

The costs of chronic pain—Long-term estimates

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Abstract

Background: Chronic pain is a condition with severe impact on many aspects of life, including work, functional ability and quality of life, thereby reducing physical, mental and social well-being. Despite the high prevalence and burden of chronic pain, it has received disproportionately little attention in research and public policy and the societal costs of chronic pain remain largely unknown. This study aimed to describe the long-term healthcare and work absence costs of individuals with and without self-identified chronic pain.

Methods: The study population were participants in two Norwegian population health studies (HUNT3 and Tromsø6). Participants were defined as having chronic pain based on a self-reported answer to a question on chronic pain in the health studies in 2008. Individuals in the study population were linked to four national register databases on healthcare resource use and work absence.

Results: In our study, 36% ($n = 63,782$) self-reported to have chronic pain and the average years of age was 56.6. The accumulated difference in costs between those with and without chronic pain from 2010 to 2016 was €55,003 (CI: 54,414–55,592) per individual. Extrapolating this to the entire population suggests that chronic pain imposes a yearly burden of 4% of GDP. Eighty per cent of the costs were estimated to be productivity loss.

Conclusion: Insights from this study can provide a greater understanding of the extent of healthcare use and productivity loss by those with chronic pain and serve as an important basis for improvements in rehabilitation and quality of care, and the education of the public on the burden of chronic pain.

Significance: This was the first study to estimate the economic burden associated with chronic pain in the general population using linked individual-level administrative data and self-reported survey answers. We provide calculations showing that annual costs of chronic pain may be as high as €12 billion or 4% of GDP. Findings from this study highlight the need for a greater understanding of the substantial healthcare use and productivity losses among individuals with chronic pain.

Audun Stubhaug and Johan Liseth Hansen contributed equally to this work.

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1 | INTRODUCTION

Chronic pain is a common condition with a severe impact on many aspects of life, including work, functional ability and quality of life (Becker et al., 1997; Gureje et al., 1998; Katz, 2002), thereby reducing physical, mental and social well-being. Despite the high prevalence and burden of chronic pain (Breivik et al., 2006), it has received disproportionately little attention in research and public policy (Breivik et al., 2013). This may at least in part be because chronic pain is by definition a subjective experience and, prior to the introduction of ICD-11, has not been a diagnosis in its own right and therefore not systematically recorded in, for example, patient registries and reimbursement statistics (Clauw et al., 2019; Goldberg & McGee, 2011; McGee et al., 2011; Treede et al., 2015). As such, there are large unmet treatment needs and goals, and untapped potential for future research advancements and priorities in public health (Breivik et al., 2013; Goldberg & McGee, 2011). Worldwide, it is estimated that about 31% of the population has chronic pain (Steingrimsdóttir et al., 2017).

Cost-of-illness studies of chronic pain have been conducted across the world (Azevedo et al., 2016; Gannon et al., 2013; Gaskin & Richard, 2012; Gustavsson et al., 2012; Hogan et al., 2016; Kronborg et al., 2009; Mayer et al., 2019; Raftery et al., 2012; Takura et al., 2015) with a range of different methodologies (e.g. means of identifying chronic pain cases, cost categories included, data sources and comparisons to the general population) making direct comparisons of cost estimates difficult. The limitations of the studies conducted to date include a combination of small sample sizes (Azevedo et al., 2016; Gannon et al., 2013; Kronborg et al., 2009; Mayer et al., 2019; Raftery et al., 2012), survey-reported resource use instead of administrative data (Azevedo et al., 2016; Gannon et al., 2013; Gaskin & Richard, 2012; Mayer et al., 2019; Raftery et al., 2012; Takura et al., 2015), lack of costs related to work absence (Hogan et al., 2016), lack of cost comparison to a matched population (Azevedo et al., 2016; Gannon et al., 2013; Gustavsson et al., 2012; Kronborg et al., 2009; Mayer et al., 2019; Raftery et al., 2012) or reliance on diagnostic codes in administrative data alone for identifying chronic pain cases (Gustavsson et al., 2012). Consequently, the healthcare and work absence costs associated with chronic pain compared to individuals without chronic pain remain largely unknown. Quantifying the economic burden of chronic pain provides policymakers with the information to make informed decisions when prioritizing finite healthcare resources.

Our study addresses the limitations of previous studies by identifying individuals with self-reported chronic pain in large-population health studies with high participation

rates and linkages to administrative data on resource use. The aim of this study was to estimate the economic burden associated with chronic pain over time by describing healthcare and work absence costs for individuals self-identified with chronic pain compared to individuals without self-identified chronic pain.

2 | METHODS

2.1 | Study design

We carried out a retrospective study based on a matched cohort design, using population-based data to estimate the direct healthcare costs and indirect work absence costs, based on healthcare resource use and work absence from 2010 to 2016. The study population were participants in two Norwegian population-based health studies conducted between 2006 and 2008: the third wave of the Health Study in North-Trøndelag (HUNT3) and the sixth wave of the Tromsø Study (Tromsø6).

HUNT is one of Norway's largest population-based health studies (Krokstad et al., 2012). Data have been obtained through several study waves. In this study, we utilized data from the third wave (HUNT3), which was conducted between October 2006 and June 2008. 93,860 people were invited to participate in HUNT3 and 50,807 participated (54.1% participation rate). The Tromsø Study is a population-based, prospective health study (Eggen et al., 2013). The Tromsø Study consists of seven waves of data collection that have been conducted in the municipality of Tromsø. In this study, we utilized data from the sixth wave of the Tromsø Study (Tromsø6), which was conducted from October 2007 to December 2008. 19,762 people were invited to participate and 12,984 participated (65.7% participation rate).

Participants were classified to be individuals with chronic pain (cases) based on self-reported answers in the health studies from 2008. Cases were matched 1:1 to individuals without self-reported pain from the same health study based on age and sex to be used as a comparison group to those with chronic pain, and then from 2010 to 2016 data on resource use and work absence for these individuals were collected. The reporting of costs (2010–2016) many years after case ascertainment (2008) enabled us to study the long-term and persistent burden associated with chronic pain.

2.2 | Data sources

The individuals in this study population were linked through the unique personal identification

number assigned to all Norwegians, and available in all data sources, connecting their information in four national register databases on healthcare resource use and work absence: the Norwegian Patient Register (specialty care), the KUHR database (primary care), the Norwegian Prescription Database (purchased prescriptions from Norwegian pharmacies) and the FD-Trygd register (work absence). **Table 1** describes all administrative registers in the study, while **Figure 1** presents an overview of the linkage process between data sources.

The HUNT3 and Tromsø6 studies have received ethical approvals, and their participants gave written informed consent to use their information for further research, including linkage with other data sources (Eggen et al., 2013; Krokstad et al., 2012). Ethical approval for our study, from the regional ethical review board (Regional Committee of Medical and Health Research Ethics—North), was deemed unnecessary

TABLE 1 Description of administrative registers.

Administrative registers

The Norwegian Patient Register (NPR) (Bjørnelv et al., 2020):

The Norwegian Patient Register is maintained by the Norwegian Directorate of Health and receives administrative data on patients from hospitals and private contract specialists. NPR contains patient data, geographical data, administrative data and medical data for both inpatient and outpatient hospital care in Norway. The register contains main and secondary ICD-10 diagnostic codes for each admission and outpatient visit as well as procedure codes.

The KUHR database (KUHR) (Sørensen et al., 2016):

The KUHR database (for the control and payment of reimbursements to health service providers) is maintained by the Norwegian Directorate of Health. The KUHR database consists of data related to reimbursement of, among others, primary care physicians, private specialists, chiropractors and physiotherapists. Data is available on the type of health care professional, patient, treatment (time of contact, amount reimbursed, type of service rendered) as well as diagnosis (ICPC and/or ICD-10 codes).

The Norwegian Prescription Database (NorPD) (Haugnes et al., 2019): The Norwegian Prescription Database (NorPD) is maintained by the Norwegian Institute of Public Health (NIPH) and contains information on all prescriptions dispensed at pharmacies. Data for each prescription include brand name, ATC code, dispensing date, strength, pack size, number of packs and amount (number of defined daily doses). NorPD does not capture drugs dispensed in hospitals, nursing homes, directly from the physician or non-prescription drugs sold over-the-counter.

