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Original Reports

Predictors of Sickness Absence in a Clinical Population With Chronic Pain

Riccardo LoMartire,[*,†] Örjan Dahlström,[‡] Mathilda Björk,[§] Linda Vixner,[†] Paolo Frumento,[¶] Lea Constan,[‖] Björn Gerdle,[§] and Björn Olov Äng[*,†,#]

[*]*Division of Physiotherapy, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden,* [†]*School of Health and Welfare, Dalarna University, Falun, Sweden,* [‡]*Department of Behavioural Sciences and Learning, Linköping University, Linköping, Sweden,* [§]*Pain and Rehabilitation Centre, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden,* [¶]*Department of Political Sciences, University of Pisa, Pisa, Italy,* [‖]*Department of Arts and Crafts, Konstfack: University of Arts, Crafts and Design, Stockholm, Sweden,* [#]*Center for Clinical Research Dalarna-Uppsala University, Falun, Sweden*

Abstract: **Chronic pain-related sickness absence is an enormous socioeconomic burden globally. Optimized interventions are reliant on a lucid understanding of the distribution of social insurance benefits and their predictors. This register-based observational study analyzed data for a 7-year period from a population-based sample of 44,241 chronic pain patients eligible for interdisciplinary treatment (IDT) at specialist clinics. Sequence analysis was used to describe the sickness absence over the complete period and to separate the patients into subgroups based on their social insurance benefits over the final 2 years. The predictive performance of features from various domains was then explored with machine learning-based modeling in a nested cross-validation procedure. Our results showed that patients on sickness absence increased from 17% 5 years before to 48% at the time of the IDT assessment, and then decreased to 38% at the end of follow-up. Patients were divided into 3 classes characterized by low sickness absence, sick leave, and disability pension, with eight predictors of class membership being identified. Sickness absence history was the strongest predictor of future sickness absence, while other predictors included a 2008 policy, age, confidence in recovery, and geographical location. Information on these features could guide personalized intervention in the specialized healthcare.**

Perspective: ***This study describes sickness absence in patients who visited a Swedish pain specialist interdisciplinary treatment clinic during the period 2005 to 2016. Predictors of future sickness absence are also identified that should be considered when adapting IDT programs to the patient's needs.***

Key words: *Chronic pain, epidemiology, machine learning, productivity loss, sickness absence.*

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Address reprint requests to Riccardo LoMartire, RPT, MSc, Division of Physiotherapy, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Alfred Nobels allé 23, 141 83 Huddinge, Sweden. E-mail: riccardo.lo.martire@ki.se

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Chronic pain affects a third of the global population with several of its causes established among the leading contributors to non-fatal disability.[20,57,64] Although its heterogeneous manifestations and the overlap with other conditions complicate accurate quantification of its socioeconomic consequences, it reportedly represents between 3 to 10% of gross domestic product in western economies.[10,18,47,63] Indirect costs due to sickness absence are often identified as the main contributor.[10,18,21,47] Indeed, conditions linked to chronic pain constitute the most common causes of prolonged sick

leave and disability pension, with musculoskeletal disorders, mental disorders, and injuries consistently being reported among the leading diagnoses.[2,16,27,37,65] Furthermore, it is recognized that social insurance benefits are unevenly distributed so that a minority of affected individuals represent a disproportionate amount of the costs.[23,24,28] For instance, 2 studies of pain-related US worker compensation claims revealed that 5 to 9% of long-term claims accounted for 60 to 85% of the total costs.[23,24] It is therefore important to isolate different patterns of sickness absence, so that interventions can be tailored to the most likely trajectory of the patient.

To accomplish this goal, a clear overview of sickness absence and its predictors is necessary. A number of studies have described sickness absence relating to the causes of chronic pain, but research specific to the condition itself is nearly non-existent, which combined with methodological variations, has contributed to a fragmented overview of the topic.[2,21,35,37] The understanding of predictors of sickness absence linked to chronic pain is further impeded by a tendency to examine sick leave and disability pension separately, and to limit the field of study to musculoskeletal diagnoses.[14,29,30,32,35,52,66] Nevertheless, a considerable amount of research supports that past sickness absence is a strong predictor of future sick leave and disability pension.[14,29,30,32,35,52,66] Other frequently identified risk factors include age, sex, socioeconomic status, employment status, and multimorbidities.[30,35,52,66] In addition, the analytical tradition of the medical sciences has focused on describing sample-level associations reliant on statistical assumptions behind the data generating process.[9,53] The emerging machine learning-based analytical strategy has shifted the focus to predicting future observations for the individual.[9,25,39,40,53] Driven by the data itself to select the most appropriate algorithm for a given circumstance, this strategy can more effectively identify complex patterns in large datasets.[25]

In summary, sickness absence linked to chronic pain presents an enormous and unevenly distributed socioeconomic burden. Information on social insurance benefits linked to chronic pain is currently fragmented and, to the detriment of national health policy and patient-tailored intervention, the applicability of its predictors is uncertain for the chronic pain population. We therefore described sickness absence in chronic pain patients, isolated sickness absence trajectories, and identified predictors of the trajectories.

Methods

Design and Participants

This longitudinal register-based observational study was built on microdata from 5 Swedish national registers, linked via unique personal identification numbers held by all Swedish residents.[42] The study population was defined through the Swedish Quality Registry for Pain Rehabilitation, which contains information on chronic pain patients that are eligible for rehabilitation at any of the 44 specialist interdisciplinary treatment (IDT) clinics across Sweden.[44] Swedish Quality Registry for Pain Rehabilitation patients represent those with particularly complex chronic pain symptoms that have not responded to primary care interventions, corresponding to roughly 0.5‰ of the Swedish population annually. Patients eligible for IDT during the period 2005 to 2016 with musculoskeletal pain for a minimum of 90 days and aged 18 to 64 years at IDT assessment (t0) were included, while those with a registered ICD-10 neoplasm diagnosis (C00-D49) in the 5 years prior to t0 were excluded.

Information on sickness absence stored in the Micro Data for Analysis of the Social Insurance register was obtained from the Swedish Social Insurance Agency in February 2019 and sociodemographic information stored in the Longitudinal Integration Database for Health Insurance and Labour Market Studies was procured from Statistics Sweden in March 2019.[43,45] Meanwhile, data on specialized health care and on dispensed prescription pharmaceuticals stored in the National Patient Register and the Prescribed Drug Register, respectively, were acquired from the National Board of Health and Welfare in February 2020.[41,68] Data covered a 7-year period from 5 years before to 2 years after t0 (ie, January 2000−November 2018), with the exception of the National Patient Register and Prescribed Drug Register, which were initialized in 2001 and 2005, respectively. This study was approved by Uppsala's Medical Research Ethics Committee (DNR 2018/036) and all participants signed a written informed consent form.

