| Moderate to severe pain & clinical insomnia & current depression | **3.07 (2.17 – 4.35)** | **3.74 (1.96 – 7.13)** | **7.96 (3.51 – 18.07)** | **3.76 (2.33 – 6.05)** |

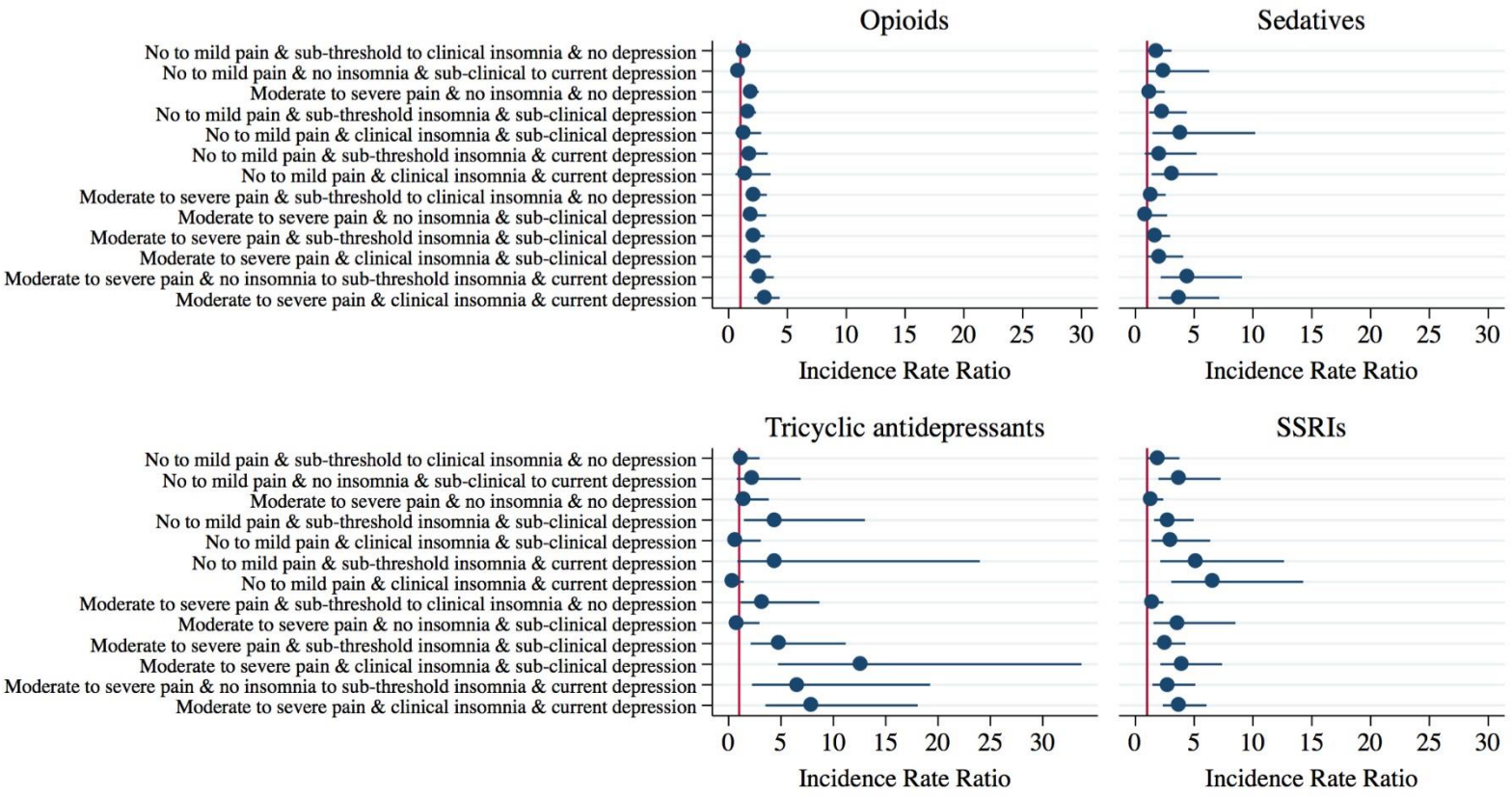
a. Reference group is "No pain & no insomnia & no depression".

IRR: incidence rate ratio; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors.

Incidence rate ratios and confidence intervals that are significant are in bold.

Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 2.A2 Individual and combined effects of pain, insomnia and depression on medication use (days of supply) adjusted for the use prior to the index date*




*1) Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health; 2) SSRIs: selective serotonin reuptake inhibitors; and 3) Reference group is "No pain & no insomnia & no depression".

Table 2.A4 Individual and combined effects of pain, insomnia and depression on medication use (days of supply) without adjustment for the use prior to the index date

| Category [a] | Opioids IRR (95% CI) | Sedatives IRR (95% CI) | Tricyclic antidepressants IRR (95% CI) | SSRIs IRR (95% CI) |
|---|---|---|---|---|
| No to mild pain & sub-threshold to clinical insomnia & no depression | **1.76 (1.11 – 2.79)** | **2.41 (1.40 – 4.15)** | **2.33 (1.12 – 4.83)** | 0.95 (0.60 – 1.49) |
| No to mild pain & no insomnia & sub-clinical to current depression | 1.00 (0.56 – 1.77) | 2.29 (0.97 – 5.41) | 0.77 (0.28 – 2.13) | **3.41 (2.29 – 5.06)** |
| Moderate to severe pain & no insomnia & no depression | **2.98 (2.04 – 4.36)** | 1.56 (0.84 – 2.90) | 1.41 (0.64 – 3.10) | 0.88 (0.57 – 1.36) |
| No to mild pain & sub-threshold insomnia & sub-clinical depression | **2.39 (1.54 – 3.72)** | **4.12 (2.44 – 6.95)** | 1.23 (0.56 – 2.71) | 1.46 (0.99 – 2.15) |
| No to mild pain & clinical insomnia & sub-clinical depression | 1.15 (0.54 – 2.43) | **5.84 (2.73 – 12.49)** | 1.42 (0.30 – 6.60) | 1.14 (0.52 – 2.53) |
| No to mild pain & sub-threshold insomnia & current depression | 1.83 (0.85 – 3.97) | 2.25 (0.96 – 5.25) | **4.20 (1.23 – 14.31)** | **2.72 (1.75 – 4.24)** |
| No to mild pain & clinical insomnia & current depression | 1.98 (0.77 – 5.07) | **6.22 (3.07 – 12.59)** | 0.98 (0.20 – 4.77) | **2.27 (1.38 – 3.74)** |
| Moderate to severe pain & sub-threshold to clinical insomnia & no depression | **3.53 (2.36 – 5.28)** | **3.16 (1.75 – 5.69)** | 1.80 (0.85 – 3.82) | 1.08 (0.70 – 1.67) |
| Moderate to severe pain & no insomnia & sub-clinical depression | **4.38 (2.37 – 8.06)** | 0.87 (0.31 – 2.41) | 2.71 (0.66 – 11.12) | **3.22 (2.16 – 4.81)** |
| Moderate to severe pain & sub-threshold insomnia & sub-clinical depression | **4.19 (2.75 – 6.39)** | **2.51 (1.46 – 4.33)** | **2.36 (1.20 – 4.63)** | **2.06 (1.49 – 2.84)** |
| Moderate to severe pain & clinical insomnia & sub-clinical depression | **3.31 (2.04 – 5.37)** | **4.63 (2.58 – 8.30)** | 2.00 (0.65 – 6.13) | **2.10 (1.41 – 3.13)** |
| Moderate to severe pain & no insomnia to sub-threshold insomnia & current depression | **8.11 (5.16 – 12.75)** | **6.24 (3.68 – 10.58)** | **4.28 (2.06 – 8.90)** | **2.48 (1.78 – 3.46)** |
| Moderate to severe pain & clinical insomnia & current depression | **9.17 (6.54 – 12.86)** | **5.10 (3.12 – 8.36)** | **5.89 (3.21 – 10.79)** | **2.76 (2.02 – 3.77)** |

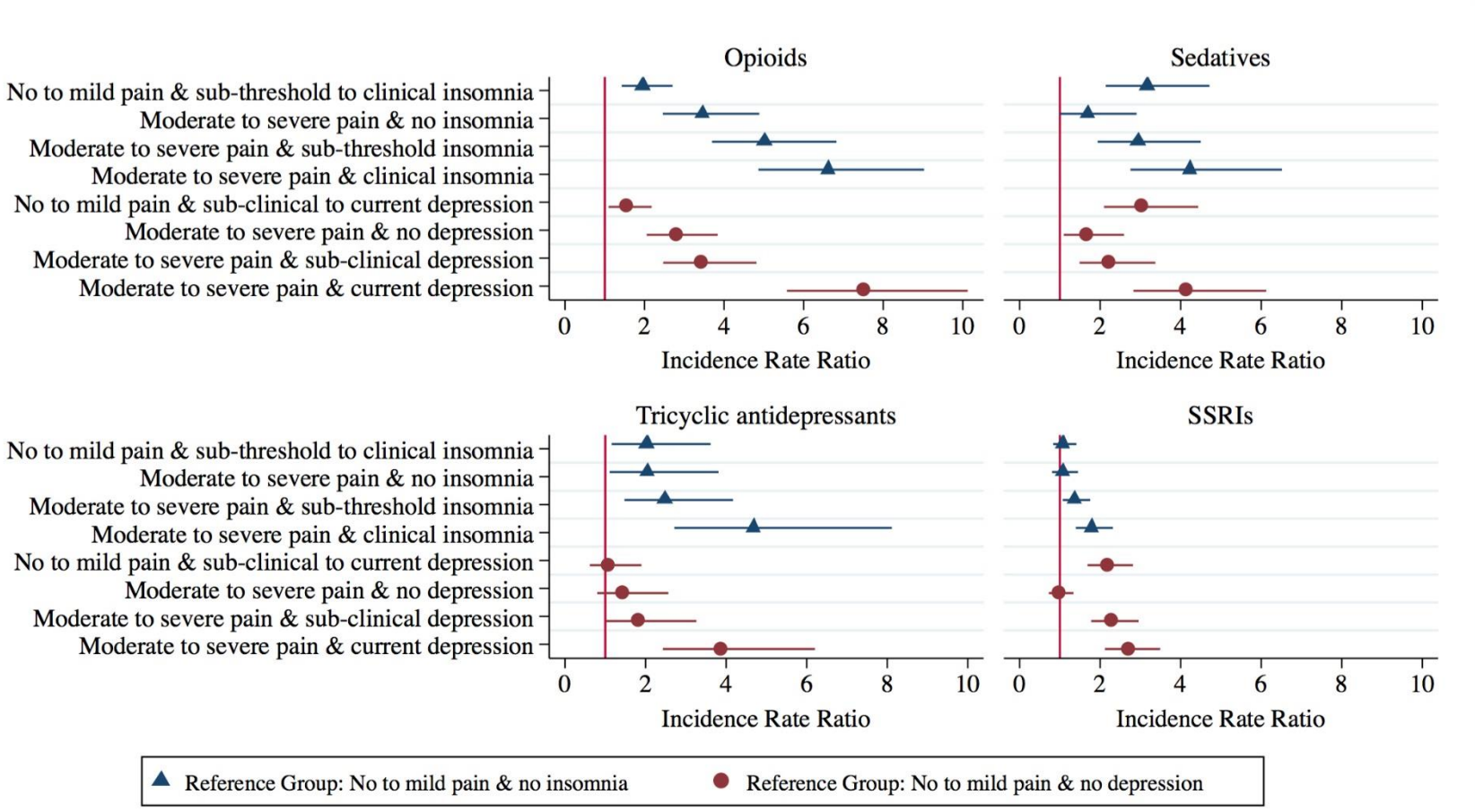
a. Reference group is "No pain & no insomnia & no depression".

