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Mental disorder prevalence in chronic pain patients using opioid versus non-opioid analgesics: A registry-linkage study --Manuscript Draft--

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Abstract:	Background: Chronic pain and mental disorders are leading causes of disability worldwide. Individuals with chronic pain are more likely to experience mental disorders compared to individuals without chronic pain, but large-scale estimates are lacking. We aimed to calculate overall prevalence of mental health diagnoses from primary and secondary care among individuals treated for chronic pain in 2019 and compare prevalence among chronic pain patients receiving opioid versus non-opioid analgesics, according to age and gender. Methods: Population-based cohort study. Linked data from nationwide health registers on dispensed drugs and diagnoses from primary (ICPC-2) and secondary (ICD-10) health care. Chronic pain patients were identified as all patients over 18 years of age filling at least one prescription of an analgesic reimbursed for non-malignant chronic pain in both 2018 and 2019 (N=139434, 69.3% women). Results: Prevalence of any mental health diagnosis was 35.6% (95% confidence interval: 35.4-35.9%) when sleep diagnoses were included and 29.0% (28.8-29.3%) when excluded. The most prevalent diagnosis categories were sleep disorders (14% [13.8-14.2%], depressive and related disorders (10.1% [9.9-10.2%]), and phobia and other anxiety disorders (5.7% [5.5-5.8%]). Prevalence of most diagnosis categories were higher in the group using opioids compared to non-opioids. The group with the highest overall prevalence was young women (18-44 years) using opioids (50.1% [47.2-53.0%]). Conclusions: Mental health diagnoses are common in chronic pain patients receiving analgesics, particularly among young individuals and opioid users. The combination of opioid use and high psychiatric comorbidity suggests that prescribers should attend to mental health in addition to somatic pain.
Additional Information:	
Question	Response
Significance (not for "Case reports") Below please give a paragraph entitled "Significance", indicating the main aspects where this work adds significantly to	This large-scale study with nation-wide registry data supports previous findings of high psychiatric burden in chronic pain patients. Opioid users had significantly higher prevalence of mental health diagnoses, regardless of age and gender compared to users of non-opioid analgesics. Opioid users with chronic pain therefore stand out as a particularly vulnerable group and should be followed up closely by their physician to

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ensure they receive sufficient care for both their mental and somatic symptoms.

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1 Mental disorder prevalence in chronic pain patients using opioid versus non-opioid 2 analgesics: A registry-linkage study 3 4 Running head: Mental disorders in chronic pain patients 5 L. C. Gjerde^{1,2}; S. Skurtveit^{1,3}; M. Handal^{3,4}; R. Nesvåg¹; T. Clausen³; T.G. Lid^{5,6}; A. Hamina³; P. 6 C. Borchgrevink^{7,8}; I. Odsbu¹ 7 8 9 Affiliations: 10 ¹Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway 11 ²Promenta Research Center, University of Oslo, Norway 12 ³Norwegian Centre for Addiction Research (SERAF), Institute of Clinical Medicine, University 13 of Oslo, Oslo, Norway 14 ⁴Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo, Norway 15 ⁵Centre for Alcohol and Drug Research (KORFOR), Stavanger University Hospital, Stavanger, 16 Norway ⁶Faculty of Health Sciences, University of Stavanger, Stavanger, Norway 17 18 ⁷Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway 19 20 ⁸Department of Pain and Complex Disorders, St. Olav's University Hospital, Trondheim, Norway 21 22 23 Correspondence: 24 Line C. Gjerde, Norwegian Institute of Public Health, Box 222, Skøyen, N-0213 Oslo, Norway. 25 Phone: 0047 21078379, email: Line.Gjerde@fhi.no 26 27 Funding sources: 28 The work was supported by the Norwegian Research Council (Grant Number 320360). The 29 funder was not involved in study design, data collection, data analysis, manuscript preparation and/or publication decisions. 30 31 32 Conflict of interest: None declared. 33 34 Original article 35 Tables: 2, Figures: 3 36 37 38 What is already known about the topic: 39 Mental disorders are more common among individuals with chronic pain and users of 40 opioid analgesics than among pain-free individuals What does this study add: 41 42 Large-scale prevalence estimates across different reimbursed analgesic user-, age 43 groups, and gender from nationwide registry data on all mental health diagnoses in 44 both primary and secondary health care.

Approximately 1/3 individuals with chronic pain had a mental health diagnosis. The
psychiatric burden was particularly high among young women using opioid
analgesics.

Significance: This large-scale study with nation-wide registry data supports previous findings of high psychiatric burden in chronic pain patients. Opioid users had significantly higher prevalence of mental health diagnoses, regardless of age and gender compared to users of non-opioid analgesics. Opioid users with chronic pain therefore stand out as a particularly vulnerable group and should be followed up closely by their physician to ensure they receive sufficient care for both their mental and somatic symptoms.

88 Abstract 89 Background: Chronic pain and mental disorders are leading causes of disability worldwide. Individuals with chronic pain are more likely to experience mental disorders compared to 90 91 individuals without chronic pain, but large-scale estimates are lacking. We aimed to calculate 92 overall prevalence of mental health diagnoses from primary and secondary care among 93 individuals treated for chronic pain in 2019 and compare prevalence among chronic pain patients receiving opioid versus non-opioid analgesics, according to age and gender. 94 95 Methods: Population-based cohort study. Linked data from nationwide health registers on 96 dispensed drugs and diagnoses from primary (ICPC-2) and secondary (ICD-10) health care. 97 Chronic pain patients were identified as all patients over 18 years of age filling at least one 98 prescription of an analgesic reimbursed for non-malignant chronic pain in both 2018 and 99 2019 (N=139434, 69.3% women). **Results:** Prevalence of any mental health diagnosis was 35.6% (95% confidence interval: 100 101 35.4-35.9%) when sleep diagnoses were included and 29.0% (28.8-29.3%) when excluded. 102 The most prevalent diagnosis categories were sleep disorders (14% [13.8-14.2%], depressive 103 and related disorders (10.1% [9.9-10.2%]), and phobia and other anxiety disorders (5.7% 104 [5.5-5.8%]). Prevalence of most diagnosis categories were higher in the group using opioids compared to non-opioids. The group with the highest overall prevalence was young women 105 106 (18-44 years) using opioids (50.1% [47.2-53.0%]). 107 Conclusions: Mental health diagnoses are common in chronic pain patients receiving 108 analgesics, particularly among young individuals and opioid users. The combination of opioid use and high psychiatric comorbidity suggests that prescribers should attend to mental 109 110 health in addition to somatic pain. 111 112 Keywords: Chronic pain; mental health diagnoses; opioid; analgesics; registry. 113 114 115 116 117 Data availability statement: This observational study is based on individual level data from population-based health 118 registers. Therefore, the authors are by law not able to make this data fully available to the 119 120 public. 121 122 123 124 125 126

INTRODUCTION

Chronic pain (pain lasting ≥3 months) is a leading cause of disability and affects ≈ 30% of individuals worldwide (Cohen, Vase, & Hooten, 2021; Steingrímsdóttir Ó, Landmark, Macfarlane, & Nielsen, 2017; Vos et al., 2016). Although first-line treatment of chronic pain should be non-pharmacological, non-opioid analgesics are often used as first-line pharmacological treatment. Opioids may be administered for moderate-to-severe pain, but evidence for long-term effectiveness of opioids is limited (Chou et al., 2020). Long-term opioid treatment should be utilized with care, as it increases risk of abuse and addiction and is associated with increased overdose-related mortality (Stannard, 2016).

Mental disorders are another leading cause of disability (Vos et al., 2016), and individuals with chronic pain are more likely to experience mental disorders compared to pain-free individuals (Burke, Mathias, & Denson, 2015; Velly & Mohit, 2018). Common mental health diagnoses among chronic pain patients are anxiety, depressive, somatoform, personality, and alcohol and substance use disorders (Dersh, Polatin, & Gatchel, 2002; Søndergård, Vaegter, Erlangsen, & Stenager, 2018). There is, however, variation across studies in which diagnoses are most common in this group. This could be because studies use various screening instruments, and are often based on self-report data, therefore lacking the full picture from both primary and secondary care (Burke et al., 2015; Velly & Mohit, 2018). Registry data are useful for estimating prevalence of individuals receiving medical treatment, but few countries have nationwide registries on somatic and mental health diagnoses. In Norway, chronic pain patients can be identified through a reimbursement scheme for prescribed analgesics. By linkage with data on contact with public health care, it is possible to provide prevalence of all registered mental health diagnoses in this group.