Sickness Absence

Swedish residents are eligible for sick leave benefits from the age of 16 and are granted for either full-time (100%) or part-time (25%, 50%, or 75%) of ordinary work hours.[45] Social insurance benefits are reimbursed by the Swedish Social Insurance Agency once they exceed the qualifying period that is most commonly 14 but on occasion up to 21 days for employees, between 3 to 93 days for self-employed workers, and as little as 1 day for students and the unemployed.[45] Individuals aged 30 to 64 years can also be granted a full or partial permanent disability pension if their working capacity is deemed to be permanently impaired. In this study, sickness absence for all disability pension and sick leave spells exceeding the employee-qualifying period in effect at the time were included. Benefits were limited to ICD-10 diagnoses related to the chronic pain spectrum: musculoskeletal system diseases (M: 00−99), nervous system diseases (G: 43−44, 47, 50−64, 82, 96−97), unclassified pain symptoms (R: 07, 10, 26, 29, 51−52), injuries and complications (S: 12−13, 22, 32, 42−43, 53; T: 85, 88, 91−94), and mental disorders (F: 32−33, 41, 43, 45).[21] Data was right-censored: at the end of the 2-year follow-up, due to the end of registration from November 2018, and at the assumed retirement of age 65.

Features

The predictive performance on sickness absence was examined for 101 features in the domains of

sociodemographics, the chronic pain experience, sickness absence history, and healthcare. Multinomial features were one-hot encoded as binary dummy variables, while ordinal features were label encoded and analyzed as numerical variables. Supplementary tables 4.1 to 4.5 and figures 4.1 to 4.6 detail the feature characteristics.

Sociodemographics included age, sex (male, female), geographical region (Stockholm/Gotland, southern Sweden, central Sweden, northern Sweden), country of birth (Sweden, other European country, non-European country), Swedish language proficiency (high, intermediate, poor), family composition (partner with children, partner without children, single with children, single without children), number of children, education level (elementary school, high school, university), employment status (employed, unemployed, student), unemployment duration, and the past 5-year mean disposable income for the patient and their family.

The chronic pain experience covered pain characteristics and their consequences in everyday life. Pain characteristics included pain duration, past week 11-point numeric rating scale pain intensity, number of anatomical pain locations (0−36), the primary pain location (head, neck/shoulder/upper extremities, lower back, abdomen, hips/lower extremities, widespread pain), and confidence in recovery (high, moderate, low). Everyday consequences were measured using four questionnaires. The Multidimensional Pain Inventory reflected the impact of pain (5 scales: pain severity, interference, life control, affective distress, support), perceived responses of significant others (3 scales: punishing, solicitous, distracting), and frequency of everyday activities (4 scales: household chores, outdoor activities, activities away from home, social activities; one activity index).[5,31] The Hospital Anxiety and Depression Scale reflected emotional distress via its IRT-based scale.[38,69] SF-36 reflected health status through 2 IRT-based summary scales (physical health, mental health) and 8 conventional scales (physical functioning, social functioning, physical role limitations, emotional role limitations, mental health, vitality, bodily pain, general health).[26,38,67] Finally, EQ-5D-3L reflected health-related quality of life through the UK time-trade-off index and the 100-step visual analogue scale.[11]

History of sickness absence included ongoing full or partial sick leave at t0, past-year full or partial sick leave spells, sustained past-year full or partial sick leave spells > 180 days, and cumulative gross sick leave days summed up annually for the 5 years prior to t0. Features distinguished between benefits related to the chronic pain spectrum and to other diagnoses.

Health care covered features related to comorbidities and health care utilization. Comorbidities were indicated from ICD-10 codes as severe mental illness (schizophrenia or bipolar disorder), substance use disorder, and past self-harm. Meanwhile, health care utilization was represented via the number of past-year specialist outpatient healthcare visits, the admitted inpatient healthcare days, and the past-year doctor visits (0, 1−3, >3). It also included a previous IDT evaluation, a previous IDT intervention, and whether the patient was currently enrolled in an IDT program. Based on ATC codes of non-opioid pain medication, opioids, antidepressants, benzodiazepines, hypnotics, mood stabilizers, antipsychotics, and AD/HD medication (supplementary table 4.5), the number of dispensed prescription pharmaceutical classes were summed up for the previous year.[48] For each of the first 5 classes, both past-year indicators and total defined daily doses were included. Finally, an indicator of whether t0 occurred from 2009 and later was included to reflect a 2008 policy that was implemented to decrease long-term sickness absence of chronic pain-related diagnoses through guaranteed access to evidence-based health care.[6,36]

Statistical Analysis

Sequence Analysis and Clustering

Sequence analysis is a data-driven approach that is used to provide an overview of life course patterns and their differences.[1,50] Practically, a sequence is made up of a series of categorical states over a temporal range resolved into units. Sequences are compared through several available algorithms, of which optimal matching is most frequently used.[60] It computes the cost of transforming sequences into one another by inserting/deleting or substituting elements and returns a dissimilarity matrix of pairwise distances. For a comparison to be possible, the cost of element exchange needs to be specified in advance. With the dissimilarity matrix obtained, sequences can then be clustered into homogenous pattern subgroups based on pre-defined criteria. Unfortunately, cluster analysis is an inherently unstable technique with highly variable solutions depending on the exact algorithm used, which additionally provides no guarantee of cluster meaningfulness. It is, therefore, critical to interpret them in the light of both statistical quality and pertinence.[59]

Predictive Analysis

Predictive models are used to predict an outcome given a feature pattern. In their development, the aim is to isolate systematic trends of interest, while avoiding sample-specific random patterns, so that predictive generalizability is optimized.[25] In practice, this is achieved by balancing the prediction error between data used in the model development (training data) and data not yet seen by the model (evaluation data), so that the training error neither is markedly smaller (overfit) or markedly larger (underfit) than the evaluation error.[25]

With multiclass outcomes, multinomial logistic regression is a common choice to estimate the probability of class memberships. Non-parametric machine learning algorithms are a powerful alternative that offers intrinsic support for capturing complex non-linearities and higher-order feature interactions, but it requires hyperparameters (settings) to be calibrated before model training for optimal performance.[25] Three widespread machine learning algorithms are: support vector machines, gradient tree boosting, and multilayer

perceptrons.[25] Succinctly, a support vector machine identifies a decision boundary in multidimensional space that maximizes the margin between outcome classes, with orientation and direction guided by support vectors (data points near the boundary). Gradient tree boosting sequentially trains an ensemble of decision trees (a set of consecutive decisions) and combines them into a composite prediction model. With each iteration, higher weight is placed on misclassifications so that they are boosted (prioritized) in subsequent decision trees, thereby capturing data patterns with a gradually increasing level of detail. Finally, a multilayer perceptron is an artificial neural network that combines linear and non-linear functions to approximate data patterns.