IRR: incidence rate ratio; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors.

Incidence rate ratios and confidence intervals that are significant are in bold.

Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 2.A3 Individual and combined effects of pain, insomnia and depression on medication use (days of supply) without adjustment for the use prior to the index date*




*1) Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health; 2) SSRIs: selective serotonin reuptake inhibitors; and 3) Reference group is "No pain & no insomnia & no depression".

# Chapter 3. Influences of Osteoarthritis Pain, Insomnia, and Depression on Health Care Utilization in Older Adults with Osteoarthritis

## ABSTRACT

### Objective

a) To describe the prevalence of pain and comorbid insomnia and depression in older adults with osteoarthritis (OA), and b) To examine individual and combined effects of pain, insomnia, and depression on health care utilization (HCU).

### Methods

Participants were Group Health Cooperative (GHC) patients with a primary diagnosis of OA (N = 2,976). We used survey data on pain (Graded Chronic Pain Scale), insomnia (Insomnia Severity Index), depression (Patient Health Questionnaire-8), and HCU extracted from GHC medical records (office visits, length of stay [LOS], inpatient and outpatient costs, and hip/knee replacement). Negative binomial, logistic, and generalized linear models were performed for data analysis.

### Results

About 34% and 29% of participants presented at least sub-threshold insomnia and at least sub-clinical depression, respectively, in addition to concurrent moderate to severe pain. Individual effects of pain were statistically significant on all types of the examined HCU. Insomnia and depression individually only contributed to number of office visits and outpatient costs. Combined effects of pain/insomnia, and pain/depression were significant on all types of HCU, and effect on all types of HCU except for hip/knee replacement increased with insomnia/depression severity.

### Conclusion

Effects of pain on health care utilization in OA are significant and cost-effective strategies are needed for better pain management to reduce OA-related health care burden.

Significant combined effects of pain/insomnia, and pain/depression suggest the importance of addressing insomnia and depression as part of the routine assessment for OA and working collaboratively between specialists for improved symptom management in clinical practice.

## SIGNIFICANCE AND INNOVATIONS

1. Our findings reveal high prevalence of comorbid insomnia and depression in addition to OA pain and underscore a great impact of pain on health care utilization in OA.
2. Our study is the first attempt to examine the combined effects of pain with comorbid insomnia and depression in persons with OA. Study results suggest that insomnia and depression cannot be neglected in OA and clinicians should work collaboratively to better manage these symptoms in order to reduce OA-related healthcare burden.

## INTRODUCTION

OA is a debilitating disease characterized by chronic pain, joint inflammation and stiffness, and accounts for a large percentage of physical disability with a high prevalence worldwide.[1] The number of OA patients is expected to increase in the coming years in many countries, as life expectancy is also increasing and OA differentially affects older adults.[2] Nevertheless, the burden of OA not only relates to its major impact on lowering quality of life[3] but also to the heavy economic costs of the disease to individuals and health care systems.[4–10] Mean total costs were more than two times higher in patients with OA compared to those without the condition ($12,905 vs. $5,099).[11] OA patients incur significantly higher annual inpatient costs ($6,668 vs. $1,756) and outpatient costs ($7,840 vs. $3,675) compared with controls.[9] In addition, patients with knee OA were found to have, on average, 6 more annual physician office visits and 3.8 more non-physician visits than OA-free controls.[12] Total hip or knee replacements are costly and the use rates have increased steadily over the years, which is associated with the increasing costs of a hospitalization.[13,14]

Chronic pain is the main complaint of patients with OA and the primary reason to seek help from health care providers.[15] Besides pain, patients with OA often live with comorbidities, most notably insomnia and depression.[16] An increasing body of research has documented reciprocal relationships among chronic pain, sleep disturbance, and depression in OA, and yet causal relationships are still not clear.[17,18] Regardless of causality, the increased presence of comorbid conditions among patients not only adds to the cost of treatment but also increases the complexity of managing these patients. Given the substantial OA-associated health care burden and the complex associations among OA pain, insomnia and depression, it is important to understand the prevalence of these symptoms and understand how pain, insomnia, and

depression individually and jointly drive health care utilization (HCU) and cost burden to the health care system in the OA population.

Therefore, this study aims to a) describe the prevalence of pain and comorbid insomnia and depression in older adults with OA, and b) examine individual and combined effects of pain, insomnia, and depression on HCU.

## PARTICIPANTS AND METHODS

### *Participants*

The dataset used in this study was from part of a National Institutes of Health (NIH)-funded clinical trial that compared the efficacy of three group interventions for people with comorbid OA and insomnia to help them manage their pain and insomnia symptoms.[19] The study was carried out collaboratively between the University of Washington (UW) and Group Health Cooperative (GHC) (recently changed to Kaiser Permanente Washington), a Seattle-area integrated health care plan with over 600,000 enrollees. Prior to the clinical trial, from 2008 to 2010, a screening survey questionnaire was mailed to 8,057 GHC members age 60+ who had an electronic medical record OA diagnosis associated with a health care visit in the prior 3 years. The questionnaire asked respondents about the frequency and interference level of their OA pain over the previous 3 months, and the frequency and nature of their sleep problems. A total of 3,041 participants completed the screening questionnaire and gave permission to access their medical records. This study used data from the screening survey and participants' GHC medical records. The clinical trial was approved by the UW Human Subjects Division and the GHC Institutional Review Board. This secondary data analysis was reviewed by the UW Human Subjects Division and qualified for an exemption.

Inclusion criteria for receiving the screening survey were: age 60+, continuously enrolled in GHC 1 year prior to the screening, receiving primary care services at one of six regional participating clinics, not in the "No Contact for Research File," and at least one visit noted in medical record for OA in the prior 3 years. Participants were excluded if the medical record information indicated a diagnosis of: (a) rheumatoid arthritis, (b) obstructive sleep apnea, (c) periodic leg movement disorder, (d) restless leg syndrome, (e) sleep-wake cycle disturbance, (f) rapid eye movement (REM) behavior disorder, (g) dementia or receiving cholinesterase inhibitors, (h) Parkinson's disease or another neurodegenerative disease known to directly impact sleep, (i) cancer in the past year and receiving chemotherapy or radiation therapy in the past year, and/or (j) inpatient treatment for congestive heart failure within the previous 6 months.

*Dataset Elements*

Symptom measures:

*Pain*. The Graded Chronic Pain Scale (GCPS) assesses two dimensions of overall chronic pain severity: pain intensity and pain-related disability.[20] Subscale scores for pain intensity and disability are combined to calculate a chronic pain grade with five hierarchical categories, with grade 0 meaning no pain and grade IV meaning high disability-severely limiting pain.[21] Internal consistency of the GCPS has been reported to be 0.74 (Cronbach's alpha) for patients with chronic back pain.[20] The GCPS also has a high test-retest reliability and construct validity.[22,23] For this study, pain was coded as a binary variable: no to mild pain (GCPS = 1) and moderate to severe pain (2 to 4).

*Insomnia*. The Insomnia Severity Index (ISI) was designed to assess the nature, severity, and impact of insomnia and monitor treatment response in adults.[24] The ISI is a seven-item measure with scores ranging from 0 to 28, with a higher score indicating more severe insomnia

and a score ≥ 15 indicating moderate to severe clinical insomnia. ISI internal consistency is excellent for both the community and clinical samples (Cronbach's alpha of 0.90 and 0.91, respectively).[25] Convergent validity is supported by significant correlations between total ISI score and measures of fatigue, quality of life, anxiety and depression.[25] Research indicates that the ISI is a reliable and valid instrument to detect cases of insomnia and is sensitive to treatment response in clinical patients.[26] For this study, the insomnia variable was coded according to validated cut-points for this scale which were: no insomnia (≤ 7), sub-threshold insomnia (8 to 14) and clinical insomnia (15 to 28).[27]

*Depression*. The eight-item Patient Health Questionnaire depression scale (PHQ-8) has been shown to be a valid diagnostic and severity measure for depressive disorders in large clinical trials. PHQ-8 total scores range from 0 to 24, with higher scores representing more severe depression. The PHQ-8 is a reliable measure for depression in population-based studies, and a cut point ≥ 10 can be used for determining current depression.[28] The depression variable was coded according to validated cut-points for this scale as follows: no depression (≤ 4), sub-clinical depression (5 to 9) and current depression (10 to 24).[29]

Health Care Utilization

A programmer at GHC used CPT codes to identity relevant HCU variables from participants' electronic medical records. An index date was defined as the date when the screening questionnaire was mailed to the participant. Medical records of one year before (Year 1) and three years after (Year 2 – 4) were used. HCU variables include: 1) Health care visits: total numbers of health care visits overall; 2) Total length of stay (LOS) (days); 3) Surgical procedures: a) knee replacement (CPT codes: 27445-27447; ICD-9 procedure codes 2010: 81.54 – 81.56) and b) hip replacement (CPT codes: 27125, 27130, 27132; ICD-9 procedure codes

2010: 81.51 – 81.53); and 4) Health care costs: overall costs in US dollars for inpatient and outpatient utilization, separately.

Participant characteristics

Demographics were collected from the screening survey, including age, sex, race, marital status, employment status and educational levels. Variables of age and sex were verified from the medical records and replaced if participants did not report their age or sex. Months of enrollment in GHC for each of the four years and Charlson Comorbidity Index scores were calculated from participants' medical records by the programmer at the GHC.

*Data Analysis*

Participants with no enrollment in GHC after the index date were excluded (N = 6) which left a sample of 3,035. Participants with missing data on more than two of the following variables were excluded: pain (39 (1.3%)), insomnia (20 (0.7%)), depression (107 (3.5%)), education (62 (2.0%)), marital status (67 (2.2%)), race (110 (3.6%)) and employment (122 (4.0%)) with a final sample of 2,976 participants included in the final analysis. Multiple imputation technique was used with five imputations to accommodate the remaining missing information in the statistical analyses.[30] Demographics, symptoms of pain, insomnia and depression, months of enrollment, Charlson Comorbidity Index, and corresponding HCU variables were used in the imputation models.

