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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:	<p>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.</p> <p>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).</p> <p>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%]).</p> <p>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.</p>
Additional Information:	
Question	Response
<p>Significance (not for "Case reports")</p> <p>Below please give a paragraph entitled "Significance", indicating the main aspects where this work adds significantly to</p>	<p>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</p>

existing knowledge in the field, and if appropriate to clinical practice. The significance statement should be short, attention-grabbing, non-redundant with the conclusions and rigorously in line with the contents of the full article. It should not exceed 80 words and will be added to the end of the abstract at the time of typesetting. This paragraph will NOT count to the abstract's total word limit of 250 words. The statement "Significance" also applies to Review papers.

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

1 **Mental disorder prevalence in chronic pain patients using opioid versus non-opioid**
2 **analgesics: A registry-linkage study**

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4 Running head: Mental disorders in chronic pain patients

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31

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34 Original article

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36 Tables: 2, Figures: 3

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38 What is already known about the topic:

- 39
- 40 • Mental disorders are more common among individuals with chronic pain and users of
opioid analgesics than among pain-free individuals

41 What does this study add:

- 42
- 43 • Large-scale prevalence estimates across different reimbursed analgesic user-, age
44 groups, and gender from nationwide registry data on all mental health diagnoses in
both primary and secondary health care.

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

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

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88 Abstract

89 **Background:** Chronic pain and mental disorders are leading causes of disability worldwide.
90 Individuals with chronic pain are more likely to experience mental disorders compared to
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
94 patients receiving opioid versus non-opioid analgesics, according to age and gender.

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).

100 **Results:** Prevalence of any mental health diagnosis was 35.6% (95% confidence interval:
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
105 compared to non-opioids. The group with the highest overall prevalence was young women
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
109 use and high psychiatric comorbidity suggests that prescribers should attend to mental
110 health in addition to somatic pain.

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113 Keywords: Chronic pain; mental health diagnoses; opioid; analgesics; registry.

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117 Data availability statement:

118 This observational study is based on individual level data from population-based health
119 registers. Therefore, the authors are by law not able to make this data fully available to the
120 public.

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127 INTRODUCTION

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

136 Mental disorders are another leading cause of disability (Vos et al., 2016), and
137 individuals with chronic pain are more likely to experience mental disorders compared to
138 pain-free individuals (Burke, Mathias, & Denson, 2015; Velly & Mohit, 2018). Common
139 mental health diagnoses among chronic pain patients are anxiety, depressive, somatoform,
140 personality, and alcohol and substance use disorders (Dersh, Polatin, & Gatchel, 2002;
141 Søndergård, Vaegter, Erlangsen, & Stenager, 2018). There is, however, variation across
142 studies in which diagnoses are most common in this group. This could be because studies
143 use various screening instruments, and are often based on self-report data, therefore lacking
144 the full picture from both primary and secondary care (Burke et al., 2015; Velly & Mohit,
145 2018). Registry data are useful for estimating prevalence of individuals receiving medical
146 treatment, but few countries have nationwide registries on somatic and mental health
147 diagnoses. In Norway, chronic pain patients can be identified through a reimbursement
148 scheme for prescribed analgesics. By linkage with data on contact with public health care, it
149 is possible to provide prevalence of all registered mental health diagnoses in this group.

150 Although mental disorders are common in individuals using opioids for chronic pain
151 (Cicero et al., 2009; Davis, Lin, Liu, & Sites, 2017; Dobscha, Morasco, Duckart, Macey, &
152 Deyo, 2013; Quinn et al., 2019; Reid et al., 2002; Sullivan, Edlund, Zhang, Unützer, & Wells,
153 2006), prevalence estimates of mental disorder diagnoses from representative data on this
154 group compared to those using non-opioid analgesics are lacking. Information on differences
155 between individuals with chronic pain using opioids versus non-opioids may improve
156 understanding of the patient’s health problems, and aid prescribers in choosing the best
157 treatment option.

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

169

170 MATERIALS AND METHODS

171 *Study setting and data sources*

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

174 between the health registries possible (Laugesen et al., 2021). Data on filled prescriptions
175 were retrieved from the Norwegian Prescription Database (NorPD; Furu, 2009), where drugs
176 are classified according to the Anatomical Therapeutic Chemical (ATC) classification system
177 (WHO Collaborating Centre for Drug Statistics Methodology, 2021). Information on
178 indication of use is available for reimbursed prescriptions. The Norwegian Patient Registry
179 (NPR) contains information on hospitalizations and outpatient secondary health care visits
180 (Bakken, Ariansen, Knudsen, Johansen, & Vollset, 2020). Diagnoses are recorded after each
181 visit according to the International Classification of Diseases, 10th revision (ICD-10; WHO,
182 1992). The Norwegian Registry for Primary Health Care (NRPHC) contains information on all
183 patient visits in primary health care (Bakken et al., 2020). Diagnoses from primary care are
184 recorded after each visit according to the International Classification of Primary Care, 2nd
185 edition (ICPC-2; WHO, 1998). We have access to all recorded diagnoses from each visit from
186 NPR and NRPHC. Data on incident malignancies (ICD-10) were retrieved from The Cancer
187 Registry of Norway (Pukkala et al., 2018), and dates of death were retrieved from the Cause
188 of Death Registry (Pedersen & Ellingsen, 2015).