Although mental disorders are common in individuals using opioids for chronic pain (Cicero et al., 2009; Davis, Lin, Liu, & Sites, 2017; Dobscha, Morasco, Duckart, Macey, & Deyo, 2013; Quinn et al., 2019; Reid et al., 2002; Sullivan, Edlund, Zhang, Unützer, & Wells, 2006), prevalence estimates of mental disorder diagnoses from representative data on this group compared to those using non-opioid analgesics are lacking. Information on differences between individuals with chronic pain using opioids versus non-opioids may improve understanding of the patient's health problems, and aid prescribers in choosing the best treatment option.

We use a nationwide registry-linkage with complete data from both primary and secondary health care. We assume that pain is more severe in patients prescribed reimbursed versus non-reimbursed analgesics, in patients prescribed opioid- versus non-opioid analgesics, and in patients prescribed reimbursed opioids versus non-reimbursed opioids. The investigation is focused on data from 2019 to get a comprehensive snapshot of the mental health load in chronic pain patients using reimbursed analgesics. We aim to 1) investigate overall prevalence of mental health diagnoses in chronic pain patients using reimbursed analgesics; and 2) calculate and compare the prevalence of mental health diagnosis categories in: a) chronic pain patients using reimbursed opioid versus non-opioid analgesics and b) chronic pain patients using reimbursed versus non-reimbursed opioid analgesics, according to age and gender.

MATERIALS AND METHODS

Study setting and data sources

This was a cohort-design study utilizing linkage between nationwide health registries in Norway. All individuals in Norway have a unique identification number that makes linkage

between the health registries possible (Laugesen et al., 2021). Data on filled prescriptions were retrieved from the Norwegian Prescription Database (NorPD; Furu, 2009), where drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology, 2021). Information on indication of use is available for reimbursed prescriptions. The Norwegian Patient Registry (NPR) contains information on hospitalizations and outpatient secondary health care visits (Bakken, Ariansen, Knudsen, Johansen, & Vollset, 2020). Diagnoses are recorded after each visit according to the International Classification of Diseases, 10th revision (ICD-10; WHO, 1992). The Norwegian Registry for Primary Health Care (NRPHC) contains information on all patient visits in primary health care (Bakken et al., 2020). Diagnoses from primary care are recorded after each visit according to the International Classification of Primary Care, 2nd edition (ICPC-2; WHO, 1998). We have access to all recorded diagnoses from each visit from NPR and NRPHC. Data on incident malignancies (ICD-10) were retrieved from The Cancer Registry of Norway (Pukkala et al., 2018), and dates of death were retrieved from the Cause of Death Registry (Pedersen & Ellingsen, 2015).

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Reimbursement of analgesics for treatment of chronic pain in Norway

The Norwegian reimbursement scheme has previously been described thoroughly (Hamina et al., 2022). Residents of Norway have universal health and social insurance coverage, and enrolment is automatic. Thus, private medical insurance utilization is limited. Prescription drugs are paid out-of-pocket or by co-payment (39% of total price and not more than 520 NOK per prescription) up to an annual ceiling (2369 NOK in 2019) for reimbursed drugs.

Drugs can be reimbursed for predefined chronic conditions in need of long-term drug treatment (i.e., at least three months a year), and are usually dispensed for three months

and the prescription valid for one year. Chronic pain is one of the conditions that may qualify for reimbursed drugs. In 2008, Norway launched a new reimbursement scheme to facilitate the pharmacological treatment of chronic pain. A specific reimbursement code was established for this purpose (reimbursement code -71). Reimbursed drugs can be approved in advance with closely defined areas of use and terms and conditions, or individual reimbursement can be granted if the areas of use or terms and conditions are not met. For chronic pain, non-opioid analgesics are examples of pre-approved drugs, whereas opioid analgesics need individual application. On the reimbursement code -71, a patient can be prescribed non-opioids (e.g., paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentin, pregabalin, amitriptyline, carbamazepine) or opioids for the treatment of moderate to severe chronic pain regardless of the underlying diagnosis.

Reimbursement of opioid analgesics for treatment of chronic pain in Norway

To be eligible for reimbursed opioid analgesics one must have a chronic pain condition

(regardless of diagnosis), and the need for pharmacological treatment for more than three

months a year (i.e. be classified under the reimbursement code -71). In addition, several

criteria must be met for approval of the individual application: the patient's risk of addiction

must be assessed to be lower than the benefits of receiving the treatment, the pain needs to

be carefully assessed, which can be achieved using various validated instruments (e.g.,

Hawker, Mian, Kendzerska, & French, 2011), and a concrete treatment plan must be

established. For conditions other than active cancer, it must also be documented that the

patient has tried at least two other non-opioid medications without satisfactory effect. The
individual application for reimbursement of an opioid analgesic requiresthat a physician

documents these criteria on behalf of the patient to the health authorities. Initially, only

anaesthesiologists and physicians at pain clinics could prescribe reimbursed opioids. Starting in 2016, general practitioners (GPs) could apply for approval of reimbursed opioids for specific patients, on the above-mentioned criteria. There is a limit on the amount of opioids that can be prescribed. Anaesthesiologists and physicians at pain clinics can apply for approval of reimbursed prescriptions of up to 300 mg oral morphine equivalents (OMEQ) per day, whereas primary care physicians may apply for approval of reimbursed prescriptions of up to 100 mg OMEQ per day. Opioids can also be reimbursed for palliative care (reimbursement code -90).

Individuals with chronic pain can be prescribed opioid analgesics without reimbursement. This can be the case if the criteria for the individual application for reimbursement of opioid analgesics are not met, or if a higher daily dosage than 100 mg OMEQ (if GPs prescribe) or 300 mg OMEQ is required. In the latter case, the extra amount must be prescribed without reimbursement. It is also important to note that the non-reimbursed opioids may have been prescribed for other conditions than chronic pain, for instance in relation to a tooth extraction. For non-reimbursed opioids, patients must pay out-of-pocket.

In sum, the Norwegian reimbursement scheme for chronic pain represents a unique opportunity to identify individuals with chronic pain in need of pharmacological treatment.

The strict clinical criteria should limit the risk for false positives on the code -71, but reliability and validity studies are currently lacking.

Study population

We identified chronic pain patients as all individuals with at least one filled prescription of an analgesic with reimbursement code -71 in 2019 (N=255,829; approximately 6.1% of the

Norwegian population aged ≥18 years which counted 4 205 704 individuals in 2019 (Statistics Norway, 2023); Figure S1). These individuals were further divided into three mutually exclusive groups (Figure 1): (1) no opioids - individuals receiving reimbursed non-opioids only, (2a) non-reimbursed opioids - individuals receiving reimbursed non-opioids and non-reimbursed opioids, and (2b) reimbursed opioids - individuals receiving reimbursed opioids (and potentially reimbursed non-opioids and/or non-reimbursed opioids in addition). The groups were ordered hierarchically (2b > 2a > 1), meaning that if a patient for instance uses reimbursed opioids, on-reimbursed opioids as well as reimbursed non-opioids, this patient will be placed in group 2b.

Insert Figure 1 here

Due to the strict criteria and the individual application that is needed for a patient to be prescribed reimbursed opioids, we expect different results on prevalence between group 2a and b, and group 2b to be the smallest of the three groups. As we were interested in prevalent users of analgesics for chronic non-malignant pain, we excluded everyone with at least one filled prescription of reimbursed opioids for palliative care in 2019 and everyone dying in 2019. We further excluded individuals with no filled prescriptions of reimbursed analgesics in 2018. Finally, we excluded everyone with at least one recorded cancer diagnosis since 1990 and everyone below 18 years of age. The analytic sample consisted of 139,434 individuals (69.3% women).

Outcome

We identified all records of mental health diagnoses registered in primary (ICPC-2 codes P01-P99) or secondary health care (ICD-10 codes F00-F99) in 2019. Diagnoses were identified using the first three characters in the code (e.g., F10 for alcohol and related disorders).

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Statistical analyses

We counted all mental health diagnoses for each individual in primary care and secondary care separately. We also aggregated the mental health diagnoses into diagnosis categories. If an individual was registered with one or more of the diagnoses included in the category, this was counted as one incidence of that diagnosis category. Each diagnosis category was created at three levels: primary care, secondary care and for the two health care levels combined (Table S1). As can be seen from Table S1, we also included symptom diagnoses from ICPC-2 in primary care (e.g., P03 "Feeling depressed"), as we were also interested in investigating the frequencies of any mental health diagnosis. For the combined level diagnosis categories, an individual was counted with one diagnosis if they had received a diagnosis in either primary or secondary care. If the same diagnosis was registered in both levels, the diagnosis was only counted once for that individual. For the diagnosis category Any mental health diagnosis, we decided to exclude the sleep diagnoses, as sleep problems can often be secondary to pain. We include a sensitivity analysis in the supplementary material where sleep diagnoses are included. Prevalence (%) of mental health diagnosis categories was calculated as number of individuals with at least one recorded mental health diagnosis in the category, divided by the total number of prevalent users of reimbursed analgesics. Prevalence was also split on gender, age-, and analgesic user groups. Differences between the groups were investigated using 95% confidence intervals (CI). The data were analyzed using SPSS version 27.