Data analyses investigated the individual effects of pain, insomnia and depression, and combined effects of (a) pain and insomnia and (b) pain and depression on HCU. Combined effects focused on pairing the other two symptoms with pain, given that pain is the main complaint in older adults with OA. The combined effects of insomnia and depression were not examined because of the high correlation between the two symptoms in this sample (Pearson

correlation coefficient was 0.73). Two categorical patient variables were created based on the combination of symptom severities, with one variable representing the severity of pain and insomnia, and the other representing the severity of pain and depression. Although insomnia and depression are highly correlated, few studies have examined pain, insomnia and depression all together in OA populations. A third categorical variable was created based on the combination of the severities of the three symptoms. Categories with fewer than 20 participants were combined with other categories based on clinical justification. For example, the category "No to mild pain & clinical insomnia & no depression" (N = 6) was combined with the category "No to mild pain & sub-threshold to clinical insomnia & no depression" (N = 240).

All data analyses were performed using Stata version 14.0.[31] Due to the skewed distribution of the outcome variables, analyses using negative binomial models were conducted to examine the individual and combined effects of pain, insomnia, and depression on office visits and hospital LOS after the index date. The negative binomial model was appropriate because the count data was over-dispersed with the conditional variance exceeding the condition mean. Logistic regression was conducted to investigate the individual and combined effects of the three symptoms on whether participants had a hip/knee replacement or not. Generalized linear models with a gamma family and log-link function were used to assess the individual and combined effects of the three symptoms on outpatient and inpatient costs. Months of enrollment in GHC were included as an exposure variable because the length of enrollment was different in participants. All models were adjusted for demographics and Charlson Comorbidity Index. The magnitude of individual and combined effects was compared before and after adjusting the use before the index date.

Three models were examined for each HCU category (a pain/insomnia model, a pain/depression model and pain/insomnia/depression model). In the pain/insomnia models, the no to mild pain/no insomnia category was treated as reference. Individual effects of pain were determined by comparing the category with pain but not insomnia symptoms (moderate to severe pain & no insomnia) to the reference category, and individual effects of insomnia were determined by comparing the categories with insomnia but no pain (no to mild pain & sub-threshold to clinical insomnia) to the reference category. In the pain/depression models, the no to mild pain/no depression category was treated as reference. Individual effects of pain were determined by comparing the category with pain but no depression (moderate to severe pain & no depression) to the reference category, and individual effects of depression were determined by comparing the categories with depression but no pain (no to mild pain & sub-clinical to current depression) to the reference category.

In the combination pain/insomnia/depression models, the no to mild pain/no insomnia/no depression category was treated as reference. Individual effects of pain were determined by comparing the category with "pain but no insomnia and depression symptoms" (moderate to severe pain & no insomnia & no depression) to the reference category; individual effects of insomnia were determined by comparing the category with insomnia but no pain and no depression (no to mild pain & sub-threshold to clinical insomnia & no depression) to the reference category, and individual effects of depression were determined by comparing the category with depression but no pain and no insomnia (no to mild pain & no insomnia & sub-clinical to current depression). In this paper, results for the pain/insomnia and pain/depression models are reported in detail, and results for the pain/insomnia/depression are shown in

Appendix A. Incidence rate ratio (IRR), odds ratio (OR), and coefficient plus 95% confidence interval (CI) are reported; a *p* value less than .05 was considered statistically significant.

**RESULTS**

Table 3.1 and Table 3.2 present participant demographical characteristics and symptom severity, respectively. Participants were, on average, 72 years old (range 60 – 90, SD = 8.93), largely Caucasian (90.86%), female (66.23%), married (60.67%) and highly educated (57.39% community college or higher). Participants reported moderate to severe pain (47.07%), at least sub-threshold insomnia (54.95%), and sub-clinical to current depression (45.23%). About 34% of participants had concurrent moderate to severe pain and at least sub-threshold insomnia, and 29% of participants presented concurrent moderate to severe pain and at least sub-clinical depression. Table 3.3 shows that the percentage of participants with no and more than 24 office visits per year steadily increased over the 4 years. Similar to office visits, the percentage of participants with no outpatient costs or costs between $20,000 and $30,000 per year went up steadily after the index date. About 90% did not have a hospital stay, but this percentage decreased over the years and the inpatient costs had a similar trend with the hospital stay. About 4% of the participants had a hip/knee replacement and the percentage decreased after the index date.

Table 3.4, Figure 3.1 and Figure 3.2 show the individual and combined effects of pain, insomnia, and depression severity on office visits, hospital LOS, outpatient and inpatient costs, and hip/knee replacement after adjusting for demographics, Charlson Comorbidity Index, months of enrollment in GHC, and corresponding use prior to the index date. In the results section, the

analyses of the pain/insomnia models are reported first, followed by the results of the pain/depression models.

*Office visits.* In the pain/insomnia models, individual effects of pain (IRR: 1.11, 95% CI: 1.04 – 1.18) and insomnia (IRR: 1.15, 95% CI: 1.06 – 1.25) were significant. Combined effects of pain and insomnia were significant and slightly higher than the individual effects but combined effects did not increase with insomnia severity. In the pain/depression models, individual effects of pain (IRR: 1.10, 95% CI: 1.03 – 1.18) and depression (IRR: 1.16, 95% CI: 1.09 – 1.24) were significant. Combined effects of pain and depression were significant and slightly higher than the individual effects, and combined effects were similar between different depression severities.

*LOS.* Neither individual effects of insomnia nor depression were significant on LOS. Individual effects of pain were significant and similar in either the pain/insomnia (IRR: 1.89, 95% CI: 1.38 – 2.58) or the pain/depression models (IRR: 1.77, 95% CI: 1.32 – 2.37). Combined effects of pain and insomnia were significant and effects increased slightly with insomnia severity. Combined effects of pain and depression were significant and LOS was two times longer in participants with current depression (IRR: 2.61, 95% CI: 1.91 – 3.58) compared to those with no depression (IRR: 1.77, 95% CI: 1.32 – 2.37) when moderate to severe pain was present.

*Outpatient costs.* Individual effects of insomnia (IRR: 1.13, 95% CI: 1.03 – 1.24) and depression (IRR: 1.18, 95% CI: 1.07 – 1.30) were significant. Individual effects of pain were significant in either the pain/insomnia and pain/depression models. Combined effects of pain and insomnia, and combined effects of pain and depression were significant and effects increased with insomnia or depression severity.

*Inpatient costs.* Neither insomnia nor depression individually increased inpatient costs. Individual effects of pain almost doubled inpatient costs in the pain/insomnia (IRR: 2.06, 95% CI: 1.49 – 2.84) and the pain/depression models (IRR: 1.74, 95% CI: 1.32 – 2.30) compared to reference groups. Combined effects of pain and insomnia, and combined effects of pain and depression were significant but did not change much with insomnia or depression severity.

*Hip/knee replacement.* Insomnia and depression did not individually predict hip or knee replacement. Compared to reference groups, participants with the pain symptom only were about two times more likely to receive a hip or knee replacement in either the pain/insomnia models (OR: 2.33, 95% CI: 1.60 – 3.38) and the pain/depression models (OR: 2.05, 95% CI: 1.47 – 2.87) compared to reference groups. Combined effects of pain and insomnia and combined effects of pain and depression did not change with insomnia or depression severity.

Table 3.A1, Figure 3.A1 and Figure 3.A2 show results from similar models for the individual and combined effects of pain, insomnia, and depression severity but without adjustment of corresponding use prior to the index date. Regardless the significance level or the magnitude of the individual and combined effects, they were similar to those with adjustment.

## DISCUSSION

Our study used data from surveys and electronic medical records to examine how pain, insomnia, and depression individually and jointly influence HCU, specifically total office visits, hospital LOS, health care costs, and hip/knee replacement. About half the participants presented with at least one of the three symptoms (depression, insomnia, pain) and around 34% and 29% suffered from insomnia or depression, respectively, in addition to moderate to severe pain. To

our knowledge, it is the first attempt to evaluate the effects of pain considering comorbid conditions including insomnia and depression on HCU in older adults with OA.

This study revealed that pain is the major condition that individually drives HCU in older adult with OA. Participants with pain only were about two times more likely to have inpatient-related health care services, including hospital LOS (IRR: 1.91, 95% CI: 1.39 – 2.61), inpatient costs (coefficient: 2.06, 95% CI: 1.51 – 2.82) and hip/knee replacement (OR: 2.31, 95% CI: 1.59 – 3.35) compared to those without pain or insomnia. Total hip/knee replacement is the most effective intervention for pain relief and functional improvement when pain cannot be well managed in the later stage of OA.[32] Total hip/knee replacement has increased in the past two decades and makes up the largest hospital expenditure category for Medicare.[33,34] Pain was positively associated with number of hip/knee replacements, which also explains the likelihood of having longer LOS and higher inpatient costs. However, individual effects of pain were smaller on outpatient-related health care (office visits and outpatient costs). For example, participants with pain symptom only were 1.23 to 1.25 times more likely to have office visits compared to those without any of the three symptoms. Despite this finding, the significant effect of pain on health care services as a whole suggests an urgent need to manage OA pain symptoms in order to reduce OA-associated health care burden.

Insomnia and depression as comorbid conditions individually contributed to total office visits and outpatient costs but not inpatient-related health care services. The finding of higher office visits and outpatient costs associated with insomnia and depression is consistent with previous studies showing that insomnia and depression contribute to increased health care consultations and related costs.[35] In terms of individual effects of insomnia and depression on LOS and inpatient costs, previous studies have shown inconsistent results, which could be due to

different symptom measure/cut-off points and the fact that depression was often viewed as comorbid with other disease conditions.[36–38] Our study provides reliable insights into the condition of persons with OA and uses measures and cut-off points that are widely applied in literature to enhance comparability with future research.

Our study also examined combined effects of pain/insomnia and pain/depression, which has been rarely reported previously, relative to OA. It can be observed that combined effects are equivalent to the addition of individual effects where individual effects of pain/insomnia and pain/depression are already significant in HCU (e.g. office visits and outpatient costs). Although individual effects of insomnia and depression were insignificant on LOS and inpatient costs, combined effects of pain/insomnia and pain/depression were significant and increased with insomnia/depression severity. For example, participants with current depression were more likely to have longer LOS (IRR: 2.61, 95% CI: 1.91 – 3.58) compared to those had the pain symptom only (IRR: 1.77, 95% CI: 1.32 – 2.37). This association can be partially supported by previous studies that have shown that psychological factors like depression prolonged LOS in conditions like heart failure.[39,40]

However, it should be noted that combined effects of pain/insomnia and pain/depression on hip/knee replacement decreased with insomnia/depression severity while pain symptoms are present. Multiple studies reveal high prevalence of preoperative depression and postoperative sleep disturbance in patients undergoing total hip or knee replacement and negative effects of preoperative depression on poor health outcomes after the surgery, but these studies do not contribute to our understanding of how the symptoms jointly influence the likelihood of receiving hip or knee replacement.[41–43] Since we examined only a 3-year period after the index

date, our study indicates depression or insomnia may postpone the surgical procedure, and therefore, further studies are needed to understand the reasons behind this trend.