189

190 *Reimbursement of analgesics for treatment of chronic pain in Norway*

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

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

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

209

210 *Reimbursement of opioid analgesics for treatment of chronic pain in Norway*

211 To be eligible for reimbursed opioid analgesics one must have a chronic pain condition
212 (regardless of diagnosis), and the need for pharmacological treatment for more than three
213 months a year (i.e. be classified under the reimbursement code -71). In addition, several
214 criteria must be met for approval of the individual application: the patient's risk of addiction
215 must be assessed to be lower than the benefits of receiving the treatment, the pain needs to
216 be carefully assessed, which can be achieved using various validated instruments (e.g.,
217 Hawker, Mian, Kendzerska, & French, 2011), and a concrete treatment plan must be
218 established. For conditions other than active cancer, it must also be documented that the
219 patient has tried at least two other non-opioid medications without satisfactory effect. The
220 individual application for reimbursement of an opioid analgesic requires that a physician
221 documents these criteria on behalf of the patient to the health authorities. Initially, only

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

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

238 In sum, the Norwegian reimbursement scheme for chronic pain represents a unique
239 opportunity to identify individuals with chronic pain in need of pharmacological treatment.
240 The strict clinical criteria should limit the risk for false positives on the code -71, but
241 reliability and validity studies are currently lacking.

242

243 *Study population*

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

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

255

256 *Insert Figure 1 here*

257

258 Due to the strict criteria and the individual application that is needed for a patient to be
259 prescribed reimbursed opioids, we expect different results on prevalence between group 2a
260 and b, and group 2b to be the smallest of the three groups. As we were interested in
261 prevalent users of analgesics for chronic non-malignant pain, we excluded everyone with at
262 least one filled prescription of reimbursed opioids for palliative care in 2019 and everyone
263 dying in 2019. We further excluded individuals with no filled prescriptions of reimbursed
264 analgesics in 2018. Finally, we excluded everyone with at least one recorded cancer
265 diagnosis since 1990 and everyone below 18 years of age. The analytic sample consisted of
266 139,434 individuals (69.3% women).

267

268 *Outcome*

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

272

273 *Statistical analyses*

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

293

294 RESULTS

295 *Study population*

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

302

303 *Insert Table 1 here*

304

305 *Overall prevalence*

306 The overall prevalence of any mental health diagnosis in this study population was 29.0%
307 (95% CI 28.8-29.3%), when sleep diagnoses were removed. The prevalence was 35.6% (35.4-
308 35.9%) when sleep diagnoses were included (Fig S2). The contrast was large and statistically
309 significant in overall prevalence between group 2b - reimbursed opioid (34.0% [33.1-34.9%])
310 and group 1 - non-opioid analgesics (25.2% [24.9-25.5%]). No difference was observed for
311 the two opioid user groups (2b versus 2a). For the three age groups (18-44 years; 45-69
312 years; 70+ years), the overall prevalence was 42.0% (41.4-42.7%), 27.3% (27.0-27.7%), and
313 23.5% (23.1-24.0%), respectively, and hence markedly highest among the youngest age
314 group. The prevalence was higher among women than men (30.1% [29.9-30.4%] versus
315 26.5% [26.0-26.9%], respectively). The group with highest overall prevalence was young
316 women using reimbursed opioid analgesics (50.1% [47.2-53.0%]). More results on overall

317 prevalence split on analgesic user group, age group, and gender are shown in Figure 2.
318 Prevalence of all singular mental health diagnoses in primary and secondary health care,
319 including ICPC-2 symptom diagnoses is provided in the supplementary material (Table S2).

320

321 *Insert Figure 2 here*

322

323 *Diagnosis categories*

324 At the combined primary and secondary health care level, the three most prevalent
325 diagnosis categories were sleep disorders and disturbance (14.0% [13.8-14.2%]), depressive
326 and related disorders (10.1% [9.9-10.2%]), and phobia and other anxiety disorders (5.7%
327 [5.5-5.8%]). For all three diagnosis categories, there was a higher prevalence in group 2b -
328 reimbursed opioids compared to in group 1 reimbursed non-opioids (17.0% [16.3-17.7%]
329 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%]
330 versus 4.5% [4.4-4.7%], respectively). However, there were no differences observed for the
331 two opioid user groups (group 2b versus 2a). The ordering of the consecutive diagnosis
332 categories and their prevalence are shown in Table 2. More results on diagnosis categories
333 split into gender, age-, and analgesic user groups are shown in Figure 3a and 3b.

334

335 *Insert Table 2 here*

336

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

341 reimbursed opioids compared to group 1 - reimbursed non-opioids (sleep disturbance:
342 14.1% [13.4-14.7%] versus 9.5% [9.3-9.7%]; depressive disorder: 10.0% [9.5-10.6%] versus
343 7.3% [7.2-7.5%]).

344

345 *Insert Figure 3 here*

346

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

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

357

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

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

364 (e.g., for men aged 45-69 prevalence for those dispensed reimbursed non-opioids were 0.8%
365 [0.67-0.98%] compared to 0.4% [0.21-0.80%] for those dispensed reimbursed opioids).

366

367 DISCUSSION

368 Using up-to-date, nationwide, and complete registry data, we present a thorough
369 investigation of the prevalence of mental health diagnoses in different subgroups of chronic
370 pain patients receiving reimbursed analgesics. The overall prevalence was substantial, as
371 ≈30% were registered with one or more mental health diagnoses. In the general Norwegian
372 population in 2019, ≈5% of the men and ≈7% of the women utilized secondary health care
373 due to a mental disorder (The Norwegian Institute of Public Health, 2018). For primary
374 health care, the numbers were ≈14% for men and ≈21% for women. In our sample, the
375 numbers were 10.3% for men and 10.4% for women in specialist health care, and 23.9% and
376 27.6% for primary health care. It therefore seems that individuals with chronic pain have a
377 substantially higher psychiatric burden than the general population.