FD-Trygd register (FD-Trygd) (Prego-Domínguez, Khazaeipour, et al., 2021): FD-Trygd is maintained by the Norwegian Labour and Welfare Administration and accessible via Statistics Norway. The database contains data on people's social insurance status, including length and extent of sick leave and disability pension.

by the ethical review board since the project was not classified as health research (REC decision: 2018/698/REK Nord).

2.3 | Study population

The study population consisted of all participants from HUNT3 and Tromsø6. Among several questions on pain, a specific question on chronic pain in HUNT3 and Tromsø6 was used to define individuals with chronic pain.

The identifying chronic pain question was slightly different between the two health studies. In HUNT3, chronic pain was defined as pain lasting 6 months or more and the question was: Do you have physical pain now that has lasted more than 6 months? Yes/no. In Tromsø6, chronic pain was defined as pain lasting 3 months or more and the question was: Do you have persistent or recurring pain that has lasted for 3 months or longer? Yes/no. Individuals without a complete response to the question on chronic pain or who were not alive on 1 January 2008 were excluded.

To compare the costs of chronic pain to a similar comparison group based on basic covariates, individuals with self-reported chronic pain were matched to individuals without self-reported pain 1:1 without replacement. The variables included in the matching procedure were birth year (± 1 year), sex and health study (i.e. Tromsø participants were matched to other Tromsø participants). We chose to estimate the overall economic burden among individuals with chronic pain and not the incremental burden due to the underlying cause(s) of chronic pain itself as chronic pain is a multifaceted disease with multiple and often unclear causes. In light of this, to avoid overmatching, we decided to use a comparison group to those with chronic pain matched on the most basic characteristics (birth year and sex). The matched comparison group is therefore not constructed to estimate the causal incremental burden due to chronic pain.

Given the aim of the paper, to compare the costs among individuals with and without chronic pain, we chose to group data from HUNT3 and Tromsø6 together.

2.4 | Characteristics of the study population

Characteristics of the study population were collected from administrative data and are presented for two reporting years 2008 and 2016, the first and final year of the study period. The self-reported data from HUNT3 and Tromsø6 are presented together with results from 2008, even though the survey periods were 2006–2008. In reporting data for 2010 to 2016, stratified by self-reported

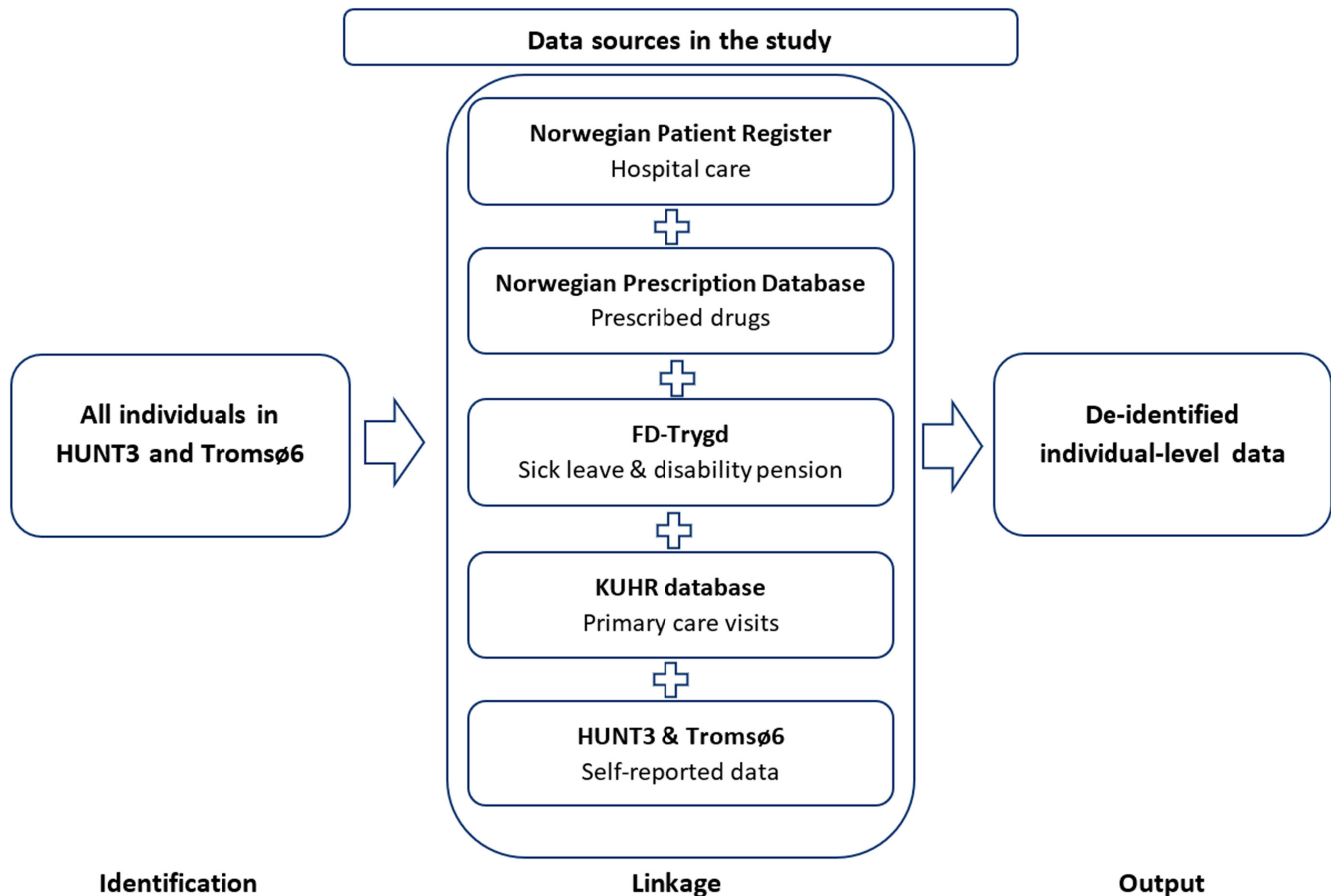


FIGURE 1 Linkage process between data sources.

chronic pain in 2008, we assumed their chronic pain condition was the same in these years as in 2008 as we wanted to study the long-term costs.

2.4.1 | Demographics and socioeconomic

Age was defined as the patient's age on January 1 in the reporting year. The percentage of individuals receiving sick leave (defined as the recorded absence beyond the first 14 days) or disability pension was based on data from FD-Trygd in the reporting year. Employment (among the working age population 18–66 years; dichotomous) was self-reported by the study participants. Self-reported education level (categorical) and household income (categorical, in EUR, shown for those of working age) were only available for participants in Tromsø6.

2.4.2 | Medications and comorbidities

Use of NSAIDs (ATC code: M01A) and opioids (ATC code: N02A) was based on dispensed prescription medications in the reporting year. All other prescriptions were

defined as non-NSAID/opioid medication. Defined daily doses (DDDs) of opioids were converted to oral morphine equivalents (OMEQ) to evaluate the percentage of high-consumption opioid users (≥ 4500 OMEQ consumed over 1 year), following a method previously applied in literature on the use of opioids for non-cancer pain (Svendsten et al., 2011). The use of non-prescription pain medication (categorical) was self-reported by the participants. The Charlson-Quan Comorbidity index (Quan et al., 2005) was calculated based on diagnoses in speciality care in the reporting year.

2.4.3 | Behavioural variables

Smoking (categorical), physical activity (categorical) and alcohol consumption (categorical) were self-reported by the participants in HUNT3 and Tromsø6.

2.4.4 | Self-reported pain

Pain intensity (categorical), the number of pain locations (categorical) and the impact of pain on daily life

(categorical) were self-reported by the participants with chronic pain.

2.4.5 | Quality of life

Quality of life (measured as EQ-5D-3L and Visual Analog Scale, VAS) was only available for participants in Tromsø6. The surveyors chose to derive the EQ-5D-3L index scores using a value set from the United Kingdom (Dolan, 1997). The VAS scale in Tromsø6 is continuous and is comprised of a line with scores ranging from 0 to 100, where 0 corresponds to 'Worst health condition you can imagine' and 100 to 'best health condition you can imagine'.