Several limitations should be noted in this study. First, although an experienced and trained programmer helped extract the medical records, errors in coding and recording of the medical records may still exist. Second, recall bias may exist since we used survey data that relied on participant self-reported information. Third, health care costs were not adjusted for inflation because participants returned the survey in different years, which made it difficult for adjustment. But this should not be a big concern as we examined the effects of symptoms on health care cost not the incremental costs. Fourth, study results that were derived from consumer-governed health plans may not be generalizable to patients with Medicaid coverage, commercially insured persons, or the uninsured.

Our study reveals a high prevalence of comorbid insomnia and depression in addition to OA pain and it has important implications. The study underscores the substantial impact of pain on HCU in OA. Total hip or knee replacement is the only long-term effective treatment for OA, but it is also the most costly, so it is important to develop cost-effective strategies to improve pain management. This is the first study to report combined effects of pain with comorbid insomnia and depression on HCU in older adults with OA. The increased combined effects suggest that clinicians should take insomnia and depression into consideration as part of the routine assessment for patients with OA and that they should work collaboratively with specialists to better manage comorbid insomnia or depression in order to reduce OA-associated health care burden.

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Table 3.1 Participant demographics

| Variable | N | Mean | SD |
|---|---|---|---|
| Age | 2,976 | 72.16 | 8.81 |
| Months of enrollment | | | |
| Y1 | 2,976 | 12 | 0.08 |
| Y2 – Y4 | 2,976 | 34.45 | 5.66 |
| | N | Number | Percentage |
| Gender | 2,976 | | |
| Female | | 1,971 | 66.23% |
| Male | | 1,005 | 33.77% |
| Education | 2,971 | | |
| Lower than college | | 1,266 | 42.61% |
| College | | 721 | 24.27% |
| Graduate or professional | | 984 | 33.12% |
| Marital status | 2,965 | | |
| Married/living as married | | 1,799 | 60.67% |
| Single/never married | | 120 | 4.05% |
| Separated/divorced | | 477 | 16.09% |
| Widowed | | 569 | 19.19% |
| Employment | 2,911 | | |
| Employed | | 678 | 23.29% |
| Unemployed | | 436 | 14.98% |
| Retired | | 1,797 | 61.73% |
| Race | 2,922 | | |
| White | | 2,655 | 90.86% |
| Asian | | 119 | 4.07% |
| African American | | 97 | 3.32% |
| Others | | 51 | 1.75% |
| Charlson Comorbidity Index | 2,976 | | |
| = 0 | | 1,917 | 64.42% |
| ≥ 1 | | 1,059 | 35.58% |
| Months of enrollment | | | |
| Y1 | 2,976 | 12 | 0.08 |
| Y2 – Y4 | 2,976 | 34.45 | 5.66 |

Notes: SD = Standard deviation; Y = year

Table 3.2 Distribution of symptom and participant categories

| Symptom/patient categories | N | Number | Percentage |
|---|---|---|---|
| Pain | 2,940 | | |
| No to mild pain | | 1,556 | 52.93% |
| Moderate to severe pain | | 1,384 | 47.07% |
| Insomnia | 2,959 | | |
| No insomnia | | 1,333 | 45.05% |
| Sub-threshold insomnia | | 1,119 | 37.82% |
| Clinical insomnia | | 507 | 17.13% |
| Depression | 2,927 | | |
| No depression | | 1,603 | 54.77% |
| Sub-clinical depression | | 711 | 24.29% |
| Current depression | | 613 | 20.94% |
| Pain & Insomnia | 2,923 | | |
| No to mild pain & no insomnia | | 931 | 31.85% |
| No to mild pain & sub-threshold insomnia | | 509 | 17.41% |
| No to mild pain & clinical insomnia | | 109 | 3.73% |
| Moderate to severe pain & no insomnia | | 383 | 13.10% |
| Moderate to severe pain & sub-threshold insomnia | | 598 | 20.46% |
| Moderate to severe pain & clinical insomnia | | 393 | 13.45% |
| Pain & Depression | 2,891 | | |
| No to mild pain & no depression | | 1,055 | 36.49% |
| No to mild pain & sub-clinical depression | | 368 | 12.73% |
| No to mild pain & current depression | | 110 | 3.80% |
| Moderate to severe pain & no depression | | 526 | 18.19% |
| Moderate to severe pain & sub-clinical depression | | 442 | 15.29% |
| Moderate to severe pain & current depression | | 390 | 13.49% |

Table 3.3 Descriptive analysis for total office visits, length of stay, total inpatient and outpatient costs, and hip/knee replacement

| Variable | Year 1 (n/%) | Year 2 (n/%) | Year 3 (n/%) | Year4 (n/%) |
|---|---|---|---|---|
| Total office visits | | | | |
| 0 | 55 (1.85%) | 86 (2.89%) | 165 (5.54%) | 236 (7.93%) |
| 1 – 6 | 1,162 (39.05%) | 1,091 (36.66%) | 1,109 (37.26%) | 1,070 (35.95%) |
| 6 – 12 | 904 (30.38%) | 921 (30.95%) | 775 (26.04%) | 787 (26.4%) |
| 12 – 24 | 668 (22.45%) | 653 (21.94%) | 691 (23.22%) | 635 (21.34%) |
| > 24 | 187 (6.28%) | 225 (7.56%) | 236 (7393%) | 248 (8.33%) |
| Length of stay (days) | | | | |
| 0 | 2,665 (89.55%) | 2,618 (87.97%) | 2,580 (86.69%) | 2,567 (86.26%) |
| 1 – 3 | 221 (7.43%) | 126 (4.23%) | 256 (8.6%) | 236 (7.93%) |
| > 3 | 90 (3.02%) | 232 (7.80%) | 140 (4.70%) | 173 (5.81%) |
| Total inpatient costs | | | | |
| 0 | 2,661 (89.42%) | 2,615 (87.87%) | 2,580 (86.69%) | 2,566 (86.22%) |
| 0 – $5,000 | 61 (2.05%) | 73 (2.45%) | 60 (2.02%) | 60 (2.02%) |
| $5000 - $10,000 | 79 (2.65%) | 58 (1.95%) | 98 (3.29%) | 88 (2.96%) |
| $10,000 – $15,000 | 86 (2.89%) | 95 (3.19%) | 79 (2.65%) | 82 (2.76%) |
| > $15,000 | 89 (2.99%) | 135 (4.54%) | 159 (5.34%) | 180 (6.05%) |
| Total outpatient costs | | | | |
| 0 | 4 (0.13%) | 13 (0.44%) | 85 (2.86%) | 160 (5.38%) |
| 0 - $10,000 | 2,379 (79.94%) | 2,250 (75.60%) | 2,076 (69.76%) | 1,982 (66.60%) |
| $10,000 – $20,000 | 391 (13.14%) | 456 (15.32%) | 494 (16.60%) | 494 (16.60%) |
| $20,000 – $30,000 | 127 (4.27%) | 138 (4.64%) | 167 (5.61%) | 175 (5.88%) |
| > $30,000 | 75 (2.52%) | 119 (4.00%) | 154 (5.17%) | 165 (5.54%) |
| Hip/knee replacement | 109 (3.66%) | 130 (4.37%) | 120 (4.03%) | 113 (3.80%) |

Table 3.4 Individual and combined effects of pain/insomnia and pain/depression on office visits, length of stay, outpatient and inpatient costs, and hip/knee replacement adjusted for the use prior to the index date

| Category | Office visits IRR (95% CI) | Length of stay IRR (95% CI) | Outpatient costs Coefficient (95% CI) | Inpatient costs Coefficient (95% CI) | Hip/knee replacement OR (95% CI) |
|---|---|---|---|---|---|
| Pain & Insomnia [a] | | | | | |
| No to mild pain & sub-threshold to clinical insomnia [b] | **1.11 (1.04 – 1.18)** | 0.84 (0.63 – 1.13) | **1.13 (1.03 – 1.24)** | 0.93 (0.69 – 1.25) | 1.15 (0.80 – 1.67) |
| Moderate to severe pain & no insomnia [c] | **1.15 (1.06 – 1.25)** | **1.89 (1.38 – 2.58)** | **1.33 (1.19 – 1.47)** | **2.06 (1.49 – 2.84)** | **2.33 (1.60 – 3.38)** |
| Moderate to severe pain & sub-threshold insomnia | **1.25 (1.16 – 1.34)** | **1.93 (1.45 – 2.58)** | **1.41 (1.28 – 1.55)** | **1.60 (1.23 – 2.08)** | **1.91 (1.35 – 2.69)** |
| Moderate to severe pain & clinical insomnia | **1.24 (1.16 – 1.33)** | **2.09 (1.53 – 2.85)** | **1.56 (1.39 – 1.76)** | **1.84 (1.36 – 2.50)** | **1.81 (1.22 – 2.69)** |
| Pain & Depression [d] | | | | | |
| No to mild pain & sub-clinical to current depression [e] | **1.10 (1.03 – 1.18)** | 1.03 (0.76 – 1.39) | **1.18 (1.07 – 1.30)** | 1.13 (0.83 – 1.52) | 1.18 (0.81 – 1.72) |
| Moderate to severe pain & no depression [f] | **1.16 (1.09 – 1.24)** | **1.77 (1.32 – 2.37)** | **1.27 (1.16 – 1.39)** | **1.74 (1.32 – 2.30)** | **2.05 (1.47 – 2.87)** |
| Moderate to severe pain & sub-clinical depression | **1.26 (1.16 – 1.37)** | **2.11 (1.60 – 2.77)** | **1.49 (1.34 – 1.66)** | **1.96 (1.50 – 2.57)** | **2.14 (1.50 – 3.04)** |
| Moderate to severe pain & current depression | **1.21 (1.13 – 1.29)** | **2.61 (1.91 – 3.58)** | **1.60 (1.42 – 1.79)** | **2.19 (1.64 – 2.92)** | **1.69 (1.13 – 2.54)** |

a. Reference group is "No pain & no insomnia".

b. Individual effects of insomnia; c. individual effects of pain in pain/insomnia model.

d. Reference group is "No pain & no depression".