378 The most common diagnosis categories at the combined primary and secondary
379 health care level were sleep disorders, depressive and related disorders, and phobia and
380 other anxiety disorders. For most of the diagnosis categories, the prevalence was higher
381 among users of opioids compared to non-opioid analgesics. There was also evidence of age
382 and gender differences. The highest prevalence was found among the youngest women (18-
383 44 years).

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

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

393 In line with our hypothesis, most of the diagnosis categories were significantly more
394 prevalent in patients using reimbursed opioid compared to non-opioid analgesics. This fits
395 well with previous findings that individuals with mental disorders more often use opioid
396 analgesics (Cicero et al., 2009; Reid et al., 2002). However, an important remaining question
397 is why these groups differ. As there are strict criteria for being prescribed reimbursed
398 opioids, it is likely that pain is more severe in this group, which in itself may increase risk for
399 mental disorders (e.g., through sleep difficulties, feelings of hopelessness, and/or social
400 isolation). Long-term opioid use itself could increase susceptibility to mental disorders, for
401 instance through neurobiological or psychosocial mechanisms (Semenkovich et al., 2014).
402 Another possibility is that individuals with co-occurring pain and some types of mental
403 disorders may wish to stay on opioid treatment, as some psychiatric symptoms can be
404 alleviated by the opioid's sedative effect (e.g., Goesling et al., 2015). However, our
405 hypothesis on significant differences between the two opioid groups was not supported. The
406 exception was for alcohol and substance use disorders, where the prevalence increased in
407 line with the hierarchy of the analgesic user groups ($2b > 2a > 1$; Fig. 3b). Regarding opioid
408 use, approximately 10% of the population was prescribed opioids in 2019 in Norway, a
409 majority only one prescription (Odsbu, 2022; Skurtveit, Sakshaug, Hjellvik, Berg, & Handal,
410 2014). Overall, a larger proportion of the Norwegian population has consistently been
411 prescribed opioids to the Swedish and Danish populations (Muller, Clausen, Sjøgren, Odsbu,

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

416 Perhaps the most striking finding was that there were so large age differences in
417 prevalence of mental health diagnoses. The youngest age group had higher prevalence of
418 almost all diagnosis categories, except sleep disorders and disturbance. Mental disorders
419 often emerge when people are in their 20s, and some mental disorders “burn out” with
420 increasing age (e.g., some personality disorders). Increasing age is also often followed by
421 more pain due to onset of rheumatic and musculoskeletal disorders. Individuals with chronic
422 pain in young age are also in a stage of life where chronic pain may influence functional
423 outcomes such as work participation to a larger degree. We could also have encountered a
424 cohort effect: younger individuals are generally more educated and open about mental
425 health symptoms and may therefore have a lower threshold for discussing such symptoms
426 with their GP. This study was not designed to investigate direction of causation.

427 Nevertheless, some discussion on this topic is warranted. Although the mechanisms behind
428 the pain and mental disorder association are not yet fully understood, several useful
429 frameworks exist. One of these is the diathesis stress model (Dersh et al., 2002). An
430 individual’s premorbid psychological functioning may act as the diathesis and pain as the
431 stressor. Individuals vary in their perception of threat and coping strategies. An individual
432 with a low threshold to activate a strong central nervous system reaction (fight or flight
433 mode) that also have the belief system that they are powerless when faced with difficulties
434 (external locus of control), may catastrophize and interpret pain conditions to be more
435 threatening and hopeless than individuals with a positive interpretation style and stronger

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

445 Chronic pain, opioid use, and mental disorders are all risk factors for suicidal ideation
446 and suicide attempts (Campbell et al., 2016; Cheatle, 2011; Racine, 2018). In Norway, there
447 are now more overdose deaths due to opioids compared to heroin (Gjersing & Amundsen,
448 2022). Although the Norwegian guidelines for prescriptions of reimbursed opioids emphasize
449 that potential risks must be outweighed by potential benefits, it is important that physicians
450 understand the vulnerability of chronic pain patients when making decisions about
451 treatment.

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

458

459 *Strengths and limitations*

460 Data from these national health registers are mandatory, which allows studying an
461 unselected population. This study presents, for the first time, a complete count of all the
462 mental health diagnoses from both primary and secondary care registered among chronic
463 pain patients using reimbursed analgesics. There are also limitations. First, we were not able
464 to include individuals with chronic pain without prescribed reimbursed analgesics.
465 Individuals in long-term care can be underrepresented, as drugs administered in hospitals
466 and nursing homes are not included in the NorPD. Approximately 20% of individuals over 90
467 years of age in Norway are in nursing homes (Statistics Norway, 2022). Here, we found that
468 6.1% of the population received reimbursed analgesics, which is significantly lower than
469 estimates of chronic pain prevalence in Europe and in the Norwegian population (~30%)
470 (Borchgrevink et al., 2022; Steingrimsdóttir Ó et al., 2017). Comparison with studies from
471 other countries is complicated because of the uniqueness of the Norwegian reimbursement
472 scheme. Regardless, our sample may not be representative of all individuals with chronic
473 pain. Second, we excluded deceased individuals. Some of these may have died because of
474 mental disorders (for instance by suicide). This may have underestimated the psychiatric
475 burden in the group. Third, counting mental health diagnoses registered the same year
476 might have led to an underestimation of the prevalence, as a person might not have been in
477 contact with the health care system that particular year. Fourth, underestimation of
478 prevalence of mental health diagnoses may also occur due to social stigma and unawareness
479 of the nature of mental health symptoms, leading to patients reporting only somatic
480 symptoms (Wittchen, Mühlhig, & Beesdo, 2003). Disorders such as depression and anxiety
481 may also sometimes present with a predominance of somatic symptoms, which could cause
482 misclassification of mental disorders as somatic disorders (Wittchen et al., 2003). Fifth, no
483 information on dosage, number of prescriptions, type of medication (other than opioid/non-