RESULTS

295 Study population

Compared to men, more women were dispensed reimbursed analgesics in 2019 (69.3%; Table 1). Both among women and men, the age group 45-69 years was the largest (55.3% and 60.6% of the sample within gender, respectively). For everyone in the cohort, non-opioid analgesics were dispensed more often (52.4%), and opioids less often (39.5% for non-reimbursed opioids and 8.1% for reimbursed opioids). In other words, there were more individuals in group 1 compared to group 2a, and in 2a compared to 2b.

Insert Table 1 here

Overall prevalence

The overall prevalence of any mental health diagnosis in this study population was 29.0% (95% CI 28.8-29.3%), when sleep diagnoses were removed. The prevalence was 35.6% (35.4-35.9%) when sleep diagnoses were included (Fig S2). The contrast was large and statistically significant in overall prevalence between group 2b - reimbursed opioid (34.0% [33.1-34.9%]) and group 1 - non-opioid analgesics (25.2% [24.9-25.5%]). No difference was observed for the two opioid user groups (2b versus 2a). For the three age groups (18-44 years; 45-69 years; 70+ years), the overall prevalence was 42.0% (41.4-42.7%), 27.3% (27.0-27.7%), and 23.5% (23.1-24.0%), respectively, and hence markedly highest among the youngest age group. The prevalence was higher among women than men (30.1% [29.9-30.4%] versus 26.5% [26.0-26.9%], respectively). The group with highest overall prevalence was young women using reimbursed opioid analgesics (50.1% [47.2-53.0%]). More results on overall

prevalence split on analgesic user group, age group, and gender are shown in Figure 2.

Prevalence of all singular mental health diagnoses in primary and secondary health care, including ICPC-2 symptom diagnoses is provided in the supplementary material (Table S2).

Insert Figure 2 here

Diagnosis categories

At the combined primary and secondary health care level, the three most prevalent diagnosis categories were sleep disorders and disturbance (14.0% [13.8-14.2%]), depressive and related disorders (10.1% [9.9-10.2%]), and phobia and other anxiety disorders (5.7% [5.5-5.8%]). For all three diagnosis categories, there was a higher prevalence in group 2b - reimbursed opioids compared to in group 1 reimbursed non-opioids (17.0% [16.3-17.7%] versus 11.8% [11.5-12.0%]; 12.1% [11.5-12.8%] versus 8.5% [8.3-8.7%]; and 7.0% [6.5-7.5%] versus 4.5% [4.4-4.7%], respectively). However, there were no differences observed for the two opioid user groups (group 2b versus 2a). The ordering of the consecutive diagnosis categories and their prevalence are shown in Table 2. More results on diagnosis categories split into gender, age-, and analgesic user groups are shown in Figure 3a and 3b.

Insert Table 2 here

At the primary care level 46,567 (33.4%) of 139,434 individuals was registered with a mental health diagnosis (Table S2). The most prevalent diagnosis categories in primary care were sleep disturbance (11.5% [11.3-11.6%]) and depressive disorder (8.6% [8.5-8.7%]). For both diagnosis categories, there was a higher prevalence among individuals in group 2b

reimbursed opioids compared to group 1 - reimbursed non-opioids (sleep disturbance:

14.1% [13.4-14.7%] versus 9.5% [9.3-9.7%]; depressive disorder: 10.0% [9.5-10.6%] versus

7.3% [7.2-7.5%]).

Insert Figure 3 here

At the secondary health care level, 14,516 (10.4%) of 139,434 individuals were registered with a mental health diagnosis (Table S2). The most prevalent diagnosis categories in secondary health care were sleep disorders (3.5% [3.4-3.6%]) and depressive and related mood disorders (3.0% [2.9-3.1%]). The prevalence was higher in group 2b compared to group 1 (sleep disorders: 4.1% [3.7-4.5%] versus 3.1% [3.0-3.2%]; depressive and related mood disorders: 3.9% [3.5-4.2%] versus 2.5% [2.4-2.7%]).

At both the primary and secondary health care level, the difference in prevalence between the two opioid user groups (2b versus 2a) of both the sleep and depressive diagnosis categories were not statistically significant. More results split into gender, age- and analgesic user groups for sleep diagnoses are shown in Figure S3.

Prevalence within opioid (group 2b) versus non-opioid users (group 1)

For some of the diagnosis categories, such as schizophrenia and related

For some of the diagnosis categories, such as schizophrenia and related disorders, somatoform and other disorders and eating disorders, the difference in prevalence between group 2b - reimbursed opioid versus group 1 - reimbursed non-opioid users was not statistically significant. For the diagnosis category schizophrenia and related disorders, there was even a clear trend of lower prevalence for men in group 2b compared to in group 1

(e.g., for men aged 45-69 prevalence for those dispensed reimbursed non-opioids were 0.8% [0.67-0.98%] compared to 0.4% [0.21-0.80%] for those dispensed reimbursed opioids).

DISCUSSION

Using up-to-date, nationwide, and complete registry data, we present a thorough investigation of the prevalence of mental health diagnoses in different subgroups of chronic pain patients receiving reimbursed analgesics. The overall prevalence was substantial, as $\approx 30\%$ were registered with one or more mental health diagnoses. In the general Norwegian population in 2019, $\approx 5\%$ of the men and $\approx 7\%$ of the women utilized secondary health care due to a mental disorder (The Norwegian Institute of Public Health, 2018). For primary health care, the numbers were $\approx 14\%$ for men and $\approx 21\%$ for women. In our sample, the numbers were 10.3% for men and 10.4% for women in specialist health care, and 23.9% and 27.6% for primary health care. It therefore seems that individuals with chronic pain have a substantially higher psychiatric burden than the general population.

The most common diagnosis categories at the combined primary and secondary health care level were sleep disorders, depressive and related disorders, and phobia and other anxiety disorders. For most of the diagnosis categories, the prevalence was higher among users of opioids compared to non-opioid analgesics. There was also evidence of age and gender differences. The highest prevalence was found among the youngest women (18-44 years).

Chronic pain patients are more likely to experience a mental disorder compared to the general population (Burke et al., 2015; Velly & Mohit, 2018). The existing literature is based on different samples measured with various instruments over several time spans, making conclusions on prevalence difficult to draw. A Danish registry study of chronic pain

patients treated at a pain clinic found an overall 10-year prevalence of mental disorders registered in secondary care of 17.8% (Søndergård et al., 2018), whereas our 1-year prevalence estimate in secondary care was 10.4%. The difference in prevalence could be due to different measurement periods (and/or that individuals admitted to pain clinics may have more severe pain and hence a higher risk of developing mental disorders).

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In line with our hypothesis, most of the diagnosis categories were significantly more prevalent in patients using reimbursed opioid compared to non-opioid analgesics. This fits well with previous findings that individuals with mental disorders more often use opioid analgesics (Cicero et al., 2009; Reid et al., 2002). However, an important remaining question is why these groups differ. As there are strict criteria for being prescribed reimbursed opioids, it is likely that pain is more severe in this group, which in itself may increase risk for mental disorders (e.g., through sleep difficulties, feelings of hopelessness, and/or social isolation). Long-term opioid use itself could increase susceptibility to mental disorders, for instance through neurobiological or psychosocial mechanisms (Semenkovich et al., 2014). Another possibility is that individuals with co-occurring pain and some types of mental disorders may wish to stay on opioid treatment, as some psychiatric symptoms can be alleviated by the opioid's sedative effect (e.g., Goesling et al., 2015). However, our hypothesis on significant differences between the two opioid groups was not supported. The exception was for alcohol and substance use disorders, where the prevalence increased in line with the hierarchy of the analgesic user groups (2b > 2a > 1; Fig. 3b). Regarding opioid use, approximately 10% of the population was prescribed opioids in 2019 in Norway, a majority only one prescription (Odsbu, 2022; Skurtveit, Sakshaug, Hjellvik, Berg, & Handal, 2014). Overall, a larger proportion of the Norwegian population has consistently been prescribed opioids to the Swedish and Danish populations (Muller, Clausen, Sjøgren, Odsbu,

& Skurtveit, 2019). Yet, Nordic countries have far lower prevalence of prescribed opioid use compared to the US (Zajacova, Grol-Prokopczyk, Limani, Schwarz, & Gilron, 2023). With respect to opioid use by persons with chronic pain, Norwegian data are not comparable with other countries due to the unique reimbursement system.