2.4.6 | Resource use

Resource use by all individuals from 2010 to 2016 was based on information from NPR, KUHR, NorPD and FD-Trygd. The number of outpatient hospital visits, hospitalizations, surgeries and rehabilitation visits were based on records from NPR, and the number of general practitioner (GP), private specialists, physiotherapists, chiropractors and psychiatric visits in the KUHR database. The number of filled prescription medications was based on prescriptions recorded in NorPD.

2.5 | Costing methods

We took a societal perspective to the cost estimation by including both direct healthcare costs and indirect productivity losses. The estimation of costs followed a bottom-up approach by applying a unit cost to each hospital visit, filled prescription and day absent from work. Costs were estimated based on resource use between 2010 and 2016. The years from 2010 to 2016 were chosen as our reporting year for resource use and costs as 2016 represented the most recent year of available data. The DRG system was also changed in 2010 when day surgeries were given their own DRG weights (Lieng et al., 2013) and DRG information was missing for 60% of contacts in the data for 2008. Thus, the cost estimates were believed to be more precise from 2010 and onwards. The costing strategy in this study follows the costing strategy in other Norwegian cost-of-illness studies (Bjørnelv et al., 2020; Grotle et al., 2011; Haugnes et al., 2019; Hylén et al., 2019; Shin et al., 2016; Sørensen et al., 2016).

All direct and indirect costs were inflation-adjusted to 2020 NOK and converted to Euros (€) using the average

monthly exchange rate for 2020 (10.7207 NOK/EUR) (Norges Bank, 2021). To compare the costs of chronic pain, differential cost estimates were derived as the difference between the costs for individuals with and without chronic pain.

2.5.1 | Direct healthcare costs

Direct costs were defined as the costs of healthcare use and purchased prescriptions. Unit costs for outpatient hospital visits, hospitalizations and surgeries were estimated using diagnosis-related group (DRG) codes and the corresponding DRG cost weight registered for all healthcare contacts. This was done by multiplying the DRG weight with the inflation-adjusted cost for a DRG weight equal to 1. Unit costs for psychiatric visits were obtained by assigning a cost to each tariff available for the contact and multiplied by 2. The tariffs are used by the practitioners to get reimbursed by the government and costs for each tariff are available in publicly available price lists (Legeforeningen, 2020). The tariff cost was multiplied by two to account for the public subsidy to the practitioners, not covered by the tariff alone, as recommended in economic evaluation guidelines by NoMA (Norwegian Medicines Agency, 2020), available in the extracted dataset.

For rehabilitation centre contacts, neither DRG weights nor tariffs were available. Therefore, unit costs were implemented, using median values (to avoid outliers) for the median daily cost of inpatient stays. For private healthcare visits (outpatient specialists, chiropractors, etc.) specific co-payment fees were assumed for each type of visit, to reflect per-capita allowances/lumpsum payments.

Dispensed prescription medications were assigned the pharmacy retail price (AUP) for each prescription.

2.5.2 | Productivity loss

Productivity loss was defined as the cost of work absence, and estimated using the human-capital approach (Zhang et al., 2011). The assumed value of lost productivity was multiplied by the number of net days of sick leave and disability pension. Each day of sick leave or disability pension was assigned a unit cost of €250 per net day of absence based on an average annual wage of €55,331 in 2019, plus holiday pay, employee fees, insurance, pension payments and an assumed 260 working days in a year. Net days were calculated by multiplying the extent of absence by the gross days of absence. Days on sick leave and disability pension were based on episodes recorded in FD-Trygd.

For more details on the costing methods and diagnosis codes, see the online supplement.

2.6 | Statistical analysis

Continuous variables are presented with mean and standard deviation and categorical variables as frequency and percentage. A two-tailed *t*-test was used to test for statistically significant differences in continuous variables and a chi-square test was used for categorical variables. The statistical significance level was set at 5% in statistical tests and for confidence intervals. Data management and analysis were performed using Stata version 16 (StataCorp, College Station, US).

2.6.1 | Sensitivity analyses

Three separate sensitivity analyses were conducted, to test the robustness of the results. The first of these required consistency in survey answers (e.g. removing controls that reported pain intensity greater than zero and cases that did not report any pain intensity). This scenario accounted for the risk of missing patients who reported their chronic pain incorrectly. The second sensitivity analysis adjusted the matching criteria to only match cases that were alive in 2016, as the mortality rate between cases and controls was different. The third analysis involved separating the HUNT3 and Tromsø6 study populations.

3 | RESULTS

3.1 | Summary characteristics of the study population

The study population included 63,782 individuals (50,801 from HUNT3 and 12,981 from Tromsø6). In total, 36% ($n=23,250$) reported to have chronic pain across studies. A successful match was defined as a 1:1 match on both sex and age between those with and without chronic pain. Successful matches were found for almost everyone (98.5%) with chronic pain. Ultimately, 22,906 individuals with chronic pain were included in the analyses with a matched individual. In 2016, the number of surviving individuals with and without chronic pain was 21,051 and 21,393, respectively. The mortality-rate ratio between the two groups was 1.0079 (CI: 1.0074–1.0083). A flow chart of the study population is presented in [Figure 2](#).

In the study population, 59.1% were female and the mean age was 56.6 years in 2008 (see [Table 2](#) on Study characteristics). Individuals with chronic pain had more comorbidities, lower alcohol consumption, less exercise and smoked less often than individuals without chronic pain. They also used more medication, in terms of

non-prescription pain medication (self-reported) and prescribed NSAIDs and opioids.

For the working-age population (age 18–66 years, 74.4% of the study population), individuals without chronic pain were more likely to be full-time employed, have a higher household income, higher education and fewer received sick leave payments or disability pension in 2008 compared to individuals with chronic pain.

Individuals with chronic pain reported lower quality of life than matched individuals without chronic pain, as measured by the EQ-5D-3L index (0.69 vs. 0.91 [p -value <0.001]) and VAS scale (68.85 vs. 81.82 [p <0.001]). A major contributor to a lower EQ-5D-3L index score was the subdimension pain/discomfort. However, individuals with chronic pain also reported more problems than matched individuals without chronic pain in other subdimensions, particularly for mobility, usual activities and anxiety/depression ([Figure 3](#)).

An overview of pain characteristics among individuals with chronic pain is presented in [Table 3](#). More than one in four individuals with chronic pain reported that their pain had a strong influence on daily activity and work. The majority of individuals reported to have pain at more than one site.

Individuals with chronic pain had comparatively more sick leave in both 2016 and 2008, although the difference attenuated over time ([Table 4](#)). Both groups experienced an increase in disability pensions in 2016 compared to 2008. The use of medication in 2016 was consistently higher among individuals with chronic pain than those without. However, for both groups, the use of NSAIDs was lower in 2016 compared to 2008, while opioid use increased. The comorbidity index increased for both cases and controls between 2008 and 2016.

3.2 | Resource use from 2010 to 2016

Individuals with chronic pain in 2006–2008 had a higher resource use in all cost categories in each year from 2010 to 2016 compared to matched individuals without chronic pain, as presented in [Figure 4](#). In the majority of categories, resource use was over 40% higher over time for those with chronic pain than individuals without chronic pain. The greatest percentage difference in healthcare utilization was found in rehabilitation centre visits, however, a low proportion in both groups utilized this resource (as indicated by the low mean values). The greatest percentage difference overall was found in disability pension. The recorded number of disability pension days was over three times higher for individuals with chronic pain than for individuals without chronic pain. In 2016, individuals with chronic pain of working age (years 18–66), received 56 days