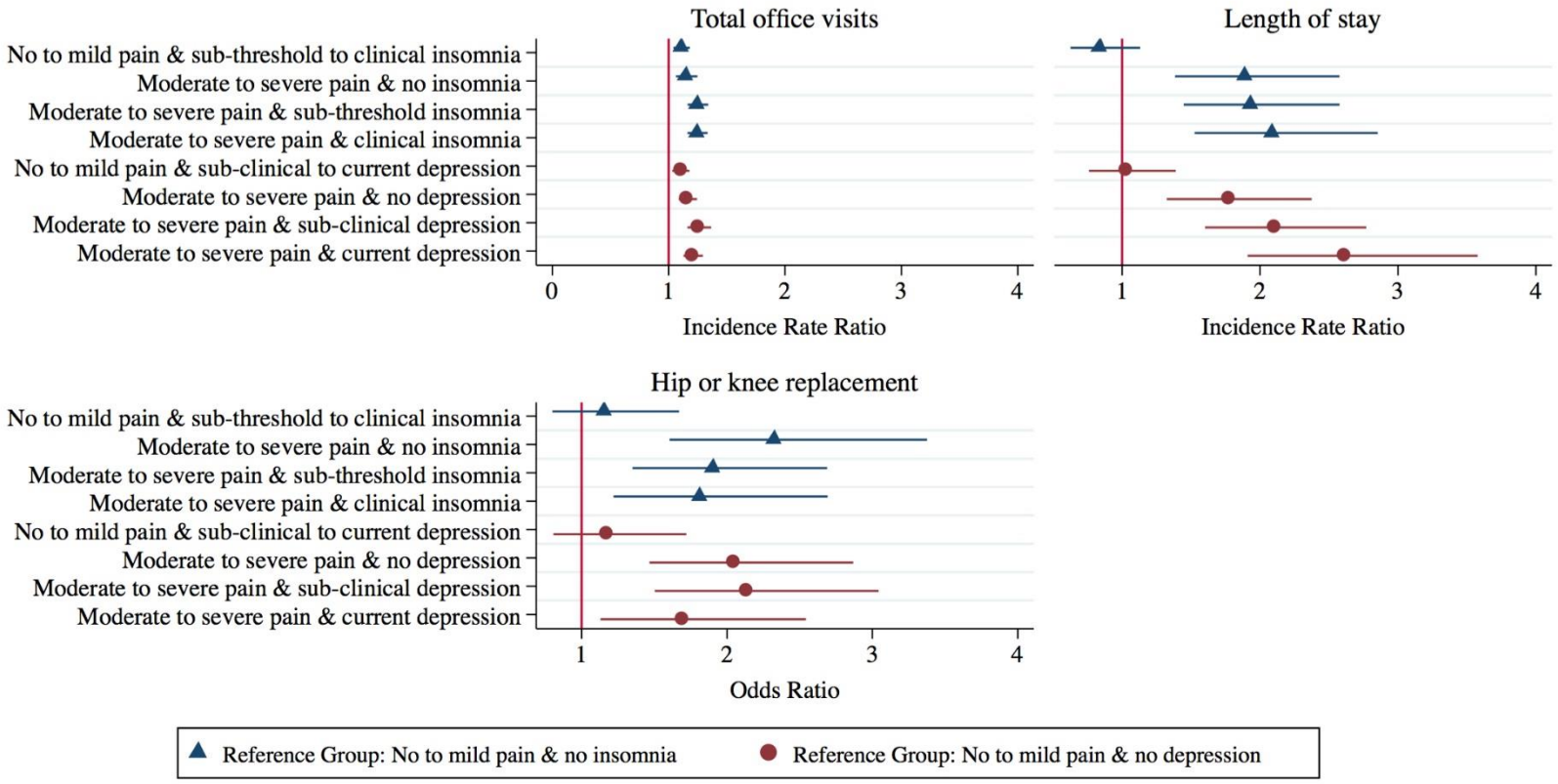
e. Individual effects of depression; f. individual effects of pain in pain/depression model.

IRR: incidence rate ratio; OR: odds ratio; CI: confidence interval.

Incidence rate ratios, odds ratios and confidence intervals that are significant are in bold.

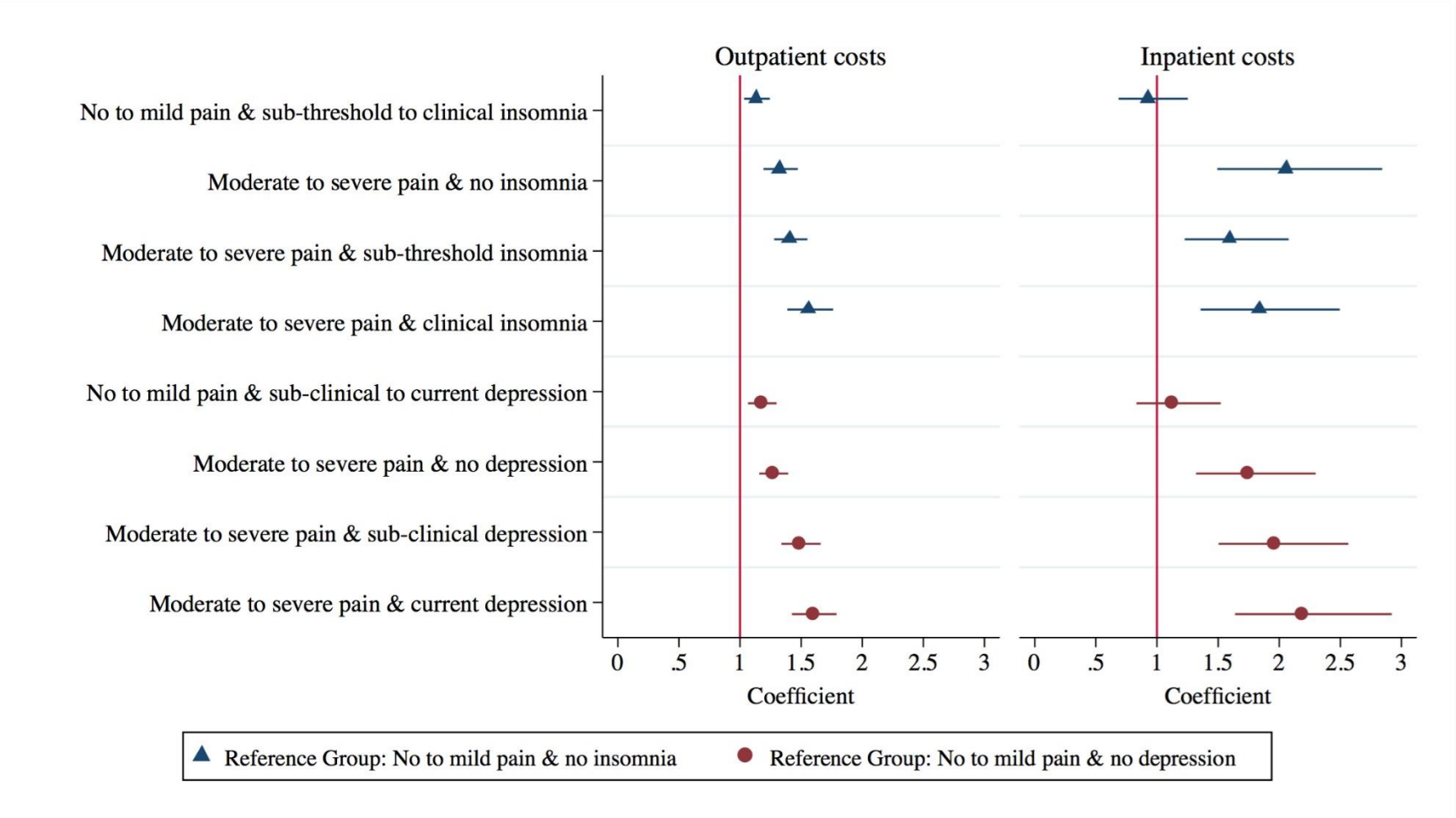
Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 3.1 Individual and combined effects of pain/insomnia and pain/depression on office visits, length of stay and hip/knee replacement adjusted for the use prior to the index date*




*Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 3.2 Individual and combined effects of pain/insomnia and pain/depression on outpatient and inpatient costs adjusted for the use prior to the index date*




*Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

# APPENDIX A

Table 3.A1 Individual and combined effects of pain/insomnia and pain/depression on office visits, length of stay, outpatient and inpatient costs, and hip/knee replacement without adjustment for the use prior to the index date

| Category | Office visits IRR (95% CI) | Length of stay IRR (95% CI) | Outpatient costs Coefficient (95% CI) | Inpatient costs Coefficient (95% CI) | Hip/knee replacement OR (95% CI) |
|---|---|---|---|---|---|
| Pain & Insomnia [a] | | | | | |
| No to mild pain & sub-threshold to clinical insomnia [b] | **1.15 (1.06 – 1.24)** | 0.83 (0.62 – 1.12) | **1.12 (1.01 – 1.23)** | 0.91 (0.68 – 1.21) | 1.13 (0.78 – 1.64) |
| Moderate to severe pain & no insomnia [c] | **1.25 (1.13 – 1.37)** | **1.91 (1.39 – 2.61)** | **1.37 (1.22 – 1.53)** | **2.06 (1.51 – 2.82)** | **2.31 (1.59 – 3.35)** |
| Moderate to severe pain & sub-threshold insomnia | **1.32 (1.22 – 1.42)** | **1.92 (1.44 – 2.56)** | **1.45 (1.30 – 1.61)** | **1.65 (1.28 – 2.14)** | **1.89 (1.34 – 2.67)** |
| Moderate to severe pain & clinical insomnia | **1.35 (1.25 – 1.47)** | **2.10 (1.54 – 2.87)** | **1.57 (1.39 – 1.79)** | **1.88 (1.39 – 2.54)** | **1.79 (1.21 – 2.67)** |
| Pain & Depression [d] | | | | | |
| No to mild pain & sub-clinical to current depression [e] | **1.14 (1.05 – 1.23)** | 1.01 (0.75 – 1.37) | **1.19 (1.07 – 1.32)** | 1.10 (0.81 – 1.48) | 1.15 (0.79 – 1.68) |
| Moderate to severe pain & no depression [f] | **1.23 (1.13 – 1.33)** | **1.77 (1.32 – 2.37)** | **1.33 (1.20 – 1.47)** | **1.74 (1.32 – 2.30)** | **2.04 (1.46 – 2.85)** |
| Moderate to severe pain & sub-clinical depression | **1.32 (1.21 – 1.44)** | **2.11 (1.61 – 2.78)** | **1.51 (1.35 – 1.69)** | **1.98 (1.51 – 2.60)** | **2.12 (1.49 – 3.02)** |
| Moderate to severe pain & current depression | **1.34 (1.24 – 1.45)** | **2.62 (1.92 – 3.58)** | **1.66 (1.48 – 1.88)** | **2.22 (1.67 – 2.96)** | **1.67 (1.11 – 2.51)** |

a. Reference group is "No pain & no insomnia".

b. Individual effects of insomnia; c. individual effects of pain in pain/insomnia model.

d. Reference group is "No pain & no depression".