Unlike multinomial logistic regression, non-parametric machine learning algorithms do not return coefficients that allow the association between individual features and the outcome to be observed directly. Instead, permutation can be used to determine their contribution by iteratively shuffling each feature randomly and measuring the effect on model performance.[8] For non-collinear features, permutation importance is a fair measure; however, the importance of collinear features is underestimated in rough proportion to the strength of the collinearity and may require separate evaluation.[9]

Protocol

This analysis could be broken down into 3 general steps: sickness absence was initially described across the 7-year period, patients were then separated into subgroups based on their post-t0 patterns, and finally predictors of sickness absence were identified in a prediction modeling procedure. An overview is provided below, and further details are available in the supplementary materials: figures 2.1 to 2.2 illustrate the sickness absence for the full sample and patient subsamples, figures 3.1-3.6 provide support for pattern subgrouping, and figures 4.7 to 4.18 detail the prediction modeling protocol.

Sequence analysis was used to examine the sickness absence related to the chronic pain spectrum (R v4.0.2; package: 'TraMineR' v2.2-0.1).[17,49,59] To describe it over the 7-year period, sequences were constructed with a daily resolution, each patient was assigned to 1 of 5 mutually exclusive states, and simultaneously occurring states were prioritized in the following order: full disability pension, full sick leave, partial disability pension, partial sick leave, and no sickness absence. Limited to the period post t0, the dissimilarity matrix was then generated from the sequences through optimal matching with a constant cost of 1 for insertion/deletion and 2 for substitution, after which it was analyzed with monothetic divisive hierarchical clustering to isolate pattern subgroups (R v4.0.2; package: 'WeightedCluster' v1.4-1).[12,49,59] Targeting state incidence, total state duration, spell timing and duration, frequency of subsequent patterns, and pattern-related measures, the algorithm searched for solutions with up to ten clusters. The statistical quality of each solution was then evaluated using the average silhouette width (range: -1, 1), the point-biserial correlation (range: -1, 1), and Hubert's C (range: 0, 1) as measures of cluster membership cohesion, the clusters' capacity to reproduce the distance matrix, and the partition obtained compared to the best possible partition given the distance matrix and the cluster solution, respectively.[59] Guidelines for the average silhouette width define 0.5 as the threshold for a reasonable structure, while higher and lower estimates indicate better quality for the point-biserial correlation and Hubert's C, respectively.[59] Once the solution with the highest statistical quality was identified, its robustness was evaluated using 2 strategies. Firstly, the same clustering protocol was repeated in separate analyses of the data randomly partitioned into fifths. Secondly, the complete sample was re-analyzed with alternative clustering algorithms (ie, variations of agglomerative hierarchical clustering and partitioned around medoids algorithms described by Studer et al, 2013).[59] Finally, the selected solution was modified in accordance with theoretical considerations to ascertain clinically meaningful clusters.

With outcome classes defined, predictive features were identified in a modeling procedure that compared the performance between multinomial logistic regression, a support vector machine, gradient tree boosting, and a multilayer perceptron (Python v3.8.3 libraries: 'scikit-learn' v0.23.2; 'XGBoost' v1.2.0; 'Tensorflow-Keras' v2.4.0).[13,19,46] Model optimization was conducted in a 3-step nested cross-validation procedure to minimize information leakage, with data randomly split into 3 training sets ($n \times 8/30$ each), 1 validation set ($n \times 3/30$), and 1 test set ($n \times 3/30$).[25] In the first step, the non-parametric machine learning-algorithms' hyperparameters were calibrated through consecutive grid searches, whereby various model configurations were iteratively trained and evaluated on the first and second training sets, respectively.[4] The initial searches were broad to provide a general direction for the hyperparameters, while subsequent searches fine-tuned them. In the second step, the feature configuration with the best predictive performance was identified for each algorithm, whereby models were trained on the first and second training sets combined and evaluated on the third training and validation sets. The full 101-feature model was initially trained and the importance of individual features was determined based on their predictive accuracy through a 100-repetition permutation; highly collinear features ($r > 0.7$) were alternated to avoid an underestimation of their importance. Subsequently, a model with the top 15 features was trained, followed by a stepwise feature elimination until only features that contributed to performance remained. The optimized models were then compared between the algorithms and the best performing model was selected as the final model. In the last step, the generalizability of the final model was confirmed on the test set and its robustness against systematic sample differences examined through sensitivity analyses of 8 separate subsamples: aged ≤ 50 and > 50 years, Swedish and non-Swedish

born, t0 < 2009 and ≥ 2009, and selected and non-selected for IDT.

Throughout the modeling procedure, 2 strategies were used to mitigate accuracy overestimation due to outcome class imbalance: the non-parametric machine learning-algorithms' training misclassification was penalized inversely proportional to the class frequencies and all algorithms' performance was evaluated through metrics sensitive to class imbalance.[7] The balanced accuracy and F1 score were chosen for overall performance, while sensitivity, specificity, the positive and negative predictive values, accuracy, and area under the ROC-curve provided a detailed assessment of individual class performance.[3] All metrics range between 0 to 1, with higher values indicating better performance.

Results

Sample Characteristics

Of 54,338 patients considered for IDT at a Swedish pain specialist clinic in the period from 2005 to 2016, 44,241 (81.4%) were included in the analysis. Excluded patients were either assessed outside the observation period (n = 929), were not within the selected age range (n = 1,960), had a pain duration of less than 90 days (n = 5,770), or had a registered neoplasm diagnosis in the 5 years preceding t0 (n = 1,438). Of the included patients, 70.0% were younger than 50 years of age, 83.1% had completed a secondary school education or higher, and 64.5% were employed. Pain duration had exceeded a year for 89.6%, with 35.3% having widespread pain, and the most common primary diagnosis being fibromyalgia at 13.6%. At t0, 37.1% and 12.8% were on ongoing sick leave or a disability pension related to chronic pain, respectively, while 24.6% and 10.7% had over 180 net days of pain-related sick leave or disability pension in the past year, respectively. Table 1 details the sample characteristics.

Sickness Absence

Fig 1A presents the sample's sickness absence across the 7-year observation period (ie, 5 years before to 2 years after t0). Participants collecting benefits related to chronic pain increased from 17.4% at the start to 49.3% at 2 months past t0, to then decrease to 38.0% at the end of follow-up (Fig 1A*I*). In contrast, benefits due to other diagnoses remained comparatively constant across the same period at roughly 10% (Fig 1A*II*). Sickness absence was unevenly distributed between patients so that 21.7% received no benefits, while 19.9% accounted for 56.2% of the total benefits over the 7 years. A closer inspection of the transitions between sickness absence states revealed the dynamics of category exchange (Fig 1B). In line with the sample state distribution, most transitions took place between the no benefits and sick leave states, while an increasing number of patients transited from sick leave to disability pension over time. Finally, a consistent but non-negligible amount also transitioned from disability pension to no benefits.