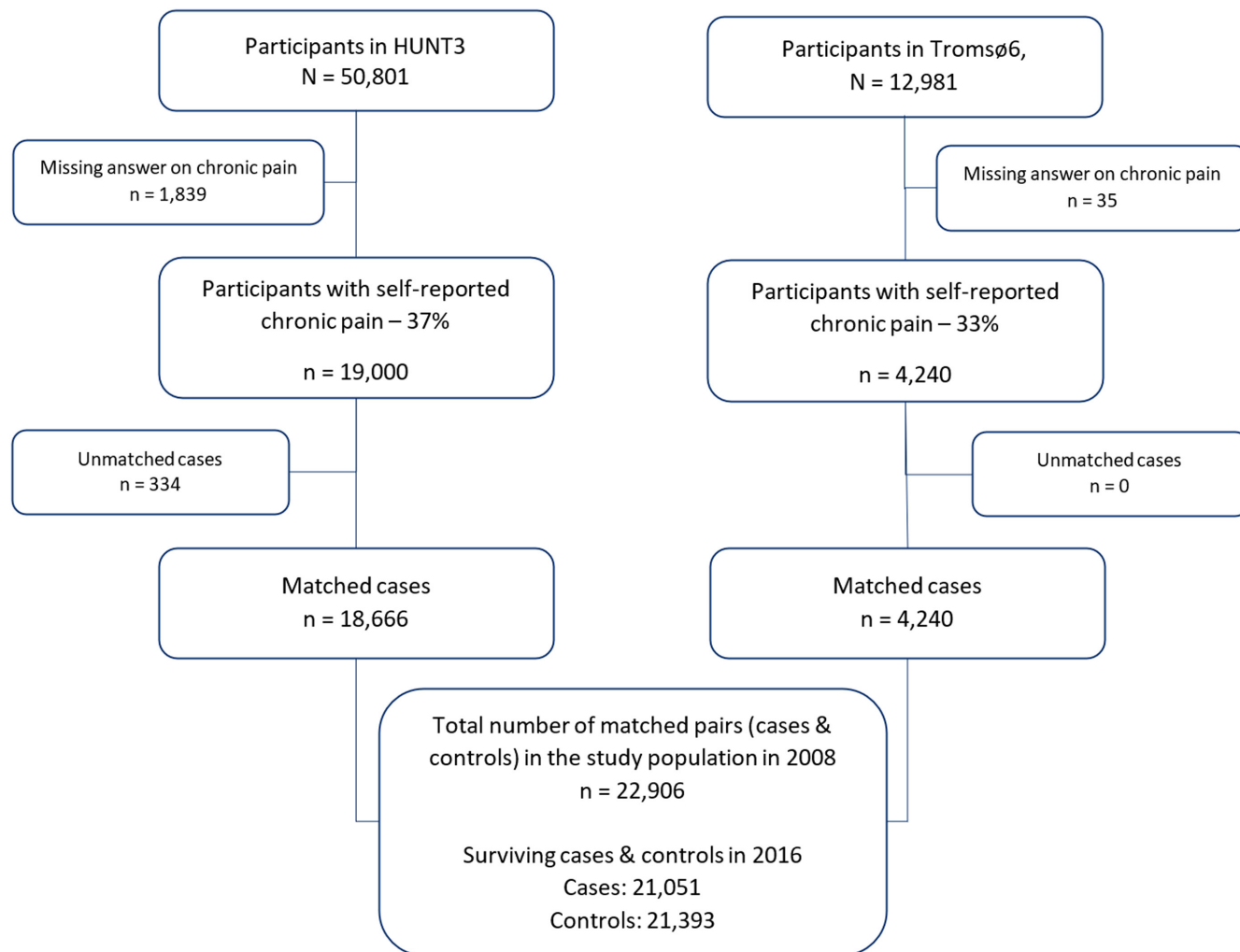


FIGURE 2 Flow chart—study population.

of disability pension on average, compared to 16 days for those with chronic pain. Sick leaves decreased over time among those reporting chronic pain but were relatively stable among those without chronic pain. Disability pension increased in both groups, but more so for those with chronic pain. The general trend over time was an increasing use of resources.

3.3 | Healthcare and work absence costs from 2010 to 2016

Healthcare and work absence (productivity loss) costs are presented in Figures 5 and 6, respectively. The average healthcare cost per individual with chronic pain increased from €3828 in 2010 (CI: 3711–3946) to €4510 (CI: 4375–4644) in 2016 compared to an increase from €2256 (CI: 2170–2341) in 2010 to €3021 (CI: 2915–3127) in 2016 among individuals without chronic pain. Thus, the difference in healthcare costs for individuals with chronic pain

versus individuals without chronic pain was €1489 in 2016 [€4510 minus €3021] (CI: 1318–1659). The largest cost components within the healthcare costs were hospitalizations and surgeries. Though individuals with chronic pain were dispensed NSAIDs and opioids almost 2.5 times more than individuals without chronic pain, the difference in the cost of NSAIDs and opioids was relatively low, as these medications are mostly inexpensive.

For those of working age in 2016, the annual productivity loss per individual with chronic pain was €18,987 (CI: 18,397–19,577) compared to €7740 (CI: 7364–8115) among individuals without chronic pain. The difference in annual productivity loss between individuals with and without chronic pain was €11,247 (CI: 10,549–11,945), of which disability pension costs constituted 88%. For all ages, the difference in productivity losses was €6722 (CI: 6301–8677). The costs of disability increased over time for both groups.

The total difference in economic costs in 2016, including direct and indirect costs (for all ages), was €8211

TABLE 2 Characteristics of the study population in 2008.

	With chronic pain	Without chronic pain
Demographics and socioeconomics		
Number of patients	22,906	22,906
Males, <i>n</i> (%)	9374 (40.9%)	9374 (40.9%)
Age, mean (SD)	56.6 (14.3)	56.6 (14.3)
Employment—working age population, <i>n</i> (%) [<i>p</i>-value]		
Not employed	4983 (29.2%)	2595 (15.3%)
Employed	11,965 (70.2%)	14,336 (84.3%) [<0.001]
Missing, <i>n</i>	97	114
Household income—(<66 years of age)—Tromsø only, <i>n</i> (%) [<i>p</i>-value]		
<18,655 EUR	243 (5.7%)	147 (3.5%)
18,656–37,311 EUR	732 (17.3%)	624 (14.7%)
37,312–65,294 EUR	1206 (28.4%)	1115 (26.3%)
>65,295 EUR	730 (17.2%)	1042 (24.6%) [<0.001]
Missing, <i>n</i>	161	144
Highest attained level of education—Tromsø only, <i>n</i> (%) [<i>p</i>-value]		
<upper secondary school	1375 (32.4%)	1188 (28%)
Upper secondary school	1498 (35.3%)	1313 (31%)
College or university—less than 4 years	646 (15.2%)	738 (17.4%)
College or university tertiary education—more than 4 years	651 (15.4%)	956 (22.5%) [<0.001]
Missing, <i>n</i>	70	45
Sick leave—(<66 years of age), <i>n</i> (%) [<i>p</i>-value]		
Not received	12,492 (73.3%)	13,944 (82%)
Received	4553 (26.7%)	3056 (18%) [<0.001]
Disability pension—(<66 years of age), <i>n</i> (%) [<i>p</i>-value]		
Not received	16,501 (96.8%)	16,847 (99.1%)
Partial	210 (1.2%)	65 (0.4%)
Full	334 (2%)	88 (0.5%) [<0.001]
Quality of life and behavioural variables		
EQ5D-3L—index score—Tromsø only, mean (SD) [<i>p</i> -value]	0.693 (0.22)	0.907 (0.13) [<0.001]
Missing	573	0
EQ5D-3L—VAS—Tromsø only, mean (SD) [<i>p</i> -value]	68.8 (17.5)	81.8 (13.57) [<0.001]
Missing	2327	0
Smoking, <i>n</i> (%) [<i>p</i>-value]		
Current smoker	7902 (34.5%)	9887 (43.2%)
Former smoker	8208 (35.8%)	7485 (32.7%)
Never	6334 (27.7%)	5058 (22.1%) [<0.001]
Missing, <i>n</i>	462	476
Physical activity, <i>n</i> (%) [<i>p</i>-value]		
Never	1539 (6.7%)	1012 (4.4%)
Less than once a week	3967 (17.3%)	3362 (14.7%)
Once a week	4671 (20.4%)	4807 (21%)
Two to three times a week	8277 (36.1%)	9067 (39.6%)
Almost every day	4107 (17.9%)	4353 (19%) [<0.001]
Missing, <i>n</i>	345	305

(Continues)

TABLE 2 (Continued)