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Perhaps the most striking finding was that there were so large age differences in prevalence of mental health diagnoses. The youngest age group had higher prevalence of almost all diagnosis categories, except sleep disorders and disturbance. Mental disorders often emerge when people are in their 20s, and some mental disorders "burn out" with increasing age (e.g., some personality disorders). Increasing age is also often followed by more pain due to onset of rheumatic and musculoskeletal disorders. Individuals with chronic pain in young age are also in a stage of life where chronic pain may influence functional outcomes such as work participation to a larger degree. We could also have encountered a cohort effect: younger individuals are generally more educated and open about mental health symptoms and may therefore have a lower threshold for discussing such symptoms with their GP. This study was not designed to investigate direction of causation. Nevertheless, some discussion on this topic is warranted. Although the mechanisms behind the pain and mental disorder association are not yet fully understood, several useful frameworks exist. One of these is the diathesis stress model (Dersh et al., 2002). An individual's premorbid psychological functioning may act as the diathesis and pain as the stressor. Individuals vary in their perception of threat and coping strategies. An individual with a low threshold to activate a strong central nervous system reaction (fight or flight mode) that also have the belief system that they are powerless when faced with difficulties (external locus of control), may catastrophize and interpret pain conditions to be more threatening and hopeless than individuals with a positive interpretation style and stronger

coping skills. Such a pattern may further result in withdrawal from daily activities, reducing life quality and, dependent on each individual's liability, various symptoms of mental disorders. Catastrophizing is also an aspect of several mental disorders. Thus, having for instance a depressive illness may increase the risk of chronic pain, both due to catastrophizing, which may amplify pain (Linton & Bergbom, 2011), but also because pain may be one of the symptoms of depression (Wise, Fishbain, & Holder-Perkins, 2007). In sum, the relationship between chronic pain and mental disorders is complex and most likely best understood through a bi-directional framework, where pain and mental disorders interact and amplify each other.

Chronic pain, opioid use, and mental disorders are all risk factors for suicidal ideation and suicide attempts (Campbell et al., 2016; Cheatle, 2011; Racine, 2018). In Norway, there are now more overdose deaths due to opioids compared to heroin (Gjersing & Amundsen, 2022). Although the Norwegian guidelines for prescriptions of reimbursed opioids emphasize that potential risks must be outweighed by potential benefits, it is important that physicians understand the vulnerability of chronic pain patients when making decisions about treatment.

Our findings imply that prescribers should be aware of the high psychiatric symptom burden in this group of patients, particularly in young adults. As chronic pain is influenced by interpretation and cognitive schemata, clinicians could offer multidisciplinary therapy, including assessment of psychological functioning, self-efficacy, and coping mechanisms. In other words, the psychological component of chronic pain needs to be addressed in addition to somatic pain to improve quality of life for these patients.

Strengths and limitations

Data from these national health registers are mandatory, which allows studying an unselected population. This study presents, for the first time, a complete count of all the mental health diagnoses from both primary and secondary care registered among chronic pain patients using reimbursed analgesics. There are also limitations. First, we were not able to include individuals with chronic pain without prescribed reimbursed analgesics. Individuals in long-term care can be underrepresented, as drugs administered in hospitals and nursing homes are not included in the NorPD. Approximately 20% of individuals over 90 years of age in Norway are in nursing homes (Statistics Norway, 2022). Here, we found that 6.1% of the population received reimbursed analgesics, which is significantly lower than estimates of chronic pain prevalence in Europe and in the Norwegian population (~30%) (Borchgrevink et al., 2022; Steingrímsdóttir Ó et al., 2017). Comparison with studies from other countries is complicated because of the uniqueness of the Norwegian reimbursement scheme. Regardless, our sample may not be representative of all individuals with chronic pain. Second, we excluded deceased individuals. Some of these may have died because of mental disorders (for instance by suicide). This may have underestimated the psychiatric burden in the group. Third, counting mental health diagnoses registered the same year might have led to an underestimation of the prevalence, as a person might not have been in contact with the health care system that particular year. Fourth, underestimation of prevalence of mental health diagnoses may also occur due to social stigma and unawareness of the nature of mental health symptoms, leading to patients reporting only somatic symptoms (Wittchen, Mühlig, & Beesdo, 2003). Disorders such as depression and anxiety may also sometimes present with a predominance of somatic symptoms, which could cause misclassification of mental disorders as somatic disorders (Wittchen et al., 2003). Fifth, no information on dosage, number of prescriptions, type of medication (other than opioid/non-

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- 484 opioid), or type of pain was included. There may be differences in prevalence between these
- different sub-populations. Lastly, our study was not designed to investigate causality or
- 486 direction of causality.

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- 488 AUTHOR CONTRIBUTIONS
- LCG drafted the manuscript. SS, IO, MH and LCG conceived the idea. IO and SS contributed to
- data acquisition. SS and LCG conducted the statistical analyses. All authors discussed the
- 491 results and commented on the manuscript.

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494 REFERENCES

- Bakken, I. J., Ariansen, A. M. S., Knudsen, G. P., Johansen, K. I., & Vollset, S. E. (2020). The Norwegian
 Patient Registry and the Norwegian Registry for Primary Health Care: Research potential of
 two nationwide health-care registries. *Scand J Public Health*, *48*(1), 49-55.
 doi:10.1177/1403494819859737
 - Borchgrevink, P. C., Glette, M., Woodhouse, A., Butler, S., Landmark, T., Romundstad, P., . . . Kaasa, S. (2022). A Clinical Description of Chronic Pain in a General Population Using ICD-10 and ICD-11 (The HUNT Pain Examination Study). *The Journal of Pain, 23*(2), 337-348. doi:10.1016/j.jpain.2021.08.007
 - Burke, A. L. J., Mathias, J. L., & Denson, L. A. (2015). Psychological functioning of people living with chronic pain: A meta-analytic review. *British Journal of Clinical Psychology*, *54*(3), 345-360. doi:https://doi.org/10.1111/bjc.12078
 - Campbell, G., Bruno, R., Darke, S., Shand, F., Hall, W., Farrell, M., & Degenhardt, L. (2016). Prevalence and Correlates of Suicidal Thoughts and Suicide Attempts in People Prescribed Pharmaceutical Opioids for Chronic Pain. *The Clinical journal of pain, 32*(4). Retrieved from https://journals.lww.com/clinicalpain/Fulltext/2016/04000/Prevalence and Correlates of Suicidal Thoughts and.3.aspx
 - Cheatle, M. D. (2011). Depression, Chronic Pain, and Suicide by Overdose: On the Edge. *Pain Medicine*, *12*(suppl_2), S43-S48. doi:10.1111/j.1526-4637.2011.01131.x
 - Chou, R., Hartung, D., Turner, J., Blazina, I., Chan, B., Levander, X., . . . Pappas, M. (2020). AHRQ Comparative Effectiveness Reviews. In *Opioid Treatments for Chronic Pain*. Rockville (MD): Agency for Healthcare Research and Quality (US).
 - Cicero, T. J., Wong, G., Tian, Y., Lynskey, M., Todorov, A., & Isenberg, K. (2009). Co-morbidity and utilization of medical services by pain patients receiving opioid medications: Data from an insurance claims database. *PAIN®*, *144*(1), 20-27. doi:https://doi.org/10.1016/j.pain.2009.01.026
 - Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain: an update on burden, best practices, and new advances. *The Lancet*, *397*(10289), 2082-2097. doi:10.1016/S0140-6736(21)00393-7
 - Davis, M. A., Lin, L. A., Liu, H., & Sites, B. D. (2017). Prescription Opioid Use among Adults with Mental Health Disorders in the United States. *The Journal of the American Board of Family Medicine*, 30(4), 407-417. doi:10.3122/jabfm.2017.04.170112
- 525 Dersh, J., Polatin, P. B., & Gatchel, R. J. (2002). Chronic pain and psychopathology: research findings 526 and theoretical considerations. *Psychosom Med*, *64*(5), 773-786.
- 527 doi:10.1097/01.psy.0000024232.11538.54