Restricting the period to the 2 final years, the complete sample was represented by 15,417 unique sickness absence patterns. Half of the participants remained in the same state the entire period: 32.6% with no benefits, 3.3% with partial sick leave, 4.9% with full sick leave, 4.3% with partial disability pension, and 4.9% with full disability pension; while 4.3% improved from > 180 days of gross sick leave in the first to none in the second year and 0.9% deteriorated in a reverse pattern. Based on the patterns, a 5-cluster structure driven by total state duration was identified as the best solution. The largest cluster corresponded to patients with low sickness absence (n = 25,294), while the remaining 4 clusters were dominated by partial sick leave (n = 5,416), full sick leave (n = 6,924), partial disability pension (n = 2,884), and full disability pension (n = 3,723). The solution had an acceptable statistical quality (overall: average silhouette width = 0.73, point-biserial correlation = 0.91, Hubert's C = 0.005; cluster-wise: average silhouette width = 0.59−0.78) and its robustness was supported by both the split-sample analyses and the alternative clustering algorithms. However, some theoretical inadequacies still warranted modification to improve the clusters' clinical relevance. Firstly, full and partial sick leave clusters were combined, as they are poorly defined and overlapping in practice. Secondly, patients with permanent disability pension in the 5 years prior to t0 were excluded (n = 9,893), as their unlikeliness to change state would inflate predictive performance. Finally, full and partial disability pension were combined due to their low prevalence and patients with any disability pension following t0 were re-assigned to the disability pension cluster. This resulted in a 3-cluster solution (Fig 1C-1F; Tables 2-3) characterized by patients with: either no sickness absence or a fast recovery from benefits (low sickness absence class; n = 21,970), a considerable amount of sick leave who either ended on sick leave or recovered during the second year (sick leave class; n = 9,660), and a substantial amount of sickness absence who transited from sick leave to disability pension (disability pension class; n = 2,718).

Prediction

Fig 2 illustrates the predictive performance of the 4 algorithms. The non-parametric machine learning techniques performed similarly to each other and consistently outperformed the multinomial logistic regression. The full 101-feature model (Fig 2A) correctly predicted nearly 70% of patients across the outcome classes with the non-parametric algorithms on both the validation and the test set (balanced accuracy: support vector machine = 0.669/0.669; gradient tree boosting = 0.685/0.701; multilayer perceptron = 0.667/0.675). In comparison, the average performance was 60% for the multinomial logistic

Table 1. Sample Baseline Characteristics

	All	*Low Sickness Absence*	*Sick Leave*	*Disability Pension*
Patients*	44,241 (100.0)	21,970 (49.7)	9,660 (21.8)	2,718 (6.1)
Age (years)†	44.0 (35.7, 51.5)	40.9 (31.5, 49.0)	43.1 (35.7, 50.1)	48.5 (41.6, 54.5)
Female*	31,610 (71.4)	14,993 (68.2)	7,227 (74.8)	1,871 (68.8)
Geographical region*				
Stockholm/Gotland	11,330 (25.6)	6,887 (31.3)	2,302 (23.8)	372 (13.7)
South	11,446 (25.9)	4,950 (22.5)	2,534 (26.2)	1,056 (38.9)
Middle	13,233 (29.9)	6,143 (28.0)	3,159 (32.7)	720 (26.5)
North	7,547 (17.1)	3,783 (17.2)	1,543 (16.0)	432 (15.9)
Country of birth*				
Sweden	34,374 (77.7)	17,177 (78.2)	7,403 (76.6)	1,921 (70.7)
Other European country	5,086 (11.5)	2,130 (9.7)	1,230 (12.7)	511 (18.8)
Non-European country	4,781 (10.8)	2,663 (12.1)	1,027 (10.6)	286 (10.5)
Education (years)*				
Elementary (<10)	7,341 (16.6)	3,275 (14.9)	1,509 (15.6)	538 (19.8)
High school (10–12)	24,905 (56.3)	11,778 (53.6)	5,588 (57.8)	1,603 (59.0)
University/college (> 12)	11,881 (26.9)	6,838 (31.1)	2,554 (26.4)	575 (21.2)
Employment status*				
Employed	28,525 (64.5)	15,203 (69.2)	7,190 (74.4)	1,836 (67.5)
Unemployed	10,696 (24.2)	4,112 (18.7)	1,999 (20.7)	714 (26.3)
Student	1,182 (2.7)	1,084 (4.9)	54 (0.6)	7 (0.3)
Family composition*				
Partner with children	18,711 (42.3)	9,596 (43.7)	4,455 (46.1)	1,160 (42.7)
Partner without children	5,700 (12.9)	2,205 (10.0)	1,061 (11.0)	514 (18.9)
Single without children	13,071 (29.5)	6,880 (31.3)	2,586 (26.8)	692 (25.5)
Single with children	6,750 (15.3)	3,280 (14.9)	1,558 (16.1)	352 (13.0)
Number of children†	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)
Past 5-year mean annual disposable income (1000 SEK)†				
Individual	175 (132, 227)	185 (127, 243)	184 (145, 229)	167 (135, 203)
Family	174 (129, 233)	183 (133, 243)	176 (134, 231)	156 (117, 208)
Pain characteristics				
Duration (years)†	5.7 (2.1, 12.5)	4.4 (1.7, 10.4)	4.0 (1.7, 9.8)	5.7 (2.7, 12.0)
NRS-10 past week pain intensity†	7 (6, 8)	7 (6, 8)	7 (6, 8)	8 (7, 9)
Number of pain locations (0–36)†	13 (8, 20)	11 (6, 18)	14 (8, 21)	15 (9, 22)
Primary pain location*				
Head	2,167 (4.9)	1,209 (5.5)	477 (4.9)	90 (3.3)
Neck, shoulders, and upper extremities	10,059 (22.7)	5,106 (23.2)	2,265 (23.4)	688 (25.3)
Upper back and chest	1,946 (4.4)	1,162 (5.3)	364 (3.8)	80 (2.9)
Lower back	8,054 (18.2)	4,173 (19.0)	1,849 (19.1)	426 (15.7)
Abdomen	558 (1.3)	372 (1.7)	87 (0.9)	15 (0.6)
Hips and lower extremities	3,904 (8.8)	2,137 (9.7)	720 (7.5)	236 (8.7)
Widespread or varying pain	15,610 (35.3)	6,806 (31.0)	3,527 (36.5)	1,076 (39.6)
Top 5 ICD-10 diagnoses*				
Fibromyalgia (M79.7)	6,026 (13.6)	2,550 (11.6)	1,511 (15.6)	332 (12.2)
Unspecified pain (R52.9)	3,515 (7.9)	1,835 (8.4)	822 (8.5)	117 (4.3)
Myalgia (M79.1)	3,299 (7.5)	1,809 (8.2)	731 (7.6)	139 (5.1)
Low-back pain (M54.5)	3,150 (7.1)	1,865 (8.5)	615 (6.4)	136 (5.0)
Cervicobrachial syndrome (M53.1)	2,426 (5.5)	1,119 (5.1)	588 (6.1)	180 (6.6)
HADS emotional distress†,‡	47 (33, 60)	46 (32, 57)	49 (37, 62)	48 (34, 61)
SF-36†,‡				
Physical health	44 (35, 52)	47 (39, 56)	40 (33, 48)	37 (30, 45)
Mental health	39 (31, 48)	41 (32, 49)	37 (29, 46)	37 (29, 46)
EQ-5D index†,§	0.2 (0.0, 0.6)	0.2 (0.1, 0.7)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)
Confidence in recovery*				
High	7,691 (17.4)	4,975 (22.6)	1,887 (19.5)	231 (8.5)
Moderate	8,948 (20.2)	5,163 (23.5)	2,206 (22.8)	419 (15.4)
Low	23,830 (53.9)	9,497 (43.2)	4,971 (51.5)	1,935 (71.2)
Baseline sickness absence status*,¶				
Full sick leave	8,670 (19.6)	1,762 (8.0)	4,358 (45.1)	1,065 (39.2)
Partial sick leave	7,759 (17.5)	2,646 (12.0)	3,603 (37.3)	825 (30.4)
Full disability pension	2,970 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)