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

487
488 AUTHOR CONTRIBUTIONS

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

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493
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629

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.

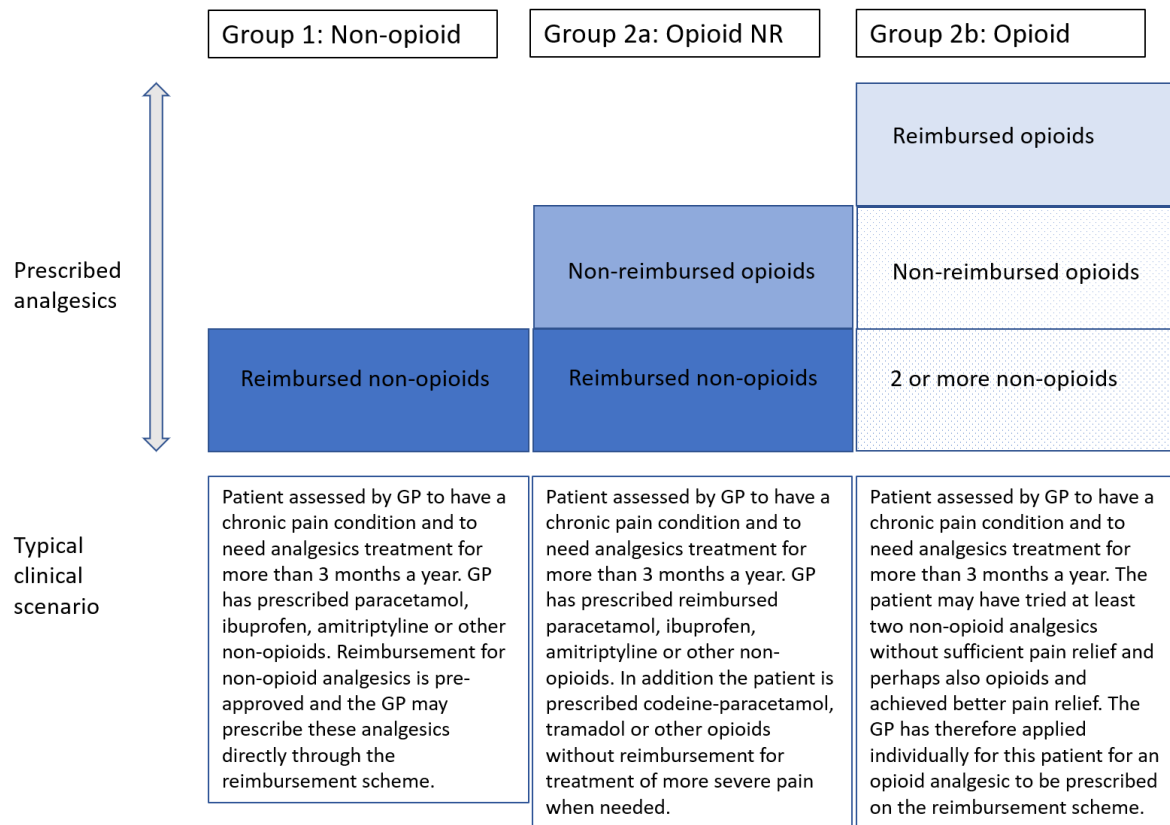
	N (%)	Age groups	N (%)	Analgesic user group [†]	N (%)
Men	42,823 (30.7%)	18-44 years	7,127 (17%)	Non-opioid	3,446 (48%)
				Non-opioid + opioid	3,098 (43%)
				Opioid	583 (8%)
		45-69 years	25,963 (61%)	Non-opioid	13,388 (52%)
				Non-opioid + opioid	10,205 (39%)
				Opioid	2,370 (9%)
		70+ years	9,733 (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) F00-F99 (ICD-10 codes) P01-P99 (ICPC-2 codes)	49,697	29.0% (28.8-29.3%)
Sleep disorders F51, G47 P06	19,531	14.0% (13.8-14.2%)
Depressive and related mood disorders F32-F34, F38, F39 P76	14,027	10.1% (9.9-10.2%)
Phobia and other anxiety disorders F40-F42, F44 P74, P79	7,892	5.7% (5.5-5.8%)
Reaction to severe stress and adjustment disorders F43 P82	5,466	3.9% (3.8-4.2%)
Alcohol and substance use disorders F10-F16, F18-F19 P15-P16, P18-P19	4,137	3.0% (2.9-3.1%)
Hyperkinetic disorders F90 P81	2,079	1.5% (1.4-1.6%)
Personality disorders F60-F66, F68-F69 P80	1,782	1.3% (1.2-1.3%)
Bipolar disorders F30-F31 P73	1,468	1.1% (1.0-1.1%)
Somatoform and related disorders F45, F48 P75, P78	1,441	1.0% (0.9-1.1%)
Unspecified mental disorder F99 P99	1,130	0.8% (0.8-0.9%)
Schizophrenia and related disorders F20-F23, F25, F28-F29 P72	681	0.5% (0.5-0.5%)
Other symptoms P04, P25, P27-P28	564	0.4% (0.4-0.4%)
Eating disorders F50 P86	307	0.2% (0.2-0.3%)
Sexual dysfunction F52	78	0.1% (0.0-0.1%)

Figure 1. Illustration of the study population groups.