- 528 Dobscha, S. K., Morasco, B. J., Duckart, J. P., Macey, T., & Deyo, R. A. (2013). Correlates of 529 prescription opioid initiation and long-term opioid use in veterans with persistent pain. The Clinical journal of pain, 29(2), 102-108. doi:10.1097/AJP.0b013e3182490bdb 530
- 531 Furu, K. (2009). Establishment of the nationwide Norwegian Prescription Database (NorPD) – new 532 opportunities for research in pharmacoepidemiology in Norway. Norsk Epidemiologi, 18(2). 533 doi:10.5324/nje.v18i2.23
 - Gjersing, L., & Amundsen, E. (2022). Increasing trend in accidental pharmaceutical opioid overdose deaths and diverging overdose death correlates following the opioid prescription policy liberalization in Norway 2010–2018. International Journal of Drug Policy, 108, 103785. doi:https://doi.org/10.1016/j.drugpo.2022.103785
 - Goesling, J., Henry, M. J., Moser, S. E., Rastogi, M., Hassett, A. L., Clauw, D. J., & Brummett, C. M. (2015). Symptoms of Depression Are Associated With Opioid Use Regardless of Pain Severity and Physical Functioning Among Treatment-Seeking Patients With Chronic Pain. J Pain, 16(9), 844-851. doi:10.1016/j.jpain.2015.05.010
 - Hamina, A., Odsbu, I., Borchgrevink, P. C., Chen, L. C., Clausen, T., Espnes, K. A., . . . Skurtveit, S. (2022). Cohort Description: Preventing an Opioid Epidemic in Norway - Focusing on Treatment of Chronic Pain (POINT) - A National Registry-Based Study. Clin Epidemiol, 14, 1477-1486. doi:10.2147/clep.S382136
- 546 Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), 549 Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant 550 Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken), 63 Suppl 11, S240-252. doi:10.1002/acr.20543
 - Laugesen, K., Ludvigsson, J. F., Schmidt, M., Gissler, M., Valdimarsdottir, U. A., Lunde, A., & Sørensen, H. T. (2021). Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. Clin Epidemiol, 13, 533-554. doi:10.2147/clep.S314959
 - Linton, S. J., & Bergbom, S. (2011). Understanding the link between depression and pain. Scand J Pain, 2(2), 47-54. doi:10.1016/j.sjpain.2011.01.005
 - Muller, A. E., Clausen, T., Sjøgren, P., Odsbu, I., & Skurtveit, S. (2019). Prescribed opioid analgesic use developments in three Nordic countries, 2006–2017. Scandinavian Journal of Pain, 19(2), 345-353. doi:doi:10.1515/sjpain-2018-0307
 - Odsbu, I., Handal, H., Hjellvik, V., Borchgrevink, P. C., Clausen, T., Nesvåg, R., Skurtveit, S. (2022). Vedvarende bruk av opioider og samtidig bruk av andre vanedannende legemidler [long-term use of opioids and concurrent use of other addictive medications]. Tidsskriftet for den Norske Legeforening, 142. doi:10.4045/tidsskr.21.0659
 - Pedersen, A. G., & Ellingsen, C. L. (2015). Data quality in the Causes of Death Registry. Tidsskrift for den Norske Laegeforening, 135, 768-770. doi:10.4045/tidsskr.14.1065
 - Pukkala, E., Engholm, G., Højsgaard Schmidt, L. K., Storm, H., Khan, S., Lambe, M., . . . Ursin, G. (2018). Nordic Cancer Registries - an overview of their procedures and data comparability. Acta Oncol, 57(4), 440-455. doi:10.1080/0284186x.2017.1407039
- 569 Quinn, P. D., Rickert, M. E., Franck, J., Sariaslan, A., Boersma, K., Lichtenstein, P., . . . D'Onofrio, B. M. 570 (2019). Associations of mental health and family background with opioid analgesic therapy: a 571 nationwide Swedish register-based study. Pain, 160(11), 2464-2472. doi:10.1097/j.pain.0000000000001643 572
- 573 Racine, M. (2018). Chronic pain and suicide risk: A comprehensive review. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 87, 269-280. 574 575 doi:https://doi.org/10.1016/j.pnpbp.2017.08.020
- 576 Reid, M. C., Engles-Horton, L. L., Weber, M. B., Kerns, R. D., Rogers, E. L., & O'Connor, P. G. (2002). 577 Use of Opioid Medications for Chronic Noncancer Pain Syndromes in Primary Care. Journal of 578 General Internal Medicine, 17(3), 173-179. doi: https://doi.org/10.1046/j.1525-