(*continued on next page*)

Table 1. Continued

	All	*Low Sickness Absence*	*Sick Leave*	*Disability Pension*
Partial disability pension	2,693 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
Past-year sickness absence[†,¶]				
Gross sick leave days	27 (0, 248)	0 (0, 69)	254 (105, 364)	297 (12, 364)
Net sick leave days	20 (0, 191)	0 (0, 49)	199 (81, 322)	209 (9, 345)
SQRP pain specialist clinic				
Current IDT program	20,794 (47.0)	10,215 (46.5)	5,675 (58.7)	1,134 (41.7)
Previous IDT program	759 (1.7)	308 (1.4)	248 (2.6)	24 (0.9)
Previous IDT evaluation	3,949 (8.9)	1,598 (7.3)	1,038 (10.7)	197 (7.2)
Past-year specialized outpatient healthcare[*,¶]				
0 visits	7,723 (22.5)	5,093 (23.2)	1,992 (20.6)	638 (23.5)
1−3 visits	20,173 (58.7)	13,129 (59.8)	5,449 (56.4)	1,595 (58.7)
> 3 visits	6,452 (18.8)	3,748 (17.1)	2,219 (23.0)	485 (17.8)
Past-year inpatient healthcare[*,¶]				
0 days	31,604 (92.0)	20,436 (93.0)	8,662 (89.7)	2,506 (92.2)
1−3 days	1,346 (3.9)	812 (3.7)	435 (4.5)	99 (3.6)
>3 days	1,398 (4.1)	722 (3.3)	563 (5.8)	113 (4.2)
Past-year dispensed prescription medication classes[*,‖]				
0	4,370 (9.9)	2,890 (13.2)	589 (6.1)	159 (5.8)
1−3	29,463 (66.6)	15,524 (70.7)	6,518 (67.5)	1,433 (52.7)
>3	6,644 (15.0)	2,414 (11.0)	1,753 (18.1)	346 (12.7)

*frequency (percent)
†median (25th, 75th percentile)
‡based on LoMartire et al, 2020 scaled as percentiles.
§based on UK time trade-off.
¶Due to ICD-10 diagnoses M(00−99), G(43−44, 47, 50−64, 82, 96−97), R(07, 10, 26, 29, 51−52), S(12−13, 22, 32, 42−43, 53), T(85, 88, 91−94), and F(32−33, 41, 43, 45).
‖classes include non-opioid pain medications, opioids, antidepressants, benzodiazepines, hypnotics, mood stabilizers, antipsychotics, and attention-deficit/hyperactivity disorder medications.

regression (balanced accuracy: 0.595/0.595), with only 25% of patients on disability pension correctly classified. Domain-specific models revealed that whereas sickness absence history contributed the most to overall performance, features related to sociodemographics and the chronic pain experience mainly improved disability pension predictions (Fig. 2C-F). Ultimately, 1 model per algorithm was identified (Fig 2B) that achieved similar performance to their respective full models (balanced accuracy: multinomial logistic regression = 0.574/0.567; support vector machine = 0.666/0.667; gradient tree boosting = 0.684/0.681; multilayer perceptron = 0.659/0.659). Ongoing chronic pain-related sickness absence at t0, the 2008 policy indicator, and age were identified as important predictors of future sickness absence by all algorithms. The non-parametric algorithms further identified confidence in recovery, gross sick leave in the second year prior to t0, and the southern Sweden geographical location. Meanwhile, gross sick leave in the past year, number of pain locations, and whether the patient was enrolled in a current IDT program was individually identified by the gradient tree boosting, the support vector machine, and the multilayer perceptron, respectively. The gradient tree boosting was selected as the final model since it slightly but consistently outperformed the other algorithms. Sensitivity analyses supported that it was robust to sample restriction (balanced accuracy): aged $\leq$ 50 and > 50 years (0.694 vs 0.599), Swedish and non-Swedish born (0.680 vs 0.710), t0 < 2009 and $\geq$ 2009 (0.676 vs 0.633), and selected and non-selected for IDT (0.662 vs 0.692).

Of the 8 features included in the final model, half were measures of sickness absence history, whereas the other half consisted of the 2008 policy indicator, age, confidence in recovery, and the southern Sweden geographical region (Fig 3B). Fig. 3C-D illustrate the average change in outcome class probability per feature. Sickness absence history had a strong association with future sickness absence. An increase in gross sick leave from zero to 365 days in either the past year or the second year prior to t0 decreased the probability of low sickness absence with more than 0.30 and 0.10, respectively, while the corresponding estimate was roughly 0.20 for both an ongoing full or partial sick leave spell at t0. Meanwhile, the remaining features were most strongly associated with future disability pension. An increased age from 18 to 64 years, a t0 before the 2008 policy, low confidence in recovery, and the southern Sweden region increased the probability of future disability pension by roughly 0.30, 0.30, 0.20, and 0.10, respectively. Intriguingly, past-year sick leave days displayed a non-linear interaction with age, whereby sick leave days largely influenced both whether patients below 30 years would have low sickness absence and whether patients older than 50 years would receive disability pension (Fig 3D).