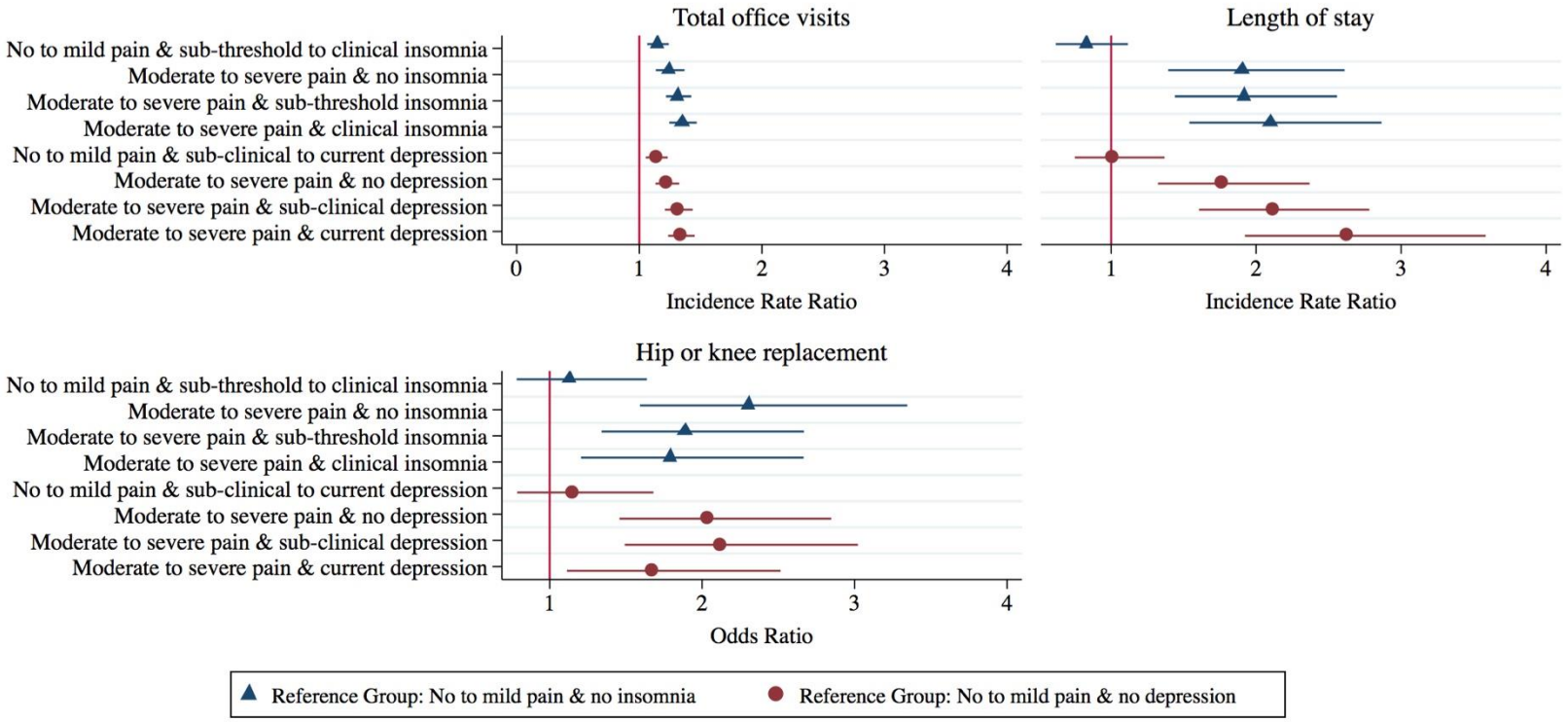
e. Individual effects of depression; f. individual effects of pain in pain/depression model.

IRR: incidence rate ratio; OR: odds ratio; CI: confidence interval.

Incidence rate ratios, odds ratios and confidence intervals that are significant are in bold.

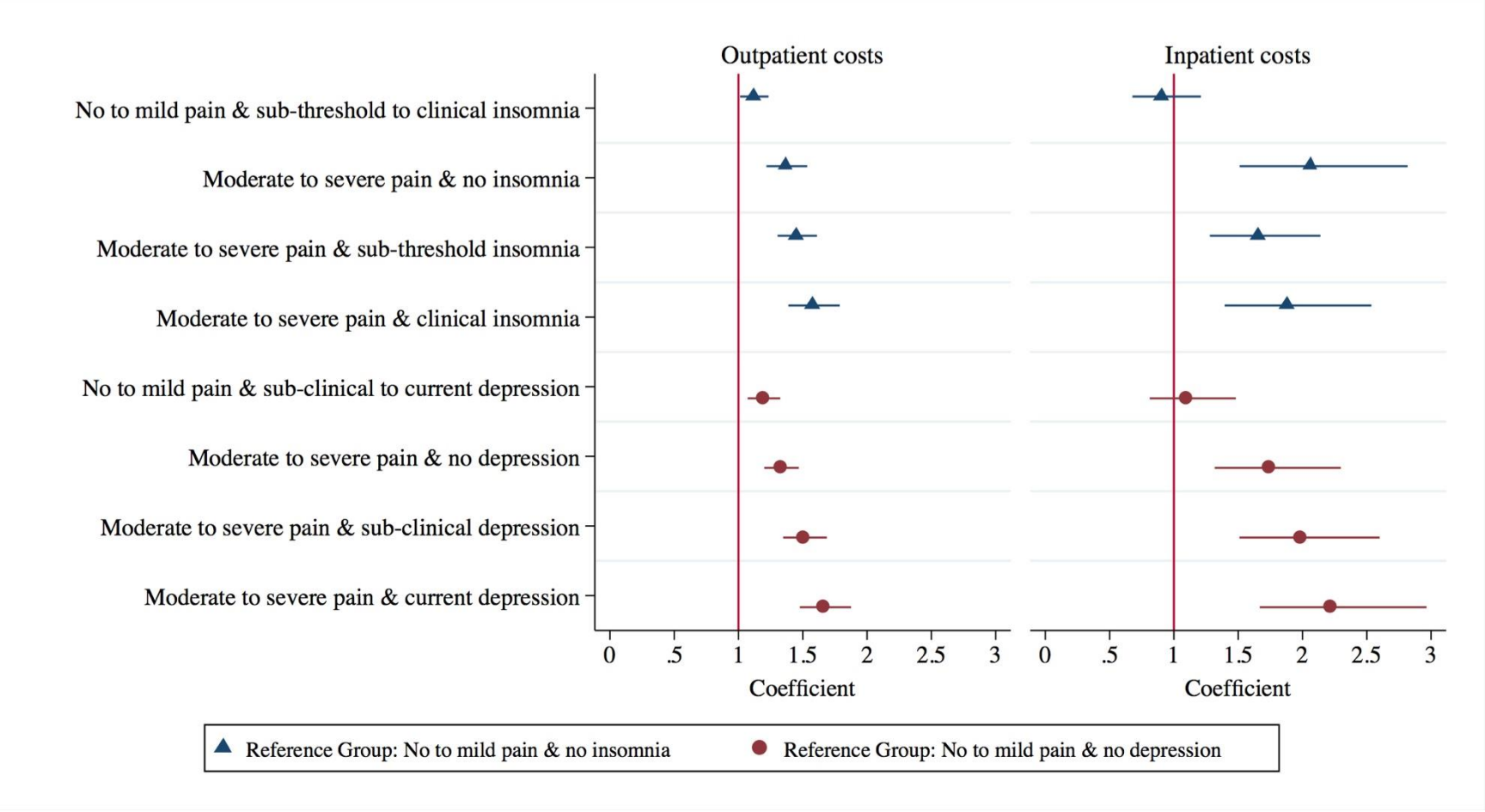
Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 3.A1 Individual and combined effects of pain/insomnia and pain/depression on office visits, length of stay and hip/knee replacement without adjustment for the use prior to the index date*




*Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 3.A2 Individual and combined effects of pain/insomnia and pain/depression on outpatient and inpatient costs without adjustment for costs prior to the index date*




*Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Table 3.A2 Distribution of participant categories by three symptoms (N = 2,883)

| Participant category | Number | Percentage |
|---|---|---|
| No to mild pain & no insomnia & no depression | 805 | 27.92% |
| No to mild pain & sub-threshold to clinical insomnia & no depression | 246 | 8.53% |
| No to mild pain & no insomnia & sub-clinical to current depression | 113 | 3.92% |
| Moderate to severe pain & no insomnia & no depression | 297 | 10.30% |
| No to mild pain & sub-threshold insomnia & sub-clinical depression | 211 | 7.32% |
| No to mild pain & clinical insomnia & sub-clinical depression | 53 | 1.84% |
| No to mild pain & sub-threshold insomnia & current depression | 53 | 1.84% |
| No to mild pain & clinical insomnia & current depression | 47 | 1.63% |
| Moderate to severe pain & sub-threshold to clinical insomnia & no depression | 227 | 7.87% |
| Moderate to severe pain & no insomnia & sub-clinical depression | 70 | 2.43% |
| Moderate to severe pain & sub-threshold insomnia & sub-clinical depression | 250 | 8.67% |
| Moderate to severe pain & clinical insomnia & sub-clinical depression | 122 | 4.23% |
| Moderate to severe pain & no insomnia to sub-threshold insomnia & current depression | 147 | 5.10% |
| Moderate to severe pain & clinical insomnia & current depression | 242 | 8.39% |

Table 3.A3 Individual and combined effects of pain, insomnia and depression on office visits, length of stay, outpatient and inpatient costs, and hip/knee replacement adjusted for the use prior to the index date

| Category [a] | Office visits IRR (95% CI) | Length of stay IRR (95% CI) | Outpatient costs Coefficient (95% CI) | Inpatient costs Coefficient (95% CI) | Hip/knee replacement OR (95% CI) |
|---|---|---|---|---|---|
| No to mild pain & sub-threshold to clinical insomnia & no depression | 1.06 (0.97 – 1.16) | 0.59 (0.39 – 0.87) | 1.06 (0.93 – 1.20) | 0.61 (0.41 – 0.91) | 1.04 (0.61 – 1.76) |
| No to mild pain & no insomnia & sub-clinical to current depression | 1.04 (0.92 – 1.17) | 0.76 (0.46 – 1.26) | 1.12 (0.93 – 1.35) | 0.79 (0.46 – 1.34) | 1.04 (0.51 – 2.11) |
| Moderate to severe pain & no insomnia & no depression | **1.13 (1.03 – 1.23)** | **1.67 (1.17 – 2.40)** | **1.28 (1.14 – 1.43)** | **1.77 (1.21 – 2.59)** | **1.96 (1.28 – 3.00)** |
| No to mild pain & sub-threshold insomnia & sub-clinical depression | 1.09 (0.99 – 1.20) | 0.92 (0.63 – 1.34) | **1.13 (1.00 – 1.28)** | 1.02 (0.66 – 1.59) | 1.24 (0.73 – 2.12) |
| No to mild pain & clinical insomnia & sub-clinical depression | 1.07 (0.89 – 1.29) | 1.60 (0.64 – 4.01) | 1.19 (0.82 – 1.74) | 1.79 (0.82 – 3.90) | 1.69 (0.72 – 3.95) |
| No to mild pain & sub-threshold insomnia & current depression | **1.17 (1.01 – 1.36)** | 0.94 (0.54 – 1.63) | **1.21 (1.01 – 1.45)** | 1.17 (0.68 – 2.02) | 2.01 (0.89 – 4.51) |
| No to mild pain & clinical insomnia & current depression | **1.43 (1.21 – 1.69)** | 0.80 (0.35 – 1.85) | **1.64 (1.26 – 2.12)** | 0.73 (0.37 – 1.40) | Omitted |
| Moderate to severe pain & sub-threshold to clinical insomnia & no depression | **1.25 (1.14 – 1.36)** | 1.52 (0.97 – 2.40) | **1.31 (1.15 – 1.50)** | 1.26 (0.88 – 1.79) | **2.15 (1.37 – 3.38)** |
| Moderate to severe pain & no insomnia & sub-clinical depression | **1.31 (1.11 – 1.55)** | **2.33 (1.33 – 4.08)** | **1.55 (1.25 – 1.91)** | **2.88 (1.61 – 5.12)** | **4.25 (2.32 – 7.79)** |
| Moderate to severe pain & sub-threshold insomnia & sub-clinical depression | **1.30 (1.16 – 1.45)** | **1.86 (1.31 – 2.66)** | **1.49 (1.30 – 1.70)** | **1.64 (1.18 – 2.29)** | **1.89 (1.21 – 2.95)** |
| Moderate to severe pain & clinical insomnia & sub-clinical depression | **1.20 (1.07 – 1.33)** | **1.71 (1.13 – 2.58)** | **1.50 (1.22 – 1.85)** | 1.31 (0.87 – 1.96) | 1.58 (0.84 – 2.95) |

| | | | | | |
|---|---|---|---|---|---|
| Moderate to severe pain & no insomnia to sub-threshold insomnia & current depression | **1.16 (1.05 – 1.28)** | **2.37 (1.48 – 3.80)** | **1.55 (1.30 – 1.84)** | **1.79 (1.19 – 2.69)** | 1.46 (0.79 – 2.70) |
| Moderate to severe pain & clinical insomnia & current depression | **1.28 (1.17 – 1.39)** | **2.42 (1.66 – 3.54)** | **1.67 (1.45 – 1.93)** | **2.20 (1.54 – 3.13)** | **2.03 (1.27 – 3.25)** |