	With chronic pain	Without chronic pain
Alcohol consumption, <i>n</i> (%) [<i>p</i> -value]		
Never	2377 (10.4%)	2066 (9%)
Less than once a month	16,594 (72.4%)	16,399 (71.6%)
Two to three times a week	2839 (12.4%)	3250 (14.2%)
More than four times a week	634 (2.8%)	739 (3.2%) [<0.001]
Missing, <i>n</i>	462	452
Medications and comorbidities		
At least two NSAID prescriptions, <i>n</i> (%) [<i>p</i> -value]	3886 (17%)	1559 (6.8%)
At least one opioid prescription, <i>n</i> (%) [<i>p</i> -value]	4680 (20.4%)	1689 (7.4%)
High-use opioid users (≥ 4500 OMEQ), <i>n</i> (%) [<i>p</i> -value]	552 (2.4%)	36 (0.2%) [<0.001]
Use of non-prescription pain medication, <i>n</i> (%) [<i>p</i> -value]		
Not used	9631 (42%)	15,636 (68.3%)
Less than every week	5076 (22.2%)	2724 (11.9%)
Every week	2005 (8.8%)	378 (1.7%)
Daily	2090 (9.1%)	238 (1%) [<0.001]
Missing, <i>n</i>	4104	3930
Charlson-Quan comorbidity index, mean SD [<i>p</i> -value]	0.304 (1.017)	0.25 (0.932) [<0.001]
Five most common Charlson-Quan comorbidities in cases, <i>n</i> (%) [<i>p</i> -value]		
Cerebrovascular disease	580 (2.5%)	464 (2%) [<0.001]
Chronic pulmonary disease	781 (3.4%)	442 (1.9%) [<0.001]
Rheumatic disease	703 (3.1%)	168 (0.7%) [<0.001]
Diabetes	766 (3.3%)	496 (2.2%) [<0.001]
Malignancy	853 (3.7%)	737 (3.2%) [0.003]

Note: The statistical tests were performed between those with and without self-reported chronic pain.

(CI: 7745–8677). Work absence costs accounted for 80% of the overall burden. The accumulated cost difference from 2010 to 2016, including all categories for healthcare resource use and work absence, was €55,003 (CI: 54,414–55,592).

3.4 | Sensitivity analyses

Three sensitivity analyses were conducted to test the impact on the overall difference in cost burden between individuals with and without pain. Two sensitivity analyses gave comparable results to the main results, with deviations less than €54 from the main difference of €8211 in costs for the year 2016. When requiring consistency in self-reported pain answers between the two groups, the number of matched pairs was reduced to 22,765 (against 22,906) and the difference in 2016 costs was €8265 [CI: 7797–8732] compared to €8211. When adjusting the matching criteria to include only living cases in 2016, the difference in cost burden was €8171 (CI: 7701–8642) in 2016. A comparison of the matched populations from

HUNT3 and Tromsø6 found that the average age in 2008 was 57.5 and 53.7, respectively, with a similar sex composition. The difference in costs between those with and without chronic pain in 2016 was €8442 (CI: 7.915–8968) and €7229 (CI: 6243–8216) for HUNT3 and Tromsø6 participants. A complete presentation of the stratified HUNT3/Tromsø6 results is provided in the online supplement.

4 | DISCUSSION

This is the first study to estimate the economic burden, including healthcare and work absence costs, associated with chronic pain in the general population using linked individual-level administrative register data and self-reported survey answers. In our study, individuals reporting chronic pain used more of all types of health care resources and had a higher absence from work than matched individuals without chronic pain throughout the entire study period. The total annual economic burden per individual in the chronic pain group was estimated to

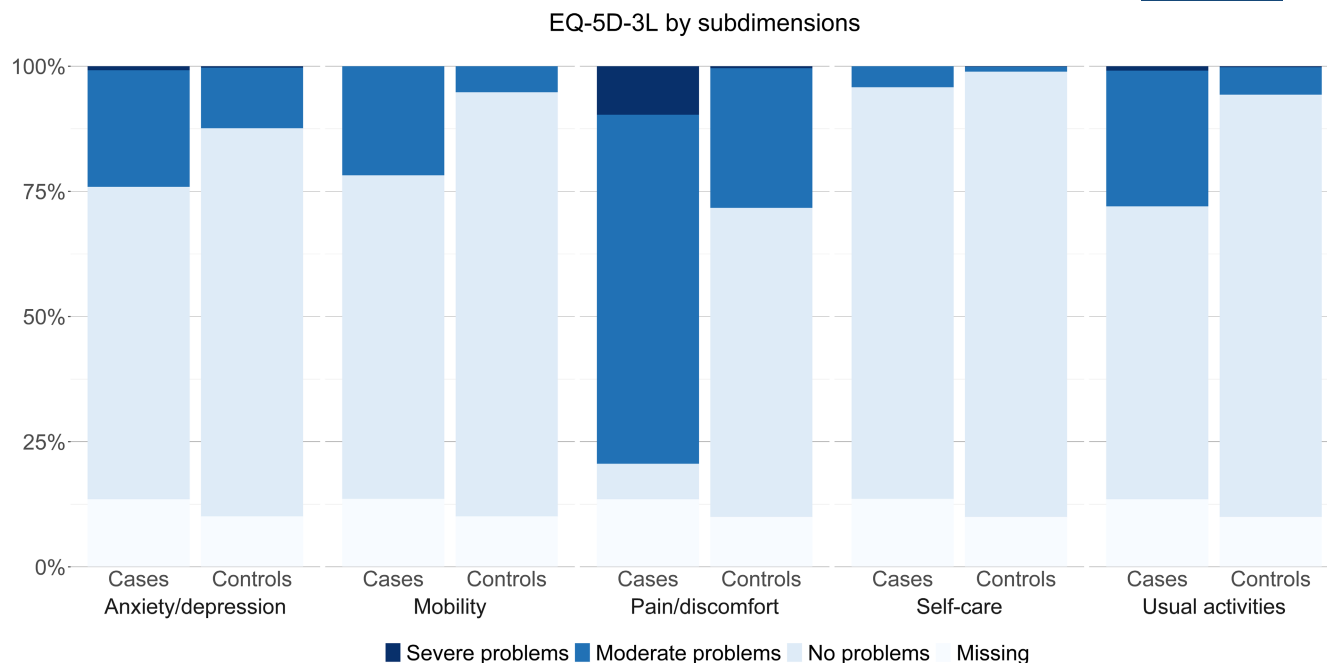


FIGURE 3 EQ-5D-3L subdimensions. By individuals with chronic pain and matched individuals without chronic pain. All differences had a p -value <0.005 .

be €15,825 based on resource use in 2016 and was more than double that of individuals in the comparison group (€7614). Of the total difference in the economic burden of chronic pain (€8211), 80% was attributable to work absence and the associated productivity loss. In earlier years, the differences and composition were largely the same. The difference in economic burden persisted each year after case ascertainment, highlighting the potential long-term implications among individuals self-identifying to have chronic pain.

We did not seek to estimate the incremental burden due to the isolated costs of chronic pain. Therefore, our cost differences between those with and without self-reported chronic pain are likely due to a mix of factors, such as; the burden due to chronic pain itself (e.g. arthritis), secondary effects of chronic pain (e.g. mental health disorders) and conditions that are more prevalent among individuals with chronic pain (e.g. diabetes). This is illustrated in the higher prevalence of Charlson-Quan comorbidities and the index score in 2008 and 2016 (Tables 2 and 4), including lower educational levels and incomes among those with chronic pain. Previous literature has reported on the associations between socioeconomic status, chronic pain and comorbidities in line with our results (Prego-Domínguez, Khazaeipour, et al., 2021). We chose not to include these factors in the matching procedure to avoid overmatching and keep a descriptive aim of the study. In addition to these factors, there are likely also other factors not reported in this study that may influence the presence

of chronic pain and driving costs. Such factors may be genetic predispositions and pain sensitivities (Diatchenko et al., 2004), and modifiable risk factors (Mills et al., 2019).

While cost estimates are difficult to directly compare between studies, our single-year cost estimates are higher than previous estimates from Portugal, Sweden, Austria, Ireland, Denmark and Japan (Azevedo et al., 2016; Gannon et al., 2013; Gaskin & Richard, 2012; Gustavsson et al., 2012; Kronborg et al., 2009; Mayer et al., 2019; Raftery et al., 2012; Takura et al., 2015). Hogan et al. studied incremental healthcare costs in Canada compared to the general population (Hogan et al., 2016), and their estimates were equivalent to approximately €2000, which is higher than our 2016 estimate of €1489. However, their study included long-term care facilities, information we did not have. Regardless, both studies highlight the difference in cost burden between chronic pain and the general population. Incremental or comparable cost methodology is preferable in cost-of-illness research as these estimates are the most relevant for policymakers; they reflect the potential extra cost incurred from a disease or condition and so represent potential savings if the condition is resolved.