The final model had a balanced accuracy of 68% on the test set compared to 33% by chance, with 64 to 70%

Table 2. Sample Sickness Absence and Health Care Utilization During the Final 2 Years

	All	Low Sickness Absence	Sick Leave	Disability Pension
Patients with ≥ 1 spell*				
Full sick leave	19,441 (43.9)	7,013 (31.9)	7,317 (75.7)	1,702 (62.6)
Partial sick leave	16,408 (37.1)	6,790 (30.9)	6,208 (64.3)	1,268 (46.7)
Full disability pension	5,894 (13.3)	0 (0.0)	0 (0.0)	1,666 (61.3)
Partial disability pension	4,745 (10.7)	0 (0.0)	0 (0.0)	1,214 (44.7)
First-year sickness absence†,‡				
Gross sick leave days	12 (0, 291)	0 (0, 51)	364 (327, 364)	259 (56, 364)
Net sick leave days	10 (0, 222)	0 (0, 36)	317 (225, 364)	194 (41, 322)
Gross disability pension days	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 153)
Net disability pension days	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 107)
Second-year sickness absence†,‡				
Gross sick leave days	0 (0, 177)	0 (0, 0)	362 (245, 364)	0 (0, 177)
Net sick leave days	0 (0, 133)	0 (0, 0)	274 (169, 362)	0 (0, 138)
Gross disability pension days	0 (0, 0)	0 (0, 0)	0 (0, 0)	334 (169, 364)
Net disability pension days	0 (0, 0)	0 (0, 0)	0 (0, 0)	182 (99, 364)
Specialized outpatient healthcare*,‡				
0 visits	10,944 (24.7)	5,949 (27.1)	1,681 (17.4)	765 (28.1)
1–3 visits	15,626 (35.3)	8,181 (37.2)	2,883 (29.8)	977 (35.9)
> 3 visits	17,671 (39.9)	7,840 (35.7)	5,096 (52.8)	976 (35.9)
Inpatient healthcare ≥ 1 day*,‡	4,688 (10.6)	1,673 (7.6)	1,376 (14.2)	257 (9.5)
Dispensed prescription medication classes*,§				
0	4,033 (9.1)	2,823 (12.8)	440 (4.6)	177 (6.5)
1–3	30,413 (68.7)	15,728 (71.6)	6,411 (66.4)	1,943 (71.5)
>3	9,795 (22.1)	3,419 (15.6)	2,809 (29.1)	598 (22.0)

*frequency (percent).
†median (25th, 75th percentile).
‡Due to ICD-10 diagnoses M(00–99), G(43–44, 47, 50–64, 82, 96–97), R(07, 10, 26, 29, 51–52), S(12–13, 22, 32, 42–43, 53), T(85, 88, 91–94), and F(32–33, 41, 43, 45).
§classes include non-opioid pain medications, opioids, antidepressants, benzodiazepines, hypnotics, mood stabilizers, antipsychotics, and attention-deficit/hyperactivity disorder medications.

of true positives and 82 to 87% of true negatives identified across the outcome classes (Fig 3A; Table 3). However, a consequence of the imbalanced class distribution was that only 1 in 4 positive disability pension predictions were correct (positive predictive value = 0.256). The model was therefore primarily useful in discriminating between patients with low and high future sickness absence; most mispredictions were in the most similar class and the high sickness absence classes were typically misclassified as each other. When sick leave and disability pension classes were merged, performance was markedly increased (balanced accuracy = 0.805; F1 score = 0.794; sensitivity and specificity ≥ 0.794; positive and negative predictive values ≥ 0.701).

Discussion

This study described the sickness absence over a 7-year period in 44,241 chronic pain patients evaluated at specialist IDT clinics and identified predictors of sickness absence. Our results showed that study participants with social insurance benefits increased from 17% 5 years before to 48% at the time of the IDT evaluation to

Table 3. Performance Metrics of the Final Gradient Tree Boosting Model

	Overall	Low Sickness Absence	Sick Leave	Disability Pension
Accuracy	0.789§	0.765	0.770	0.833
ROC curve area	0.764¶	0.787	0.733	0.771
F1 score*	0.596§	0.790	0.624	0.375
Sensitivity†	0.681§,‖	0.702	0.641	0.699
Specificity		0.872	0.824	0.843
Positive predictive value‡		0.903	0.607	0.256
Negative predictive value		0.631	0.844	0.973

Model estimated on the training set and evaluated on the test set.
*harmonic mean of precision and sensitivity.
†also known as recall.
‡also known as precision.
§unweighted mean of the class estimates.
¶also known as AUNU.
‖also known as balanced accuracy.