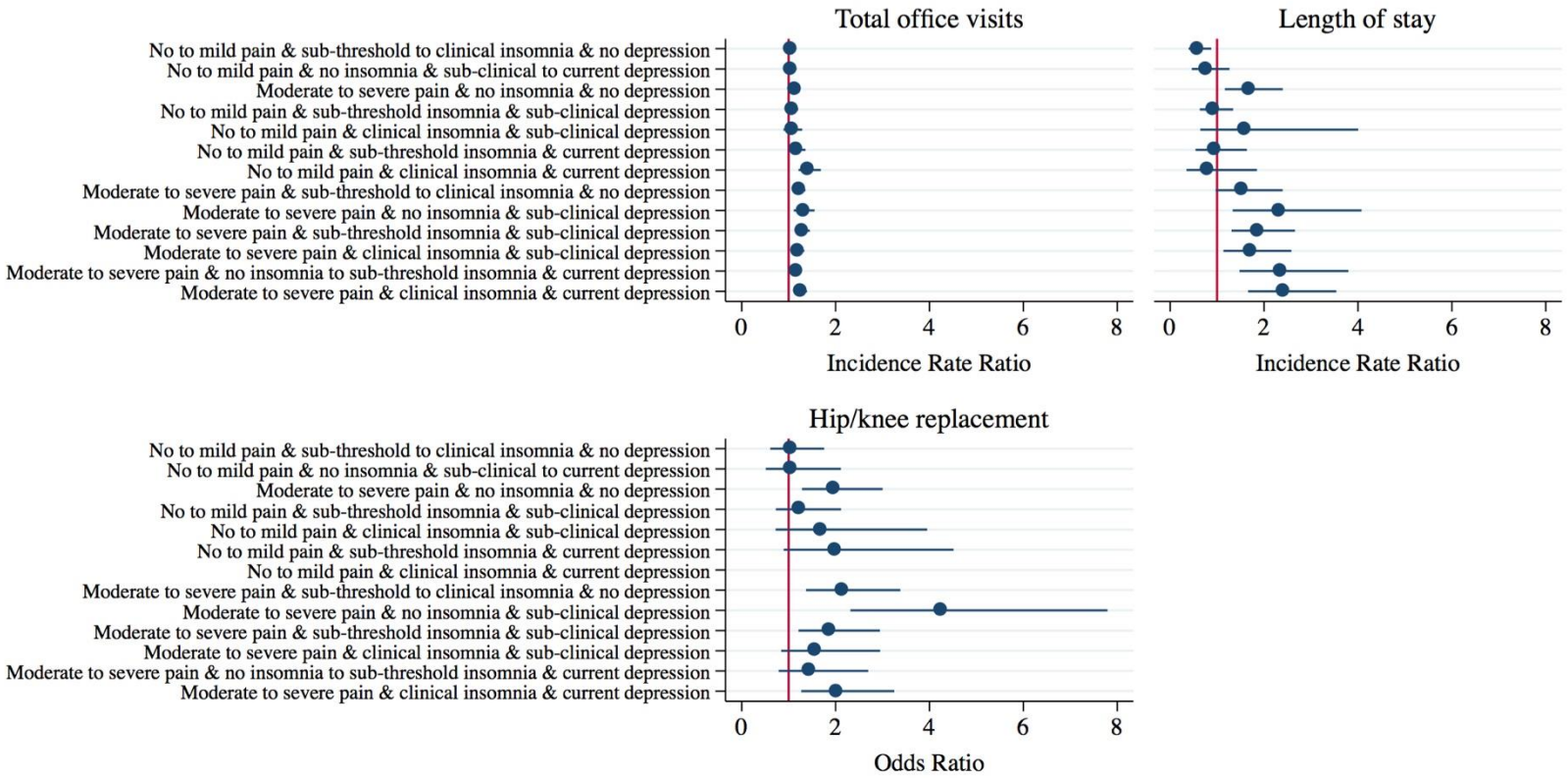
a. Reference group is "No pain & no insomnia & no depression".

IRR: incidence rate ratio; OR: odds ratio; CI: confidence interval.

Incidence rate ratios, odds ratios and confidence intervals that are significant are in bold.

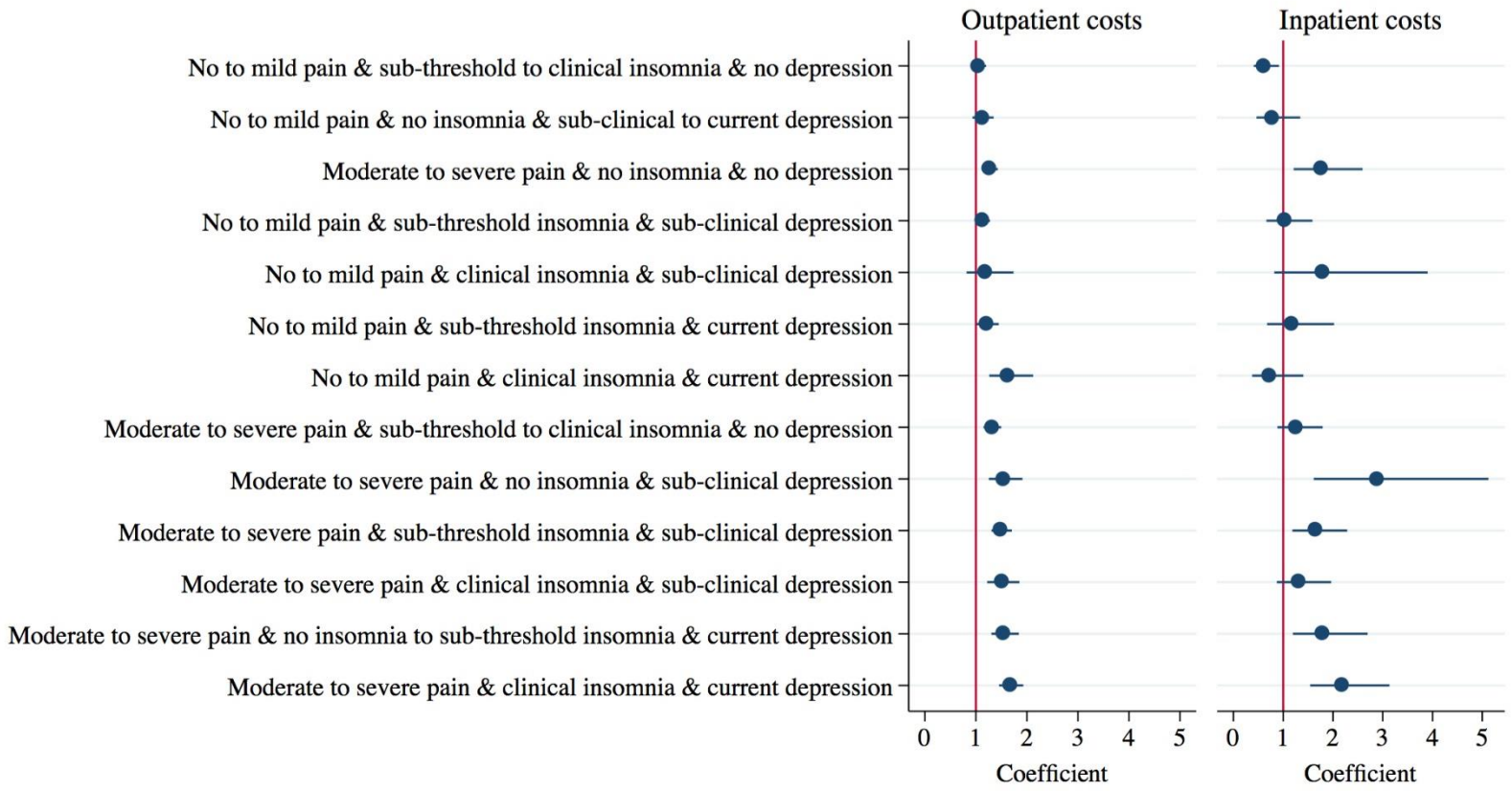
Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 3.A3 Individual and combined effects of pain, insomnia and depression on office visits, length of stay and hip/knee replacement adjusted for the use prior to the index date*




*1) Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health; and 2) Reference group is "No pain & no insomnia & no depression".

Figure 3.A4 Individual and combined effects of pain, insomnia and depression on outpatient and inpatient costs adjusted for costs prior to the index date*




*1) Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health; and 2) Reference group is "No pain & no insomnia & no depression".