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       Semenkovich, K., Chockalingam, R., Scherrer, J. F., Panagopoulos, V. N., Lustman, P. J., Ray, J. M., . . .
581
               Svrakic, D. M. (2014). Prescription Opioid Analgesics Increase Risk of Major Depression: New
582
               Evidence, Plausible Neurobiological Mechanisms and Management to Achieve Depression
583
               Prophylaxis. Mo Med, 111(2), 148-154.
```

- 584 Skurtveit, S., Sakshaug, S., Hjellvik, V., Berg, C., & Handal, M. (2014). Report: use of addictive drugs in 585 Norway 2005–2013 [Rapport: Bruk av vanedannende legemidler i Norge 2005–2013]. 586 Retrieved from Oslo, Norway: 587
 - https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2014/bruk-av-vanedannendelegemidler-pdf.pdf
 - Stannard, C. (2016). Opioids and chronic pain: using what we know to change what we do. Current Opinion in Supportive and Palliative Care, 10(2), 129-136. doi:10.1097/spc.0000000000000203
- 592 Statistics Norway. (2022). Care services. Retrieved from 593 https://www.ssb.no/en/helse/helsetjenester/statistikk/sjukeheimar-heimetenester-og-594 andre-omsorgstenester
- 595 Statistics Norway. (2023). Population. Retrieved from 596 https://www.ssb.no/statbank/table/07459/tableViewLayout1/

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- Steingrímsdóttir Ó, A., Landmark, T., Macfarlane, G. J., & Nielsen, C. S. (2017). Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. Pain, 158(11), 2092-2107. doi:10.1097/j.pain.0000000000001009
- Sullivan, M. D., Edlund, M. J., Zhang, L., Unützer, J., & Wells, K. B. (2006). Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use. Archives of Internal Medicine, 166(19), 2087-2093. doi:10.1001/archinte.166.19.2087
- Søndergård, S., Vaegter, H. B., Erlangsen, A., & Stenager, E. (2018). Ten-year prevalence of mental disorders in patients presenting with chronic pain in secondary care: A register linkage cohort study. European Journal of Pain, 22(2), 346-354. doi:https://doi.org/10.1002/ejp.1124
- The Norwegian Institute of Public Health. (2018). Helsetilstanden i Norge [Public Health in Norway]. Retrieved from Oslo: https://www.fhi.no/nettpub/hin/
- Velly, A. M., & Mohit, S. (2018). Epidemiology of pain and relation to psychiatric disorders. *Progress* in Neuro-Psychopharmacology and Biological Psychiatry, 87, 159-167. doi:https://doi.org/10.1016/j.pnpbp.2017.05.012
- Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., . . . Incidence, G. B. D. D. I. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet, 388(10053), 1545-1602. Retrieved from <Go to ISI>://WOS:000385285000008
- WHO. (1992). ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization.
- 618 WHO. (1998). International Classification of Primary Care (2 ed.). Oxford, UK: Oxford University Press.
- 619 WHO Collaborating Centre for Drug Statistics Methodology. (2021). ATC classification index with 620 DDDs, 2022. Retrieved from 621
 - https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/
- Wise, T. N., Fishbain, D. A., & Holder-Perkins, V. (2007). Painful physical symptoms in depression: a 622 623 clinical challenge. Pain Med, 8 Suppl 2, S75-82. doi:10.1111/j.1526-4637.2007.00352.x
- 624 Wittchen, H. U., Mühlig, S., & Beesdo, K. (2003). Mental disorders in primary care. Dialogues Clin 625 Neurosci, 5(2), 115-128. doi:10.31887/DCNS.2003.5.2/huwittchen
- 626 Zajacova, A., Grol-Prokopczyk, H., Limani, M., Schwarz, C., & Gilron, I. (2023). Prevalence and 627 correlates of prescription opioid use among US adults, 2019–2020. Plos One, 18(3), 628 e0282536. doi:10.1371/journal.pone.0282536

FIGURE LEGENDS

- 1. Illustration of the study population groups.
- 2. Prevalence of any mental health diagnosis in 2019 according to gender, age-, and analgesic user groups. 2A shows the combined prevalence for primary and secondary health care. 2B shows the prevalence in primary care, and 2C in specialist care. 3a and 3b. Prevalence of selected mental health diagnosis categories at the combined primary and specialist health care in 2019, according to gender, age-, and analgesic user groups.

Table 1. Overview of study population split into gender, age-, and analgesics user groups.

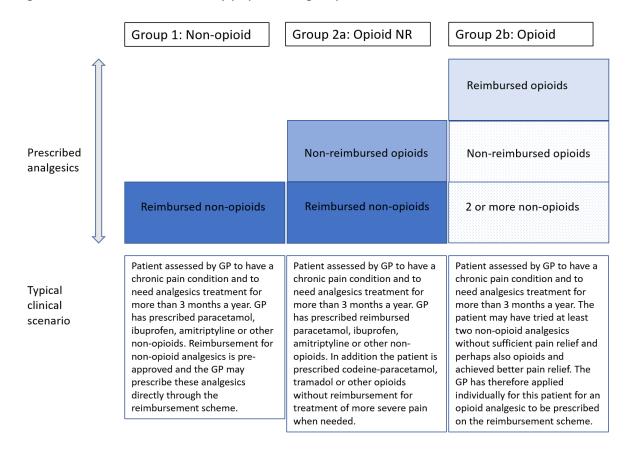
	N (%)	Age groups	N (%)	Analgesic user groups†	N (%)
Men	42,823 (30.7%)	18-44 years	7,127 (17%)	Non-opioid	3,446 (48%)
	, = = (=== , ,		, (, ,	Non-opioid + opioid	3,098 (43%)
				Opioid	583 (8%)
		45-69 years	25,963 (61%)	Non-opioid	13,388 (52%)
		•		Non-opioid + opioid	10,205 (39%)
				Opioid	2,370 (9%)
		70+ years	9,733 (23%)	Non-opioid	5,537 (57%)
				Non-opioid + opioid	3,484 (36%)
				Opioid	712 (7%)
Women	96,611 (69.3%)	18-44 years	17,820 (18%)	Non-opioid	9,064 (51%)
				Non-opioid + opioid	7,592 (43%)
				Opioid	1,164 (7%)
		45-69 years	53,421 (55%)	Non-opioid	28,685 (54%)
				Non-opioid + opioid	20,750 (39%)
				Opioid	3,986 (7%)
		70+ years	25,370 (26%)	Non-opioid	12,991 (51%)
				Non-opioid + opioid	9,952 (39%)
				Opioid	2,427 (10%)
Total	139,434		139,434		139,434

[†]Non-opioid = prevalent users of reimbursed non-opioid analgesics; Non-opioid + opioid = prevalent users of reimbursed non-opioid analgesics and non-reimbursed opioid analgesics; Opioid = prevalent users of reimbursed opioid analgesics. N (%) = The number of individuals in each group expressed as counts, and percentage of the total sample in column 1, the gender groups in column 2, and within the gender and age groups in column 3.

Table 2. Prevalence in 2019 of diagnosis categories at the combined primary and secondary health care level. Total N = 139,434.

Diagnosis category	N	Prevalence (95% CI)
Any mental health diagnosis (excluding sleep diagnoses)	49,697	29.0% (28.8-29.3%)
F00-F99 (ICD-10 codes)		, ,
P01-P99 (ICPC-2 codes)		
Sleep disorders	19,531	14.0% (13.8-14.2%)
F51, G47	•	,
P06		
Depressive and related mood disorders	14,027	10.1% (9.9-10.2%)
F32-F34, F38, F39	,	,
P76		
Phobia and other anxiety disorders	7,892	5.7% (5.5-5.8%)
F40-F42, F44	,	,
P74, P79		
Reaction to severe stress and adjustment disorders	5,466	3.9% (3.8-4.2%)
F43	,	,
P82		
Alcohol and substance use disorders		3.0% (2.9-3.1%)
F10-F16, F18-F19	4,137	, ,
P15-P16, P18-P19	.,	
Hyperkinetic disorders	2,079	1.5% (1.4-1.6%)
F90	_,0.0	, (,
P81		
Personality disorders	1,782	1.3% (1.2-1.3%)
F60-F66, F68-F69	_,	, (,
P80		
Bipolar disorders	1,468	1.1% (1.0-1.1%)
F30-F31	_,	
P73		
Somatoform and related disorders	1,441	1.0% (0.9-1.1%)
F45, F48	_,	2.070 (0.0 2.270)
P75, P78		
Unspecified mental disorder	1,130	0.8% (0.8-0.9%)
F99	_,	0.070 (0.0 0.070)
P99		
Schizophrenia and related disorders	681	0.5% (0.5-0.5%)
F20-F23, F25, F28-F29	001	0.570 (0.5 0.570)
P72		
Other symptoms	564	0.4% (0.4-0.4%)
P04, P25, P27-P28		(0)
Eating disorders	307	0.2% (0.2-0.3%)
F50	307	0.270 (0.2 0.070)
P86		