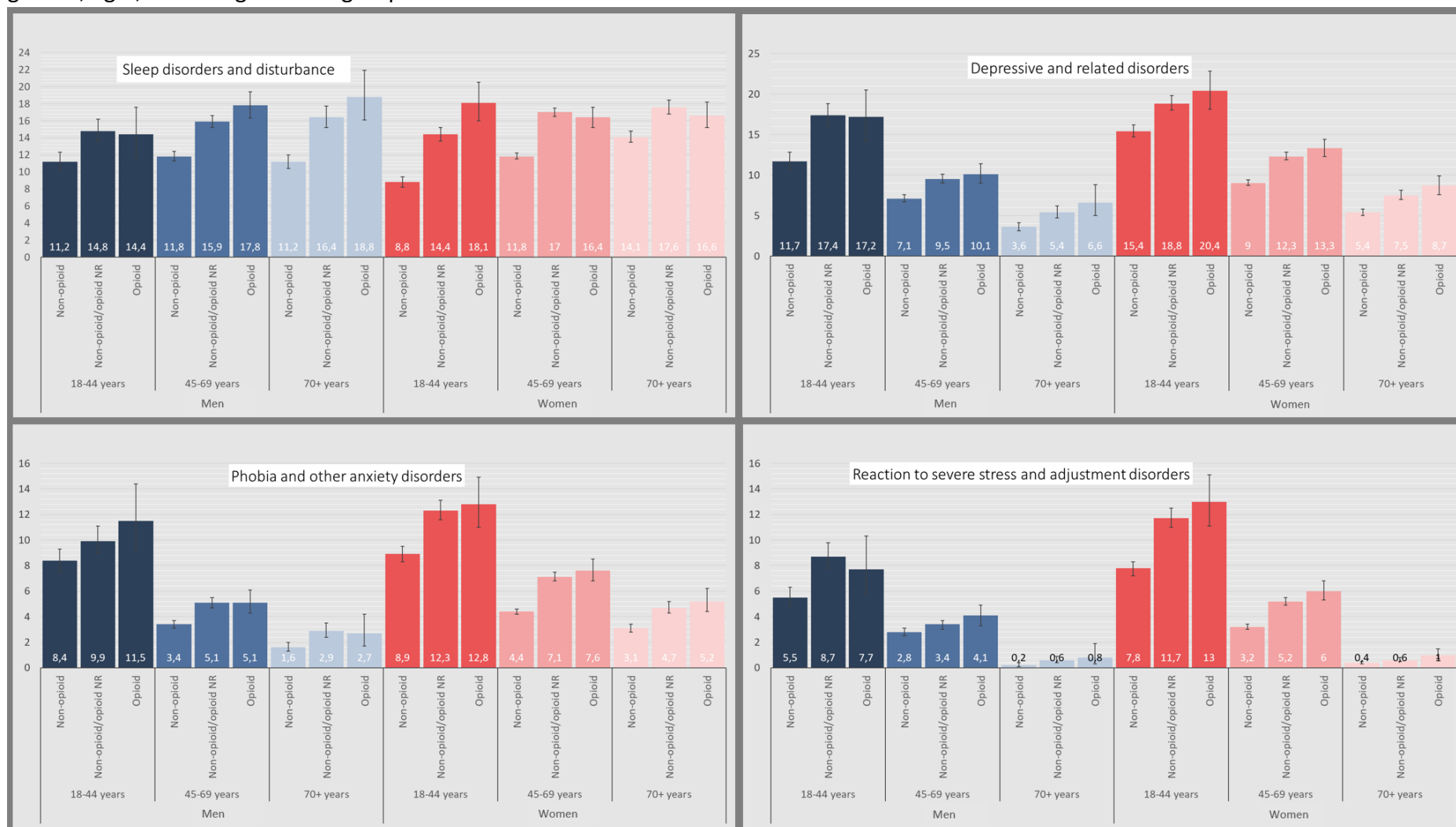


Note: NR = non-reimbursed.

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.