Table 3.A4 Individual and combined effects of pain, insomnia and depression on office visits, length of stay, outpatient and inpatient costs, and hip/knee replacement without adjustment for the use prior to the index date

| Category [a] | Office visits IRR (95% CI) | Length of stay IRR (95% CI) | Outpatient costs Coefficient (95% CI) | Inpatient costs Coefficient (95% CI) | Hip/knee replacement OR (95% CI) |
|---|---|---|---|---|---|
| No to mild pain & sub-threshold to clinical insomnia & no depression | 1.06 (0.96 – 1.18) | 0.59 (0.39 – 0.88) | 1.05 (0.92 – 1.21) | 0.61 (0.41 – 0.90) | 1.03 (0.61 – 1.76) |
| No to mild pain & no insomnia & sub-clinical to current depression | 1.01 (0.88 – 1.16) | 0.76 (0.46 – 1.26) | 1.21 (0.96 – 1.52) | 0.80 (0.48 – 1.34) | 1.04 (0.51 – 2.10) |
| Moderate to severe pain & no insomnia & no depression | **1.21 (1.09 – 1.34)** | **1.69 (1.18 – 2.44)** | **1.35 (1.18 – 1.53)** | **1.80 (1.24 – 2.59)** | **1.95 (1.28 – 2.98)** |
| No to mild pain & sub-threshold insomnia & sub-clinical depression | **1.15 (1.02 – 1.28)** | 0.91 (0.62 – 1.32) | 1.12 (0.99 – 1.27) | 1.00 (0.66 – 1.52) | 1.20 (0.71 – 2.05) |
| No to mild pain & clinical insomnia & sub-clinical depression | 1.15 (0.93 – 1.42) | 1.59 (0.64 – 3.97) | 1.24 (0.87 – 1.78) | 1.73 (0.79 – 3.79) | 1.68 (0.73 – 3.91) |
| No to mild pain & sub-threshold insomnia & current depression | **1.18 (1.01 – 1.38)** | 0.91 (0.53 – 1.58) | 1.16 (0.99 – 1.37) | 1.11 (0.64 – 1.93) | 1.94 (0.86 – 4.35) |
| No to mild pain & clinical insomnia & current depression | **1.55 (1.22 – 1.98)** | 0.78 (0.34 – 1.80) | **1.63 (1.25 – 2.14)** | 0.73 (0.37 – 1.41) | Omitted |
| Moderate to severe pain & sub-threshold to clinical insomnia & no depression | **1.28 (1.15 – 1.43)** | 1.49 (0.95 – 2.34) | **1.36 (1.18 – 1.56)** | 1.30 (0.93 – 1.83) | **2.14 (1.36 – 3.35)** |
| Moderate to severe pain & no insomnia & sub-clinical depression | **1.38 (1.15 – 1.67)** | **2.31 (1.32 – 4.04)** | **1.49 (1.21 – 1.84)** | **2.82 (1.59 – 4.98)** | **4.21 (2.29 – 7.75)** |
| Moderate to severe pain & sub-threshold insomnia & sub-clinical depression | **1.34 (1.19 – 1.50)** | **1.87 (1.31 – 2.66)** | **1.51 (1.31 – 1.74)** | **1.74 (1.25 – 2.43)** | **1.89 (1.22 – 2.95)** |
| Moderate to severe pain & clinical insomnia & sub-clinical depression | **1.30 (1.14 – 1.48)** | **1.72 (1.14 – 2.60)** | **1.57 (1.27 – 1.95)** | 1.30 (0.88 – 1.93) | 1.54 (0.82 – 2.88) |

| | | | | | |
|---|---|---|---|---|---|
| Moderate to severe pain & no insomnia to sub-threshold insomnia & current depression | **1.32 (1.17 – 1.50)** | **2.37 (1.48 – 3.78)** | **1.70 (1.42 – 2.03)** | **1.79 (1.21 – 2.65)** | 1.41 (0.76 – 2.61) |
| Moderate to severe pain & clinical insomnia & current depression | **1.40 (1.26 – 1.54)** | **2.46 (1.69 – 3.57)** | **1.70 (1.47 – 1.97)** | **2.23 (1.58 – 3.15)** | **2.03 (1.27 – 3.25)** |

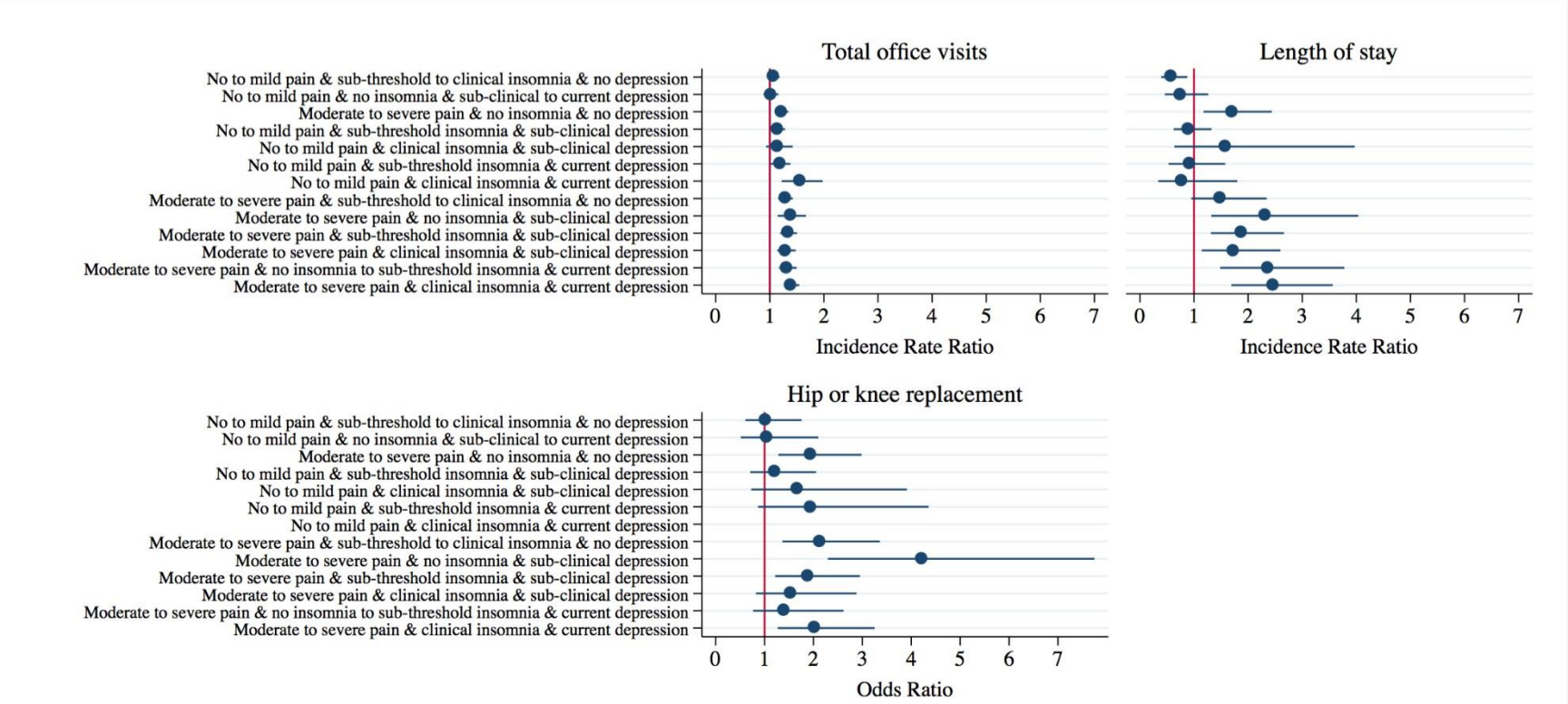
a. Reference group is "No pain & no insomnia & no depression".

IRR: incidence rate ratio; OR: odds ratio; CI: confidence interval.

Incidence rate ratios, odds ratios and confidence intervals that are significant are in bold.

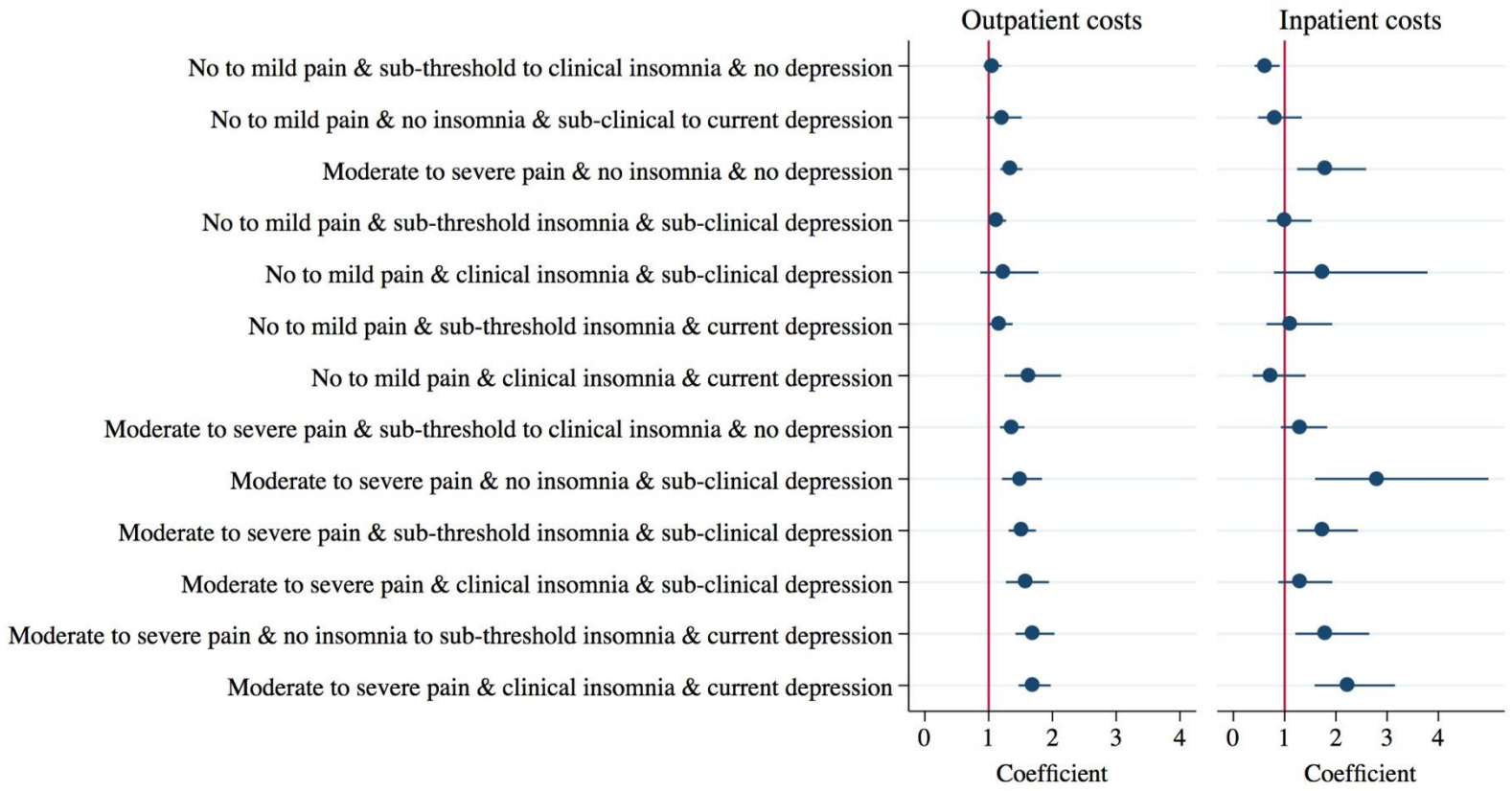
Models adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health.

Figure 3.A5 Individual and combined effects of pain, insomnia and depression on office visits, length of stay and hip/knee replacement without adjustment for the use prior to the index date*




*1) Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health; and 2) Reference group is "No pain & no insomnia & no depression".

Figure 3.A6 Individual and combined effects of pain, insomnia and depression on outpatient and inpatient costs without adjustment for costs prior to the index date*




*1) Adjusted for demographics, Charlson Comorbidity Index, and months of enrollment in Group Health; and 2) Reference group is "No pain & no insomnia & no depression".