Sexual dysfunction	78	0.1% (0.0-0.1%)
F52	, 0	0.170 (0.0 0.170)
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Figure 1. Illustration of the study population groups.



Note: NR = non-reimbursed.

Figure 2. Prevalence of any mental health diagnosis (excluding sleep diagnoses) in 2019 according to gender, age-, and analgesic user groups. 2A shows the combined prevalence for primary and secondary health care. 2B shows the prevalence in primary care, and 2C in specialist care. NR = Non-reimbursed. Error bars depict 95% confidence intervals.

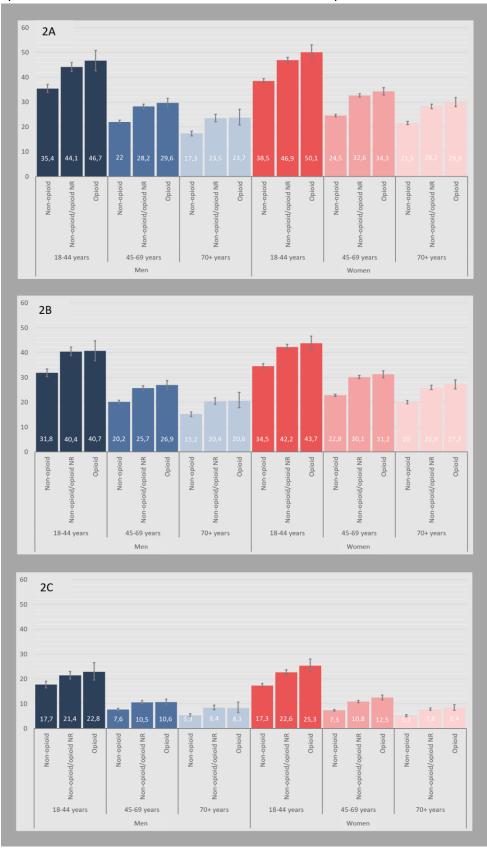
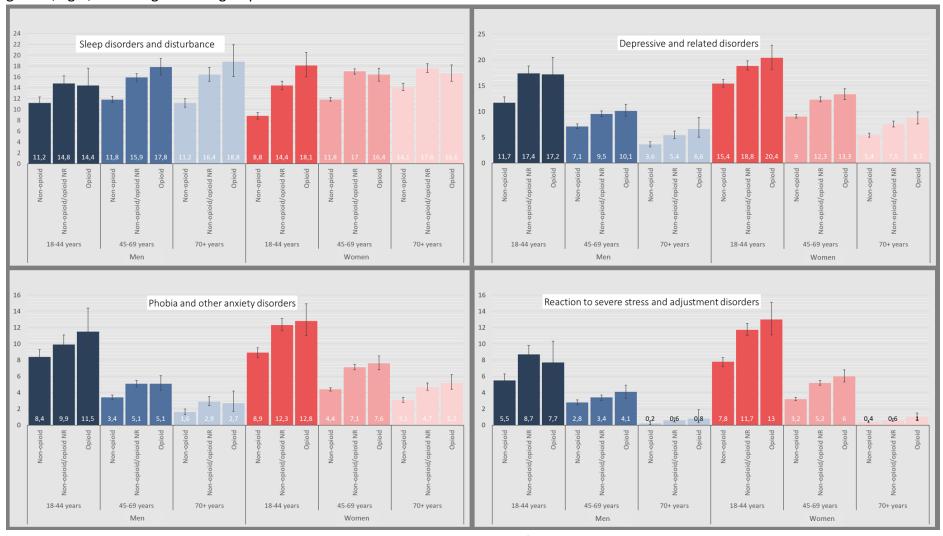
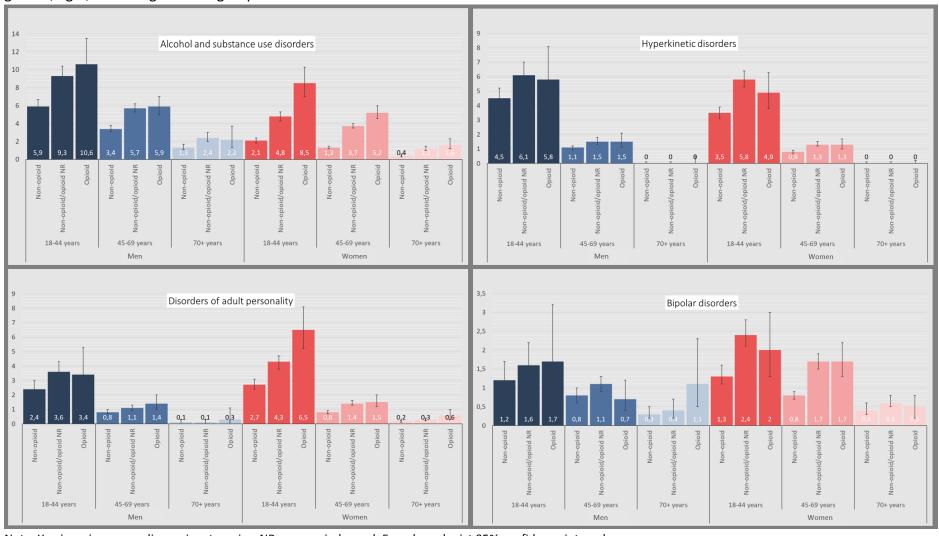


Figure 3a. Prevalence of selected mental health diagnosis categories at the combined primary and specialist health care in 2019, according to gender, age-, and analgesic user groups.



Note: Y-axis varies across diagnosis categories. NR = Non-reimbursed. Error bars depict 95% confidence intervals.

Figure 3b. Prevalence of selected mental health diagnosis categories at the combined primary and specialist health care in 2019, according to gender, age-, and analgesic user groups.



Note: Y-axis varies across diagnosis categories. NR = non-reimbursed. Error bars depict 95% confidence intervals.

Supplementary material.

- 1. Table S1. Overview of included mental health diagnosis categories at the primary and specialist health care levels
- 2. Table S2. Overview of frequencies of all mental health diagnoses registered in 2019 in primary and secondary care among prevalent users of analgesics reimbursed for chronic pain
- 3. Figure S1. Flow chart of the study population
- 4. Figure S2. Prevalence of any mental health diagnosis, including sleep diagnoses, in 2019 according to gender, age-, and analgesic user groups. 2A shows the combined prevalence for primary and secondary health care. 2B shows the prevalence in primary care, and 2C in specialist care. NR = Non-reimbursed.
- 5. Figure S3. Prevalence of sleep diagnoses in primary and secondary health care in 2019 according to gender, age-, and analgesic user groups

Table S1. Overview of included mental health diagnosis categories at the primary and secondary health care levels

			Diagnosis categories				
Combined secondary and primary health care level			Secondary health care	elevel	Primary health care level		
	ICD-10 codes	ICPC-2 codes		ICD-10 codes		ICPC-2 codes	
Any mental health diagnosis*	F00-P99	P01-F99	Any mental health diagnosis*	F00-F99	Any mental health diagnosis*	P01-P99	
Alcohol and	F10-F16	P15	Alcohol and substance abuse	F10-F16	Alcohol and substance abuse	P15	
substance abuse	F18	P16	disorders	F18	disorders	P16	
disorders	F19	P18 P19		F19		P18 P19	
Schizophrenia and	F20-F23	P72	Schizophrenia and related	F20-F23	Schizophrenia	P72	
related disorders	F25		disorders	F25			
	F28			F28			
	F29			F29			
Bipolar disorders	F30	P73	Bipolar disorders	F30	Affective psychosis	P73	
	F31			F31			
Depressive and	F32-F34	P76	Depressive and related mood	F32-F34	Depressive disorder	P76	
related mood	F38		disorders	F38			
disorders	F39			F39	Feeling depressed		
						P03	
Phobia and other	F40-F42	P74	Phobia and other anxiety	F40-F42	Phobia and other anxiety	P74	
anxiety disorders	F44	P79	disorders	F44	disorders	P79	
					Feeling	P01	
					anxious/nervous		
Reaction to severe	F43	P82	Reaction to severe stress and	F43	Post-traumatic stress disorder	P82	
stress and			adjustment disorders				
adjustment					Acute stress reaction		
disorders						P02	
Somatoform and	F45	P75	Somatoform and	F45	Somatization disorder and	P75	
neurasthenia	F48	P78	neurasthenia disorders	F48	neuraesthenia	P78	
disorders							

Eating disorders	F50	P86	Eating disorders	F50	Anorexia nervosa/bulimia	P86
Sleep disorders	F51	P06	Sleep disorders	F51		
and disturbance	G47			G47	Sleep disturbance	P06
Sexual dysfunction	F52		Sexual dysfunction	F52		
					Sexual	P07
					desire/fulfillment reduced	P08
Disorders of adult	F60-F66	P80	Disorders of adult personality	F60-F66	Personality disorder	P80
personality and	F68		and behaviour	F68		
behaviour	F69			F69		
Hyperkinetic disorders	F90	P81	Hyperkinetic disorders	F90	Hyperkinetic disorder	P81
					Other symptoms	P04 P25 P27-P28
Unspecified mental disorder	F99	P99	Unspecified mental disorder	F99	Psychological disorders other Psychological	P99
					symptom/complaint other	P29

Note: ICPC-2 symptom diagnoses were not embedded in the combined secondary and primary health care disorder categories, with the exception of sleep disturbance. *Sleep diagnoses were excluded from this diagnosis category, as sleep problems are often secondary to pain.

Table S2. Overview of frequencies of all mental health diagnoses registered in 2019 in primary and secondary care among prevalent users of analgesics reimbursed for chronic pain.

	Primary care			Secondary care			
Main groups of mental	ICPC-2	Description	N (%)	ICD-10	Description	N (%)	
disorders	code			code			
Any mental health diagnosis	P01-P99		46567 (33.4%)	F00-F99		14516 (10.4%)	
Organic, including				F00	Dementia in Alzheimer disease	267 (0.2%)	
symptomatic disorders	P70	Dementia	1600 (1.1%)	F01	Vascular dementia	483 (0.3%)	
				F02	Dementia in other diseases	83 (0.1%)	
				F03	Unspecified dementia	343 (0.2%)	
	P71	Organic psychosis other	366 (0.3%)	F04	Organic amnesic syndrome	6 (0.0%)	
				F05	Delirium	495 (0.4%)	
				F06	Other mental disorders due to brain damage/dysfunction/physical	707 (0.5%)	
					disease		
				F07	Personality and behavioural disorders due to brain	206 (0.1%)	
					disease/damage/dysfunction		
				F09	Unspecified organic or symptomatic mental disorder	11 (0.0%)	
Symptoms and ailments	P05	Senility, feeling/behaving old	412 (0.3%)	-			
Alcohol and substance abuse	P15	Chronic alcohol abuse,	1027 (0.7%)	F10	Alcohol related disorders	1022 (0.7%)	
disorders	P16	Acute alcohol abuse	303 (0.2%)				
	P19	Drug abuse	944 (0.7%)	F11	Opioid related disorders	1067 (0.8%)	
				F12	Cannabis related disorders	213 (0.2%)	
	P18	Medication abuse	1172 (0.8%)	F13	Sedative, hypnotic or anxiolytic related disorders	630 (0.5%)	
				F14	Cocaine related disorders	16 (0.0%)	
				F15	Other stimulant related disorders	209 (0.1%)	
				F16	Hallucinogen related disorders	6 (0.0%)	
	P17	Tobacco abuse	255 (0.2%)	F17	Nicotine dependence	106 (0.1%)	
				F18	Inhalant related disorders	<5 (0.0%)	
				F19	Other psychoactive substance related disorders	411 (0.3%)	
Schizophrenia and related	P72	Schizophrenia	465 (0.3%)	F20	Schizophrenia	204 (0.1%)	
disorders				F21	Schizotypal disorder	7 (0.0%)	
	P98	Psychosis NOS/other	0 (0%)	F22	Delusional disorders	119 (0.1%)	
				F23	Brief psychotic disorder	46 (0.0%)	
				F24	Induced delusional disorder	0 (0.0%)	
				F25	Schizo-affective disorder	95 (0.1%)	
				F28	Other nonorganic psychotic disorders	5 (0.0%)	
				F29	Unspecified psychosis	50 (0.0%)	