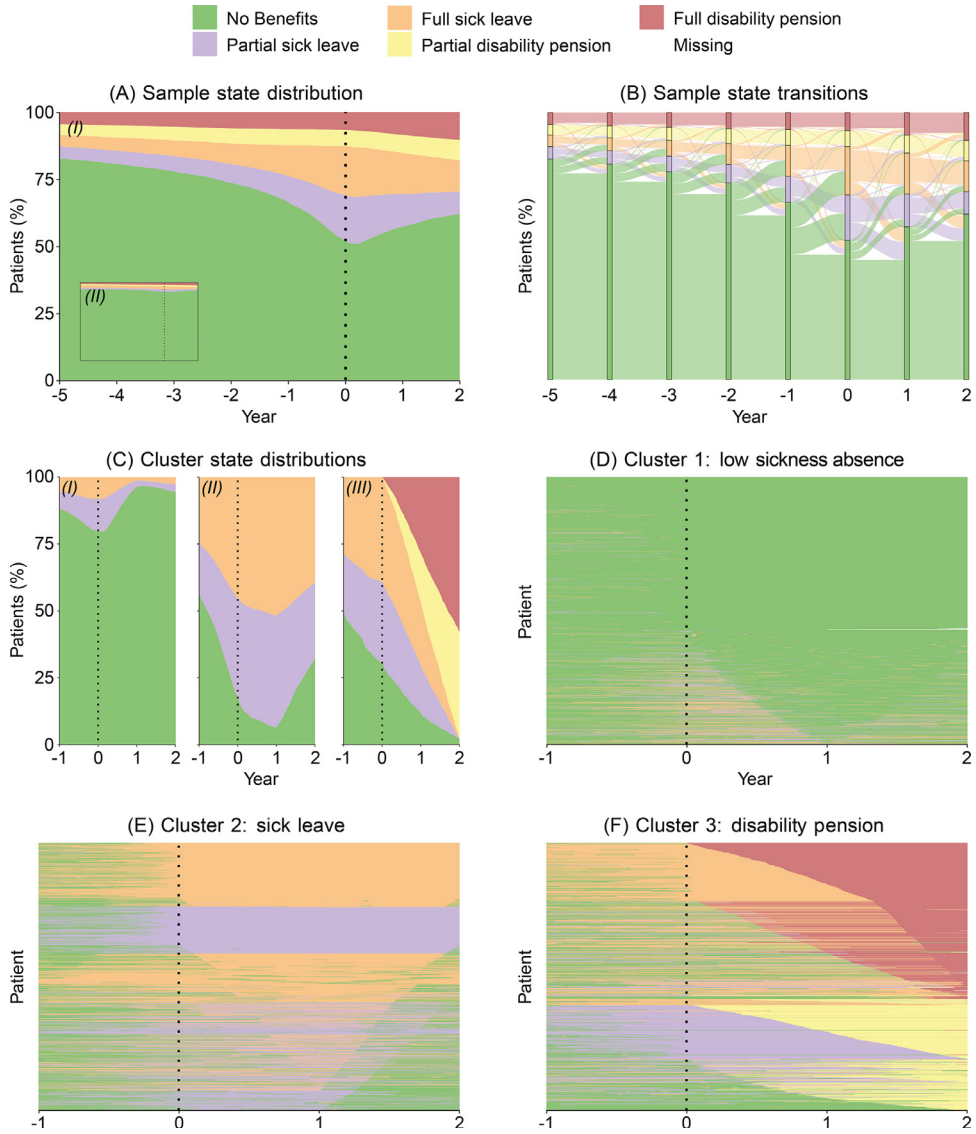

Figure 1. Sample sickness absence. (A) Chronograms of the sample's daily transversal state distribution; the main *(I)* and inset *(II)* plots show benefits related to chronic pain and other diagnoses, respectively. (B) Alluvial diagram of the sample's state transitions across the first day of each year. (C) Chronograms per cluster for low sickness absence *(I)*, sick leave *(II)*, and disability pension *(III)*. (D-F) Cluster-wise sequence index plots of daily individual patient patterns. The dotted vertical line marks the time of the IDT assessment (t0).

then decrease to 38% 2 years after. Eight predictors of future sickness absence were identified. Sickness absence history was the strongest predictor, while other predictors included the 2008 policy, age, confidence in recovery, and geographical region.

Consistent with previous research, our results show that sickness absence caused by musculoskeletal disorders, mental disorders, and injuries is high in chronic pain patients.[2,16,27,37] With data centered at IDT evaluation, nearly a fifth of our sample received benefits at any given time, with the mean annual net sickness absence ranging from 54 to 145 days per patient. In comparison, official Swedish statistics have reported that the general population in the age bracket 16 to 64 years received benefits for 27 to 43 days across the period 2000 to 2016.[62] These figures are not directly comparable, as they were computed over relative versus absolute time periods, respectively. Nevertheless, our lowest estimate was higher than their upper extreme and the difference in estimates is likely to be conservative as our data was from a period corresponding to lower benefits received by the general population.[62] The sample trend of monotonously increasing benefits that peaked in the first year post-IDT evaluation could be attributed to specialist IDT referral procedure that prioritizes patients with complex clinical presentations. The subsequent decrease in benefits indicates that the IDT procedure represents a sorting point from temporary sick leave to either no benefits or a disability pension. This pattern was consistent in all sensitivity analysis subsamples (Figure 2.2 in supplementary materials). When comparing the trajectories of the selected and non-selected IDT patients, a more pronounced decrease in benefits was observed in the former, which could represent either a treatment or selection effect. A previous study restricted to a subsample of our data observed

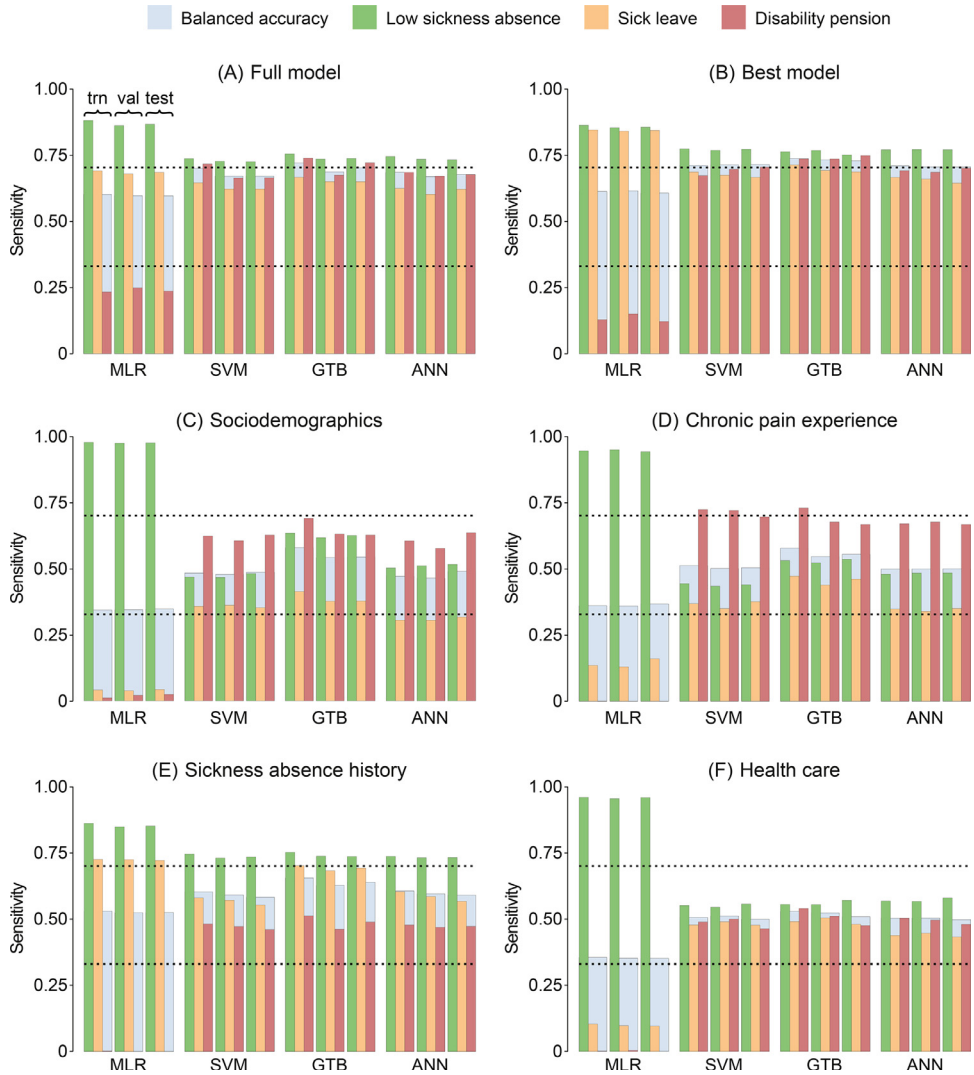

Figure 2. Predictive performance of the 4 algorithms. Balanced accuracy and class-wise sensitivities per algorithm for the full (A), final (B), and domain-wise models (C-F) when estimated on the training set (trn) and evaluated on trn, the validation set (val), and the test set (test), respectively. The dotted horizontal lines mark 0.33 and 0.70 of balanced accuracy. MLR, multinomial logistic regression. SVM, support vector machine. GTB, gradient tree boosting. ANN, multilayer perceptron artificial neural network.

patients selected for IDT from 1 year before to 2 years after the intervention and reported a similar pattern in benefits.[51] However, whereas they observed that the benefits had decreased to the previous-year level already 1 year after evaluation, the benefits in our sample had still not decreased to that level at the end of follow-up. This discrepancy was due to markedly lower pre-evaluation benefits in our study and is unlikely to be caused by methodological differences, as we approximately reproduced their results when restricting the data to their sampling criteria. Instead, it is more likely to be related to the sample time frame.