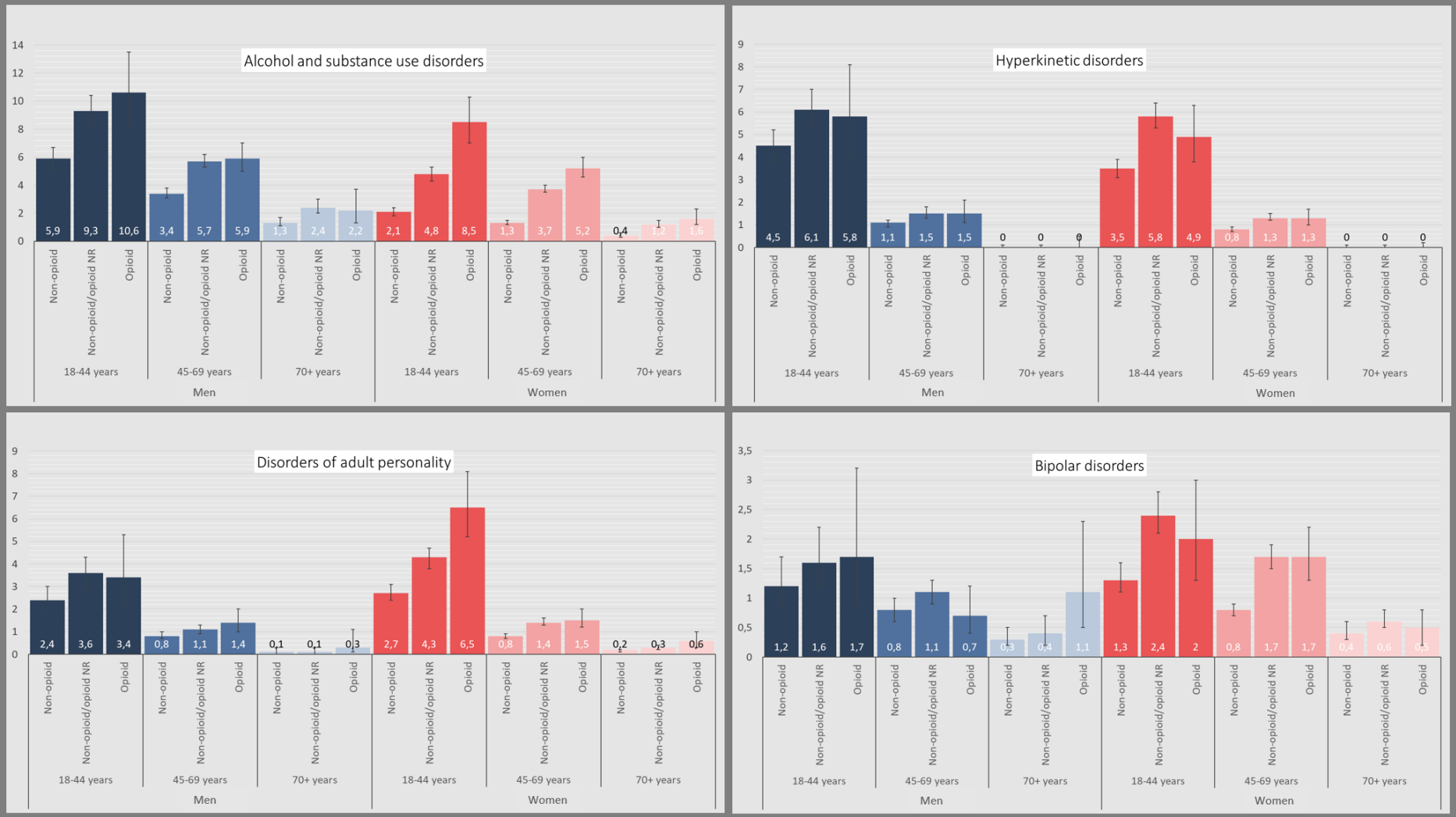


Figure 3a. Prevalence of selected mental health diagnosis categories at the combined primary and specialist health care in 2019, according to gender, age-, and analgesic user groups.



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 level		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 substance abuse disorders	F10-F16 F18 F19	P15 P16 P18 P19	Alcohol and substance abuse disorders	F10-F16 F18 F19	Alcohol and substance abuse disorders	P15 P16 P18 P19
Schizophrenia and related disorders	F20-F23 F25 F28 F29	P72	Schizophrenia and related disorders	F20-F23 F25 F28 F29	Schizophrenia	P72
Bipolar disorders	F30 F31	P73	Bipolar disorders	F30 F31	Affective psychosis	P73
Depressive and related mood disorders	F32-F34 F38 F39	P76	Depressive and related mood disorders	F32-F34 F38 F39	Depressive disorder Feeling depressed	P76 P03
Phobia and other anxiety disorders	F40-F42 F44	P74 P79	Phobia and other anxiety disorders	F40-F42 F44	Phobia and other anxiety disorders Feeling anxious/nervous	P74 P79 P01
Reaction to severe stress and adjustment disorders	F43	P82	Reaction to severe stress and adjustment disorders	F43	Post-traumatic stress disorder Acute stress reaction	P82 P02
Somatoform and neurasthenia disorders	F45 F48	P75 P78	Somatoform and neurasthenia disorders	F45 F48	Somatization disorder and neurasthenia	P75 P78