While this study provides evidence of the high economic burden of chronic pain, the study does not address why and how individuals with chronic pain are treated, how patients journey through the healthcare system or what constitutes proper care. Furthermore, this study does not explore subgroup analyses, which may shed light on the heterogeneity in economic burden between different

TABLE 3 Self-reported pain in individuals with chronic pain.

	All
Pain intensity—common format, <i>n</i> (%)	
No pain	85 (0.4%)
Mild	4706 (20.5%)
Moderate	12,640 (55.2%)
Severe	4590 (20%)
Missing, <i>n</i>	885
Pain intensity—Tromsø6, mean (SD)	
Missing	751
Pain intensity—HUNT3, <i>n</i> (%)	
No pain	78 (0.4%)
Very mild	841 (4.5%)
Mild	3125 (16.7%)
Moderate	10,672 (57.2%)
Strong	3450 (18.5%)
Very strong	366 (2%)
Missing, <i>n</i>	134
Number of pain sites, <i>n</i> (%)	
One	2942 (12.8%)
Two to four	10,906 (47.6%)
Five or more	3008 (13.1%)
Missing, <i>n</i>	6050
Impact of pain on daily and work life, <i>n</i> (%)	
No influence	5709 (24.9%)
Some influence	4132 (18%)
Strong influence	5959 (26%)
Missing, <i>n</i>	7106

underlying causes, degrees of severity and other factors. The self-reported pain characteristics (Table 3) reveal heterogeneity among the chronic pain population in terms of pain intensity, number of sites and impact on daily life. These are important research questions to study in the future given the high individual and societal burden of pain.

Our findings indicate that individuals with chronic pain have lower socioeconomic status, in terms of lower employment, income and educational level than individuals without chronic pain. This is in line with a recent meta-analysis which demonstrates the increased risk of chronic pain associated with lower socioeconomic status (Prego-Domínguez, Skillgate, et al., 2021).

In our study, the prevalence of chronic pain was 36%, which is higher than other estimates from Norway, ranging between 24% and 30% (Breivik et al., 2006; Hansen et al., 2016; Landmark et al., 2012; Rustøen et al., 2004). This may indicate we are capturing a wider population of individuals with pain, potentially with less severe pain, than in other studies. Assuming a similar rate of chronic

pain (36%) in the general adult Norwegian population for 2016 (4,086,583) as in HUNT3 and Tromsø6 with a difference in cost of €8211, the additional economic burden associated with chronic pain in Norway was approximately €12 billion in 2016. Thus, the increased healthcare resource use and productivity loss of individuals with chronic pain compared to the general population may be compared to 4% of Norway's gross domestic product (Statistics Norway, 2021) in 2016. Compared to US estimates of 2% (Gaskin & Richard, 2012), our estimates are higher, likely driven by higher prevalence of chronic pain, however, direct comparisons are difficult to make due the differences such as the composition of GDP, healthcare system and social services.

In 2015, the Norwegian Directorate of Health conducted a top-down cost study by ICD-10 diagnosis chapters 2015 (Norwegian Directorate of Health, 2019) and found that the chapters 'Neoplasms', 'Mental, Behavioural and Neurodevelopment disorders', 'Diseases of the circulatory system' and 'Diseases in the musculoskeletal system and connective tissue' account for 14.2%, 15.2%, 11.7% and 13.8% of total societal costs. The same chapters respectively received 18.9%, 8.9%, 6.0% and 1.4% of research grants from the Research Council of Norway in 2015 (25.1% of grants were given to a combination of different chapters) (The Research Council of Norway, 2016). Chronic pain is not related to a specific ICD-10 chapter but spans multiple chapters depending on the underlying cause. However, musculoskeletal diseases are the underlying reason for chronic pain in many individuals. While all of these individuals may not be eligible to be treated at multidisciplinary pain clinics, it is telling that the total national capacity at these clinics is approximately 4000 patients a year. Assuming that musculoskeletal pain constitutes about 13.8% of the costs, but only gets 1.4% of research funding in combination with lack of pain clinics, this indicates that research funding and priorities in resource allocation are not proportional to the prevalence, impact and societal burden of chronic pain.

Productivity losses are important from a societal perspective due to the high costs. Previous research has shown that patients with chronic conditions value the ability to work as a treatment goal and as a healing mechanism (Detaille et al., 2003; Lilliehorn et al., 2013; Vooijs et al., 2017). This is also reflected in the substantial percentage of individuals saying that pain has a large impact on daily life and work life, and reduces quality of life. High work absence is an important indicator of reduced functionality in daily life for individuals with chronic pain and is most likely an indicator of undertreatment, lack of treatment efficacy or both. However, productivity losses are only one form of the potential, indirect economic burden associated with chronic pain. Other examples of

TABLE 4 Characteristics of the study population in 2016.

	With chronic pain	Without chronic pain
Demographics and socioeconomics		
Number of participants	21,051	21,393
Males, <i>n</i> (%)	8447 (40.1%)	8652 (40.4%)
Age, mean (SD)	63.7 (13.6)	66.3 (13.7)
Sick leave—(<66 years of age), <i>n</i> (%) [<i>p</i> -value]		
Not received	13,735 (82.8%)	14,321 (85.9%)
Received	2851 (17.2%)	2349 (14.1%) [<0.001]
Disability pension—(<66 years of age), <i>n</i> (%) [<i>p</i> -value]		
Not received	14,122 (85.1%)	15,879 (95.3%)
Partial	728 (4.4%)	241 (1.4%)
Full	1736 (10.5%)	550 (3.3%) [<0.001]
Medications and comorbidities		
At least two NSAID prescriptions, <i>n</i> (%) [<i>p</i> -value]	2364 (11.2%)	1214 (5.7%) [<0.001]
At least one opioid prescription, <i>n</i> (%) [<i>p</i> -value]	4548 (21.6%)	2225 (10.4%) [<0.001]
High-use opioid users (≥ 4500 OMEQ), <i>n</i> (%) [<i>p</i> -value]	812 (3.9%)	148 (0.7%) [<0.001]
Charlson-Quan comorbidity index, mean SD [<i>p</i> -value]	0.5 (1.3)	0.433 (1.2) [<0.001]
Five most common Charlson-Quan comorbidities in cases, <i>n</i> (%) [<i>p</i> -value]		
Cerebrovascular disease	654 (3.1%)	541 (2.5%) [<0.001]
Chronic pulmonary disease	1037 (4.9%)	652 (3%) [<0.001]
Rheumatic disease	607 (2.9%)	245 (1.1%) [<0.001]
Diabetes	1552 (7.4%)	1184 (5.5%) [<0.001]
Malignancy	1225 (5.8%)	1186 (5.5%) [0.22]

Note: The statistical tests were performed between those with and without self-reported chronic pain.

relevant indirect costs not explored in this study include caregiver burden (informal caregivers, such as family or friends, who take time to care for individuals with chronic pain), and presenteeism (lower at-work productivity, due to reduced mobility or additional pain caused by performing certain tasks). For estimating productivity loss, the 'friction-cost approach' is an alternative to the human capital approach used in this study. However, that approach is more data-intensive and was deemed not feasible with the available data.

4.1 | Strengths and limitations of the study

The aim of this study was not to make causal inferences on the impact of chronic pain and the study design was associative in nature. As discussed previously regarding the matching procedure, a causal study design using observational data is difficult and was outside the scope of

this study. Therefore, our cost differences between those with and without chronic pain must be interpreted as associations without a causal interpretation of the increased economic burden due to chronic pain.

As pain is by definition a subjective experience, the most accurate identification of individuals with chronic pain is through the subject's self-reported pain. The lack of a specific diagnosis code for chronic pain in the ICD-10/9 coding systems makes it difficult to rely solely on administrative health data when studying chronic pain. ICD-11 includes a chronic pain diagnosis code, but it remains to be seen how the diagnosis code will be used, particularly by others than pain specialists. Thus, a major strength of this study is the use of self-reported pain in identifying individuals with chronic pain. This is further strengthened by the fact that cost differences persisted 8 years after individuals reported to have self-reported chronic pain.