Mood disorders							
Bipolar disorders	P73	Affective psychosis	1200 (0.9%)	F30	Manic episode	25 (0.0%)	
				F31	Bipolar disorder	717 (0.5%)	

Depressive disorders	P76 P77	Depressive disorder Suicide/suicide attempt	12013 (8.6%) 385 (0.3%)	F32	Major depressive disorder, single episode	2304 (1.7%)
				F33	Major depressive disorder, recurrent	1944 (1.4%)
				F34	Persistent mood disorders	239 (0.2%)
				F38	Other mood disorders	29 (0.0%)
				F39	Unspecified mood disorder	35 (0.0%)
Symptoms and ailments	P03	Feeling depressed	2570 (1.8%)	-	·	` ′
nnxiety and related lisorders						
21301 del 3	P79	Phobia/compulsive disorder	973 (0.7%)	F40	Phobic anxiety disorders	712 (0.5%)
	P74	Anxiety disorder/anxiety state	4836 (3.5%)	F41	Other anxiety disorders (e.g. panic disorder and generalized anxiety disorder)	2114 (1.5%)
			()	F42	Obsessive-compulsive disorder	189 (0.1%)
	P82	Post-traumatic stress disorder	2778 (2.0%)	F43	Reaction to severe stress, and adjustment disorders	3883 (2.8%)
				F44	Dissociative disorders	257 (0.2%)
	P75	Somatization disorder	526 (0.4%)	F45	Somatoform disorders	503 (0.4%)
	P78	Neuraesthenia/surmenage	252 (0.2%)	F48	Other neurotic disorder (e.g. neuraesthenia)	244 (0.2%)
Symptoms and ailments	P01	Feeling anxious/nervous/tense	5351 (3.8%)	-	other neurotic disorder (e.g. neuroestrema)	211 (0.270)
Symptoms and animents	P02	Acute stress reaction	4181 (3.0%)	-		
Behavioural syndromes			- ()			
associated with physiological						
disturbances/physical factors						
Eating disorders	P86	Anorexia nervosa/bulimia	90 (0.1%)	F50	Including e.g. anorexia and bulimia	254 (0.2%)
						'
Sleep disorders	P06	Sleep disturbance	15967 (11.5%)	G47	Sleep disorders (including e.g. insomnia and narcolepsy)	4728 (3.4%)
				F51	Non-organic sleep disorders	119 (0.1%)
Other behavioural				F52	Sexual dysfunction not caused by organic disorder/disease	78 (0.1%)
syndromes				F53	Mental and behavioural disorders associated with the puerperium	<5 (0.0%)
				F54	Psychological and behavioural factors associated with disorders or diseases classified elsewhere	94 (0.1%)

				F59	Unspecified behavioural syndromes associated with physiological disturbances/physical factors	<5 (0.0%)
Symptoms and ailments	P07	Sexual desire reduced	71 (0.1%)	-		
	P08	Sexual fulfilment reduced	685 (0.5%)	-		
	P10	Stammering/stuttering/tic	54 (0.0%)	-		
Disorders of adult						
personality and behavior						
	P80	Personality disorder	775 (0.6%)	F60	Specific personality disorders	926 (0.7%)
				F61	Mixed and other personality disorders	203 (0.1%)
				F62	Enduring personality changes	151 (0.1%)
				F63	Habit and impulse disorders	73 (0.1%)
				F64	Gender identity disorders	26 (0.0%)
				F65	Disorders of sexual preference	<5 (0.0%)
				F66	Psychological and behavioural disorders associated with sexual	<5 (0.0%)
					development and orientation	
				F68	Other disorders of adult personality and behavior	18 (0.0%)
				F69	Unspecified disorder of adult personality and behavior	7 (0.0%)
Symptoms and ailments	P09	Sexual preference concern	30 (0.0%)	-		
Mental retardation	P85	Mental retardation	396 (0.3%)	F70	Mild mental retardation	91 (0.1%)
				F71	Moderate mental retardation	46 (0.0%)
				F72	Severe mental retardation	64 (0.0%)
				F73	Profound mental retardation	28 (0.0%)
				F78	Other mental retardation	7 (0.0%)
				F79	Unspecified mental retardation	66 (0.0%)
Disorders of psychological				F80	Specific developmental disorders of speech and language	22 (0.0%)
development						
				F81	Specific developmental disorders of scholastic skills	42 (0.0%)
				F82	Specific developmental disorder of motor function	0 (0.0%)
				F83	Mixed specific developmental disorders	17 (0.0%)
				F84	Pervasive developmental disorders	144 (0.1%)
				F88	Other disorder of psychological development	<5 (0.0%)
				F89	Unspecified disorder of psychological development	6 (0.0%)
Symptoms and ailments	P24	Specific learning problem	92 (0.1%)	-		
Behavioral and emotional	P81	Hyperkinetic disorder	1729 (1.2%)	F90	Hyperkinetic disorder	979 (0.7%)
disorders with onset usually		···	` '	F91	Conduct disorders	11 (0.0%)
occurring in childhood or				F92	Mixed disorders of conduct and emotions	6 (0.0%)
adolescence				F93	Emotional disorders with onset specific to childhood	7 (0.0%)
				F94	Disorder of social functioning with onset specific to childhood and	<5 (0.0%)
				F95	adolescence	38 (0.0%)
					Tic disorders	, ,
				F98	Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence	14 (0.0%)

Symptoms and ailments	P11	Eating problem in child	<5 (0.0%)	-		
	P12	Bedwetting/enuresis	12 (0.0%)	-		
	P13	Encopresis/bowel training problem	6 (0.0%)	-		
	P22	Child behavior symptom/complaint	28 (0.0%	-		
	P23	Adolescent behavior	<5 (0.0%)	-		
		symptom/complaint				
Other symptoms and	P04	Feeling/behaving irritably/angry	101 (0.1%)	-		
ailments						
	P20	Memory disturbance	1959 (1.4%)	-		
	P25	Phase of life problem adult	102 (0.1%)	-		
	P27	Fear of mental disorder	330 (0.2%)	-		
	P28	Limited function/disability	49 (0.0%)	-		
	P29	Psychological symptom/complaint	3635 (2.6%)	-		
		other				
Other mental disorders	P99	Psychological disorders other	976 (0.7%)	F99	Mental disorder, not otherwise specified	161 (0.1%)

Note: Total number of individuals included was 139434.

All patients with reimbursement code -71 in Norway in 2019 $N = 255,829 \label{eq:N}$ Patients dispensed reimbursed non-opioid analgesics and non-reimbursable opioid analgesics N = 102,246 Patients dispensed reimbursed opioid analgesics N = 18,532 Patients dispensed reimbursed nonopioid analgesics N = 135,051 In palliative care (code -90) N = 11,161 N = 132,471 N = 95,078 N = 17,119 Dead in 2019 N = 2,811N = 131,075 N = 93,883 N = 16,899 No dispensed -71 prescriptions in 2018 N = 84,224 N = 83,653 N = 60,946 N = 12,984 Malignant pain/cancer N = 17,779 N = 55,136 N = 11,244 N = 73,424 Under age 18 N = 370 N = 55,081 N = 11,242 N = 73,111

Figure S1. Flow chart of the study population.

Note: Reimbursement code -71 = A reimbursement code established by the Norwegian Medicines Agency for reimbursement of analgesics for the treatment of chronic, non-malignant pain.

Figure S2. Prevalence of any mental health diagnosis, including sleep diagnoses, in 2019 according to gender, age-, and analgesic user groups. 2A shows the combined prevalence for primary and secondary health care. 2B shows the prevalence in primary care, and 2C in specialist care. NR = Non-reimbursed.

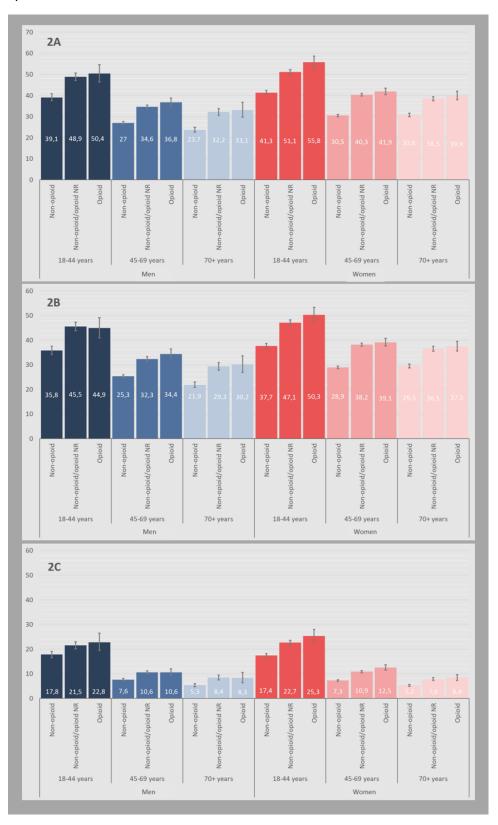


Figure S3. Prevalence of sleep diagnoses in primary and secondary health care in 2019 according to gender, age-, and analgesic user groups Sleep disturbance Primary care Sleep disorders Specialist care 18-44 years 45-69 years 18-44 years 18-44 years 70+ years 45-69 years 70+ years 45-69 years 18-44 years 45-69 years Men Women Men Women