Eating disorders	F50	P86	Eating disorders	F50	Anorexia nervosa/bulimia	P86
Sleep disorders and disturbance	F51 G47	P06	Sleep disorders	F51 G47	Sleep disturbance	P06
Sexual dysfunction	F52		Sexual dysfunction	F52	Sexual desire/fulfillment reduced	P07 P08
Disorders of adult personality and behaviour	F60-F66 F68 F69	P80	Disorders of adult personality and behaviour	F60-F66 F68 F69	Personality disorder	P80
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 symptom/complaint other	P99 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 disorders	ICPC-2 code	Description	N (%)	ICD-10 code	Description	N (%)	
Any mental health diagnosis	P01-P99		46567 (33.4%)	F00-F99		14516 (10.4%)	
Organic, including symptomatic disorders	P70	Dementia	1600 (1.1%)	F00	Dementia in Alzheimer disease	267 (0.2%)	
				F01	Vascular dementia	483 (0.3%)	
				F02	Dementia in other diseases	83 (0.1%)	
				F03	Unspecified dementia	343 (0.2%)	
				F04	Organic amnesic syndrome	6 (0.0%)	
				F05	Delirium	495 (0.4%)	
				F06	Other mental disorders due to brain damage/dysfunction/physical disease	707 (0.5%)	
				F07	Personality and behavioural disorders due to brain disease/damage/dysfunction	206 (0.1%)	
				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 disorders	P15	Chronic alcohol abuse,	1027 (0.7%)	F10	Alcohol related disorders	1022 (0.7%)	
				P16	Acute alcohol abuse	303 (0.2%)	
				P19	Drug abuse	944 (0.7%)	
	P18	Medication abuse	1172 (0.8%)	F11	Opioid related disorders	1067 (0.8%)	
				F12	Cannabis related disorders	213 (0.2%)	
				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 disorders	P72	Schizophrenia	465 (0.3%)	F20	Schizophrenia	204 (0.1%)	
				F21	Schizotypal disorder	7 (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%)	
					P98	Psychosis NOS/other	0 (0%)
Mood disorders	Bipolar disorders	P73	Affective psychosis	1200 (0.9%)	F30	Manic episode	25 (0.0%)
					F31	Bipolar disorder	717 (0.5%)

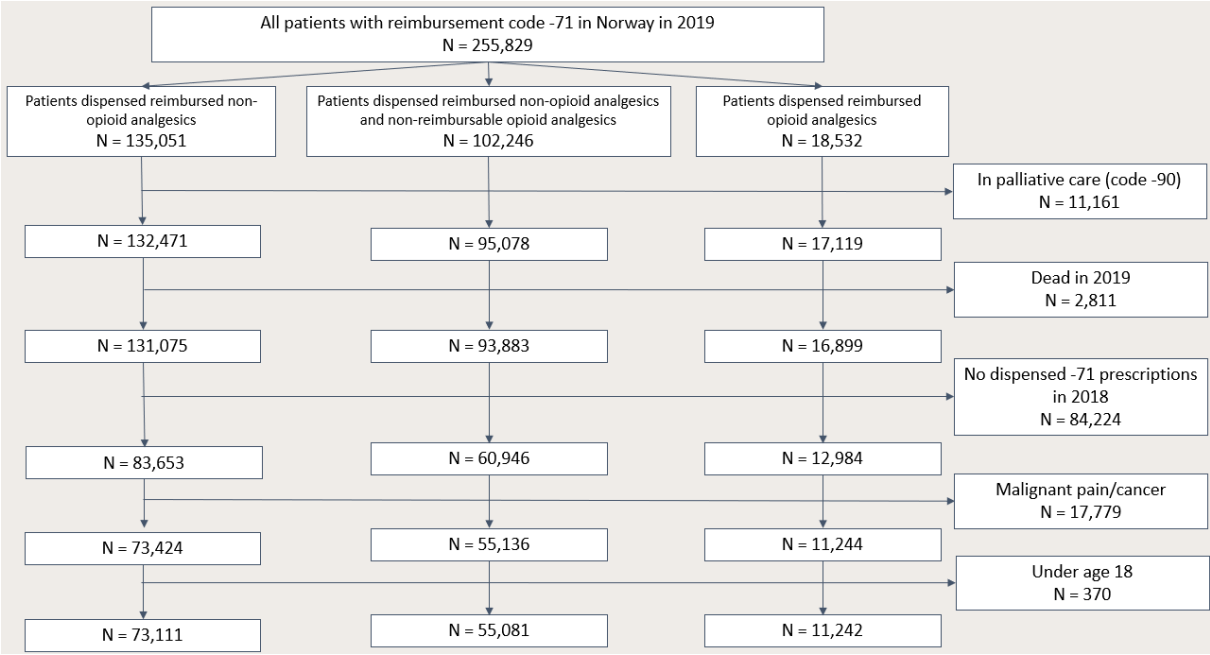
Depressive disorders	P76	Depressive disorder	12013 (8.6%)	F32	Major depressive disorder, single episode	2304 (1.7%)
	P77	Suicide/suicide attempt	385 (0.3%)	F33	Major depressive disorder, recurrent	1944 (1.4%)
				F34	Persistent mood disorders	239 (0.2%)
				F38	Other mood disorders	29 (0.0%)
				F39	Unspecified mood disorder	35 (0.0%)
Symptoms and ailments	P03	Feeling depressed	2570 (1.8%)	-		
Anxiety and related disorders						
	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%)
	P82	Post-traumatic stress disorder	2778 (2.0%)	F42	Obsessive-compulsive disorder	189 (0.1%)
	P75	Somatization disorder	526 (0.4%)	F43	Reaction to severe stress, and adjustment disorders	3883 (2.8%)
	P78	Neuraesthesia/surmenage	252 (0.2%)	F44	Dissociative disorders	257 (0.2%)
Symptoms and ailments	P01	Feeling anxious/nervous/tense	5351 (3.8%)	F45	Somatoform disorders	503 (0.4%)
	P02	Acute stress reaction	4181 (3.0%)	F48	Other neurotic disorder (e.g. neuraesthesia)	244 (0.2%)
				-		
				-		
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 syndromes				F52	Sexual dysfunction not caused by organic disorder/disease	78 (0.1%)
				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%)
				F55	Abuse of non-dependence-producing substances	31 (0.0%)