The difference in the identifying question on chronic pain between HUNT3 (pain for more than 6 months) and

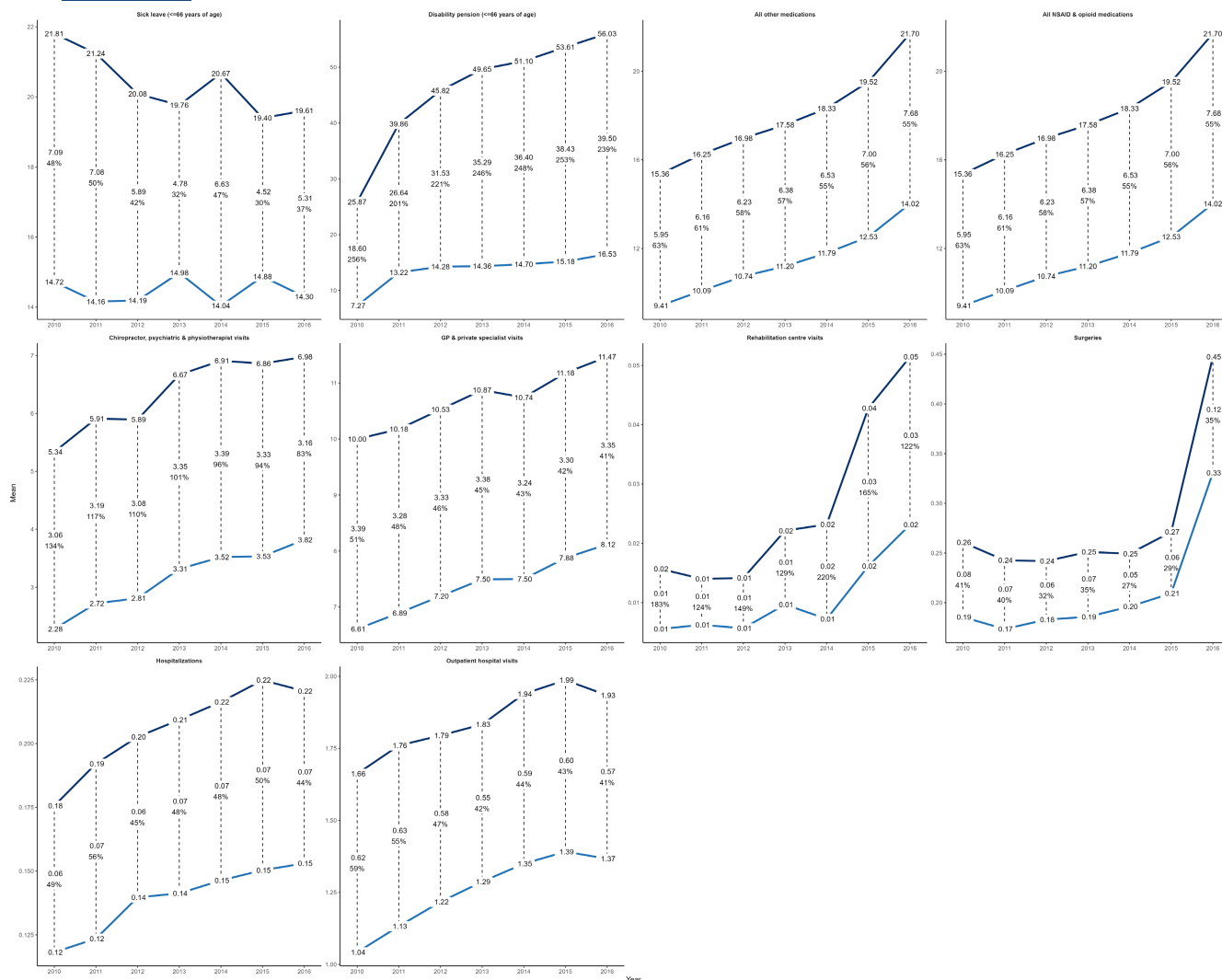


FIGURE 4 Differences in resource use between 2010 and 2016 between those with (dark blue) and those without chronic pain (light blue). The difference between groups, including confidence intervals, are indicated in the graph. All differences were statistically significant at the 95% confidence level as indicated by confidence intervals not crossing 0.

Tromsø6 (pain for more than 3 months) is not deemed to have impacted the results, as previous research has indicated the validity and consistency of the questionnaire (Hagen et al., 2010; Landmark et al., 2012). The sensitivity analyses also revealed a very small impact on the difference in cost burden between cases and controls. In the Tromsø6 survey, participants also answered a question on the length of their chronic pain and 0.17% of individuals reported to have had pain between 3 and 6 months. The numerical cost estimates were slightly different between HUNT3 (cost difference between those with and without chronic pain was €8442) and Tromsø6 (€7229). However, the cost trajectories over time were the same for both populations across all cost categories. Given the low number of Tromsø6 participants reporting pain between 3 and 6 months and the similar cost trajectories, we believe

this supports the choice to pool the HUNT3 and Tromsø6 populations.

A potential limitation of population surveys is non-responder bias. The response rates in Tromsø6 and HUNT3 are high (Galea & Tracy, 2007) (66% and 54%, respectively) and studies of non-responders in Norwegian population surveys (Knudsen et al., 2010; Langhammer et al., 2012) have found that non-participants have a lower socioeconomic status and are more female indicating we may not capture everyone with chronic pain.

There are limitations and uncertainties related to the costing method. Capital costs, pensions and some hospital services are not included in the DRG weights, and we therefore underestimate healthcare costs. Furthermore, we likely underestimated the costs of sick leave, as sick leave lasting less than 14 days is paid by the employer

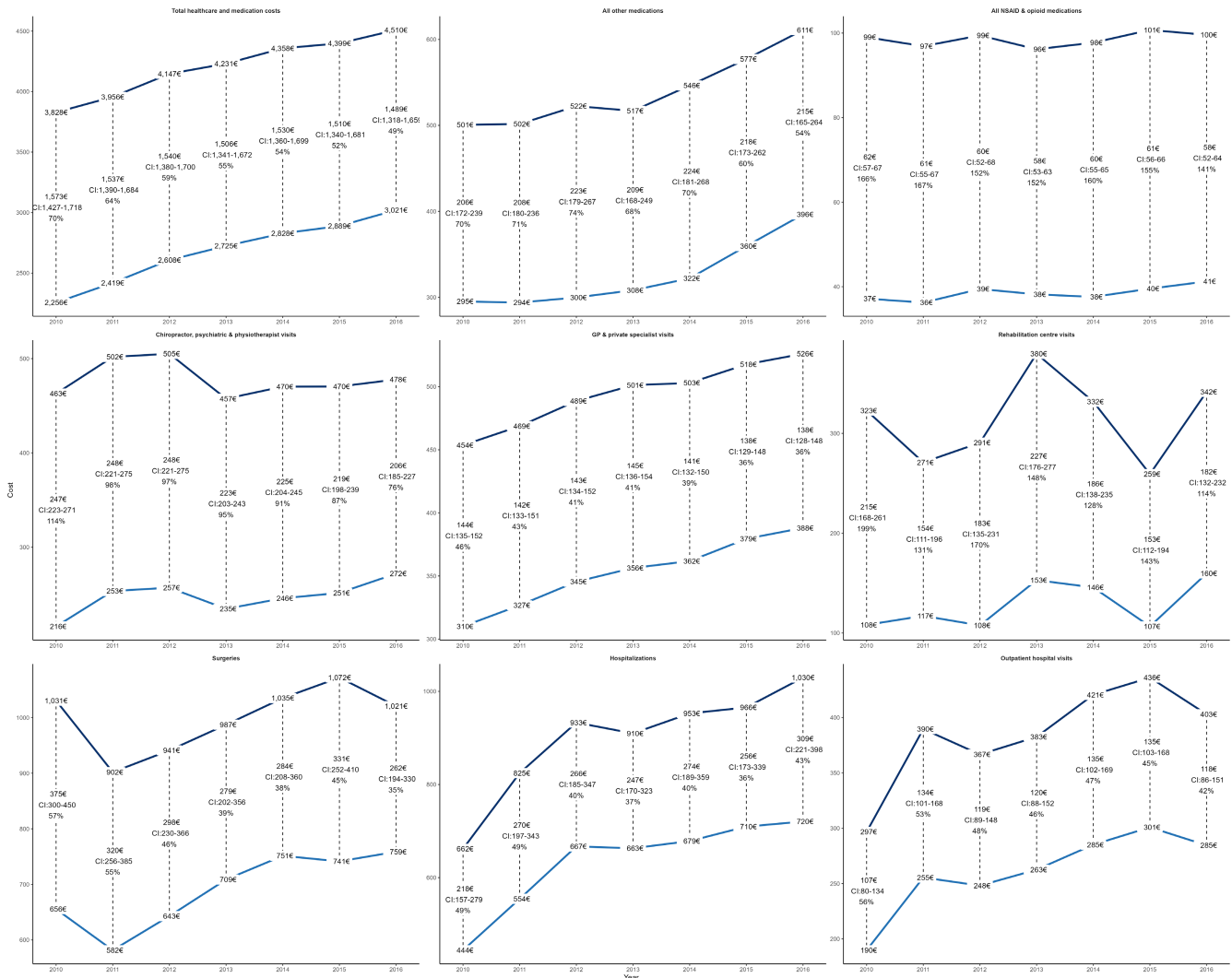


FIGURE 5 Differences in direct costs between 2010 and 2016 between those with (dark blue) and those without chronic pain (light blue). The difference between groups, including confidence intervals, are indicated in the graph. All differences were statistically significant at the 95% confidence level as indicated by confidence intervals not crossing 0. Costs are adjusted to 2020 prices.