				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 development and orientation	<5 (0.0%)
				F68	Other disorders of adult personality and behavior	18 (0.0%)
Symptoms and ailments	P09	Sexual preference concern	30 (0.0%)	F69	Unspecified disorder of adult personality and behavior	7 (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 development				F80	Specific developmental disorders of speech and language	22 (0.0%)
				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%)
Symptoms and ailments	P24	Specific learning problem	92 (0.1%)	F89	Unspecified disorder of psychological development	6 (0.0%)
				-		
Behavioral and emotional disorders with onset usually occurring in childhood or adolescence	P81	Hyperkinetic disorder	1729 (1.2%)	F90	Hyperkinetic disorder	979 (0.7%)
				F91	Conduct disorders	11 (0.0%)
				F92	Mixed disorders of conduct and emotions	6 (0.0%)
				F93	Emotional disorders with onset specific to childhood	7 (0.0%)
				F94	Disorder of social functioning with onset specific to childhood and adolescence	<5 (0.0%)
				F95	Tic disorders	38 (0.0%)
				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 symptom/complaint	<5 (0.0%)	-		
Other symptoms and ailments	P04	Feeling/behaving irritably/angry	101 (0.1%)	-		
	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 other	3635 (2.6%)	-		
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.

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.

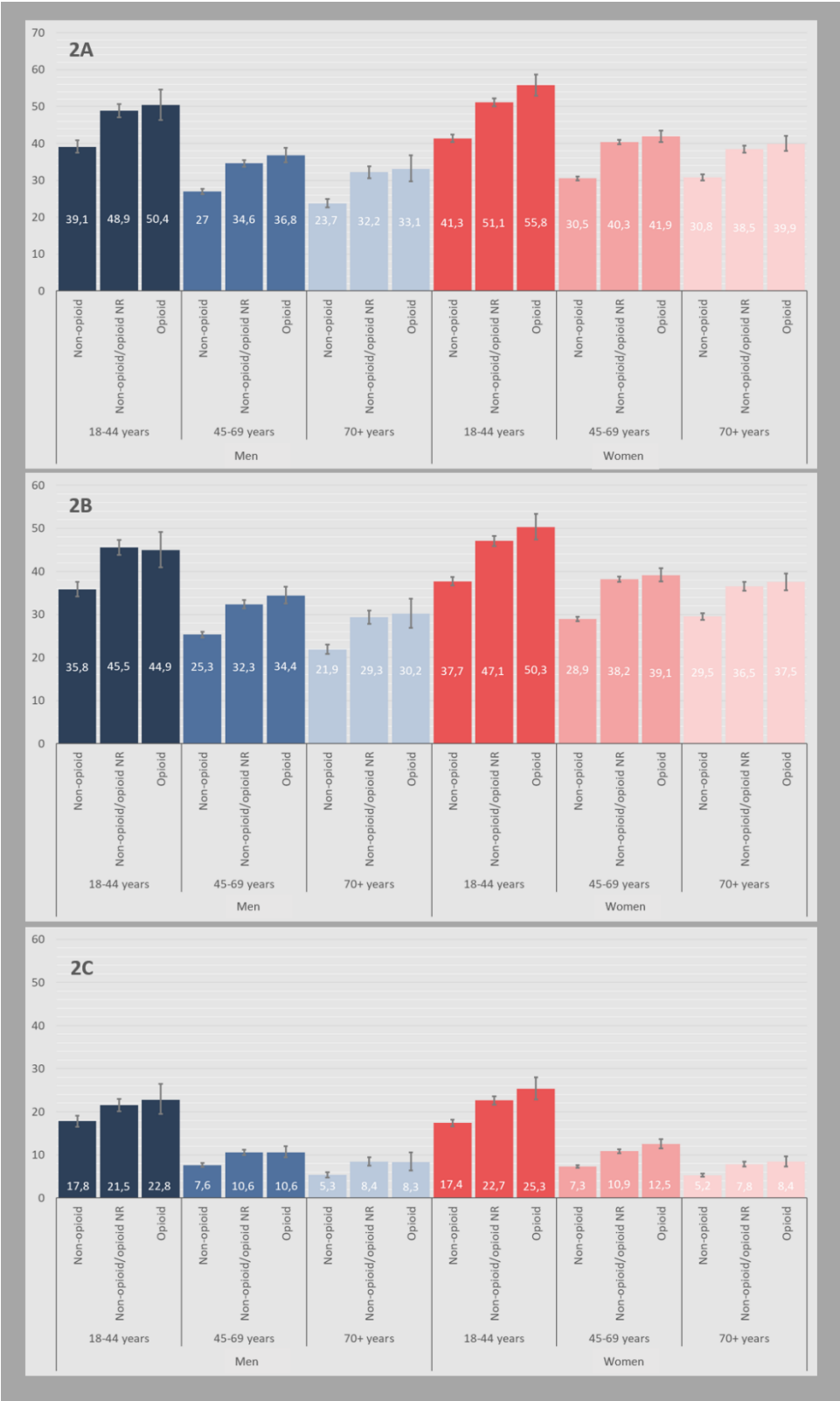


Figure S3. Prevalence of sleep diagnoses in primary and secondary health care in 2019 according to gender, age-, and analgesic user groups