and not captured by the administrative registers. Another underestimation is the lack of detailed cost information on drugs sold over the counter in stores and pharmacies. These drugs likely represent a substantial proportion of medication use in individuals with chronic pain. The latter is clearly shown in the substantial sales of over-the-counter pain drugs (Sommerschild, 2020).

Finally, it is assumed in this study that individuals' status during the survey in 2008 describes the individuals' status when the subsequent costs were collected for the respective groups each year from 2010 to 2016. However, there is a risk that the severity or existence of chronic pain has changed within both groups over this period, due to, for example, treatment of the underlying causes, emergence of new sources of pain, death, etc. This issue stems from limitations with the available data, but it is partially

explored in the sensitivity analysis requiring matching of only living patients in 2016. It is likely more probable that an individual without chronic pain in 2008 developed chronic pain over time up until 2016, than vice versa, thus cost differences may be underestimated. These same data limitations also precluded any assessment of the relationship between chronicity of pain and the subsequent socio-economic costs, which would require further assumptions to justify the comparison. However, given that annual cost differences were stable over time from 2010 to 2016, without convergence in any of our cost categories, indicates that our assumption is reasonable.

In sum, while there are several inherent limitations to this study, these mainly represent uncaptured expenses, and our estimates must therefore be considered conservative, lower-limit cost estimates.

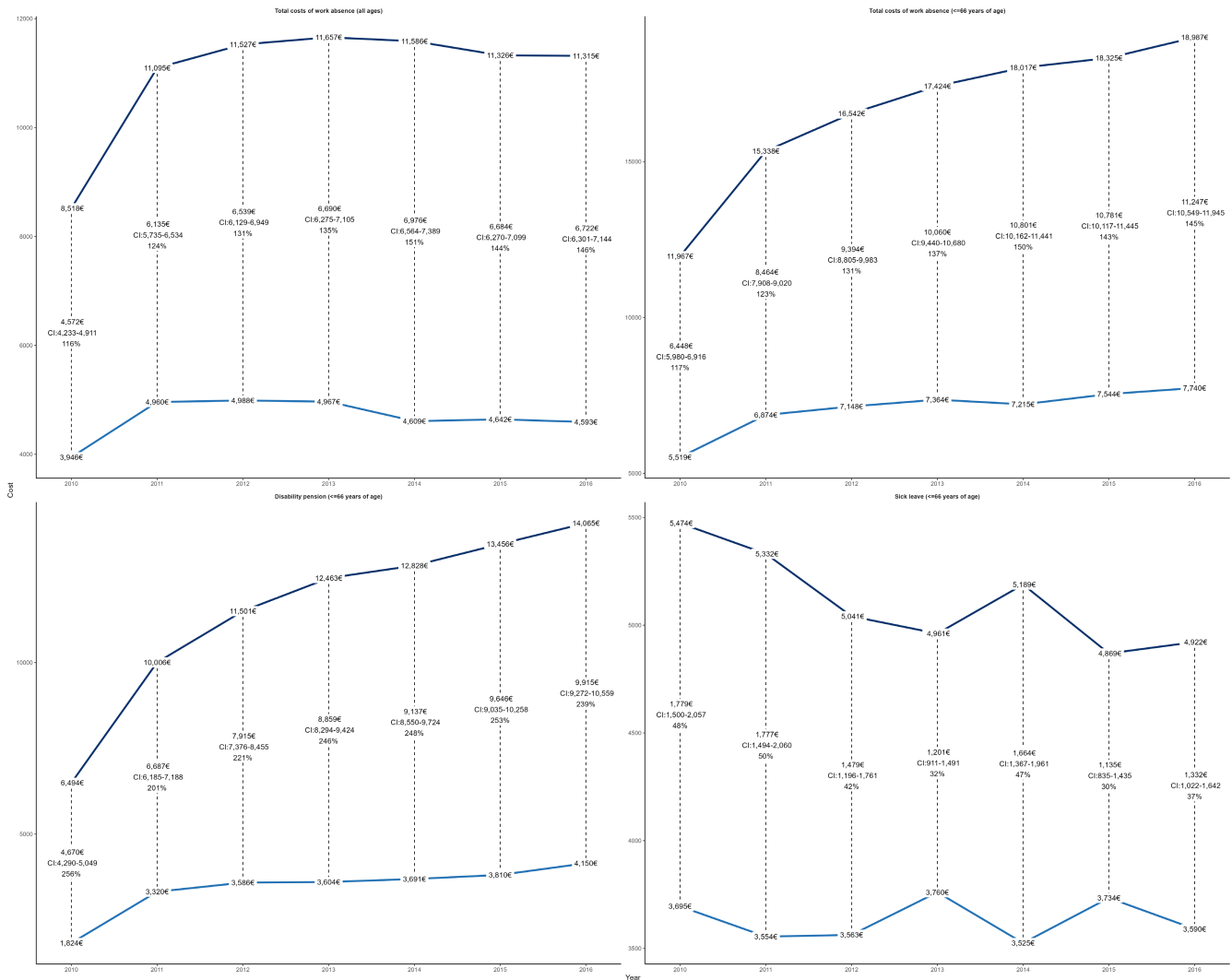


FIGURE 6 Differences in indirect costs in between 2010 and 2016 between those with (dark blue) and those without chronic pain (light blue). The difference between groups, including confidence intervals, are indicated in the graph. All differences were statistically significant at the 95% confidence level as indicated by confidence intervals not crossing 0. Costs are adjusted to 2020.

5 | CONCLUSION

In this study, we find that societal costs associated with chronic pain may be as high as 4% of GDP in Norway. While society uses great economic resources for individuals with chronic pain, more than for many other healthcare problems, very little resources and funding are specifically allocated for the treatment and research of chronic pain. A greater understanding of the extent of healthcare use and productivity loss by different groups with chronic pain could serve as an important basis for improvements in rehabilitation and quality of care, and the education of the public on the burden of chronic pain.

AUTHOR CONTRIBUTIONS

JLH contributed to the study design, data acquisition, analysis, interpretation of data, drafting of the manuscript

and critical review. AS contributed to the study design, data acquisition, interpretation of data, drafting of the manuscript and critical review. SH contributed to the study design, data acquisition, analysis, interpretation of data, drafting of the manuscript and critical review. AG contributed to the study design, interpretation of data, drafting of the manuscript and critical review. AEE contributed to the study design, interpretation of data, drafting of the manuscript and critical review. CSN contributed to the study design, interpretation of data, drafting of the manuscript and critical review. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

SH, JLH and AG (Quantify) received fees from Grünenthal to conduct this study. AS, AEE and CSN did not receive any fees to conduct this study. Grünenthal took part in initiating and designing the study but did not participate in the writing, including contents discussion, of this publication. JLH and AG are employed by Quantify Research and provide consultancy services to pharmaceutical companies and other private and public organizations and institutions. SH was an employee of Quantify Research when the work was conducted. AS has received research support from Pfizer. AEE and CSN declare no conflict of interest.

STUDY ORGANIZATION

Oslo University Hospital was the data controller and institution responsible for this research, including protocol, data applications and data management, with AS (employed at Oslo University Hospital) as principal investigator.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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