As previously reported, sickness absence was unevenly distributed so that a minority accounted for most of the social insurance benefits.[23,24,28] To reflect these differences, patients were divided into 3 classes that were used as outcome and resulted in the identification of 8 associated features. Consistent with previous research, sickness absence history was the strongest predictor of future sickness absence and accounted for most of the final model's performance.[14,29,30,32,35,52,66] Interestingly, the performance was specific to past benefits linked to chronic pain, which aligned with previous reports of the strongest association within diagnosis category.[14,29] Both ongoing sick leave at the IDT evaluation and cumulative sick leave for the 2 preceding years were positively associated with future sickness absence. This is similar to earlier findings, where the sick leave extent at baseline predicted the duration of future sick leave spells and cumulative sick leave was a strong risk factor for future disability pension.[32,52,66] To a lesser extent, age, confidence in recovery, the 2008 policy indicator, and geographical location also predicted future sickness absence. There are several reports of a positive association between age and both sick leave duration and the risk of disability pension.[30,52,66] Our results suggested that the likelihood of low sick leave decreased with age and that age largely drove the risk of disability pension, which was the highest in patients over 50 years of age. Meanwhile, confidence in recovery was inversely associated with disability pension, which aligns with an earlier review that found evidence for high confidence in

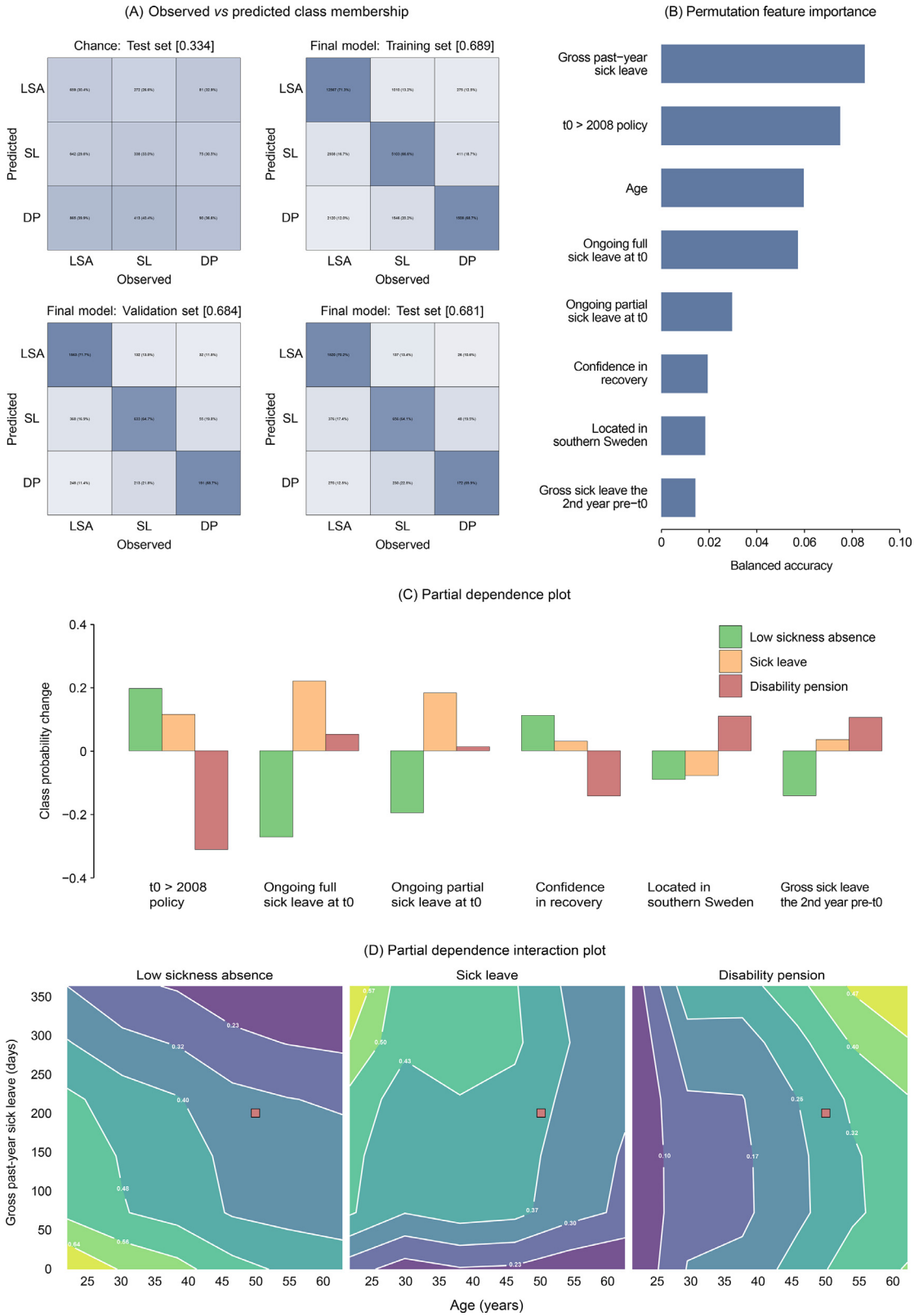

Figure 3. Gradient tree boosting final model details. (A) Cross-tables of observed versus predicted class memberships. The upper left shows performance by chance for a model estimated on the training set (n = 35,392) and evaluated on the test set (n = 4,425). The upper right, lower left, and lower right show the final model's performance when estimated on the training set and evaluated on the training, validation (n = 4,424), and test sets, respectively. Square brackets denote balanced accuracy. LSA, low sickness absence class. SL, sick leave class. DP, disability pension class. (B) Permutation feature importance for the final model, measured through the mean change in balanced accuracy across 100 repetitions. (C) Partial dependence plot of the marginal change in probability for predicted class membership with minimum and maximum values contrasted (ie, from no to yes for dichotomous features, from low to high for confidence in recovery, and from 0 to 365 days for gross sick leave). (D) Partial dependence plot of marginal change in probability for class membership with the interaction between age and gross sick leave days the past year. The figure illustrates the topography of probabilities, with the numbers on the borders showing thresholds for each color region. For example, a patient at age 50 with a gross past-year sick leave of 200 days has an increased probability of 0.32, 0.37, and 0.25 for LSA, SL, and DP, respectively (squares).

recovery as a predictor of return-to-work.[33] Since sickness absence history, age, and confidence in recovery are recurrent prognostic factors of future sickness absence in the literature, it is likely that they are directly informative in predictions for future patients. Regarding the 2008 policy, patients evaluated in the specialist healthcare after 2008 were less likely to receive disability pension, which is in accordance with previous reports; however, the extent to which the change is attributable to the policy alone is uncertain.[36,51] Likewise, geographical region was associated with disability pension, whereby patients in southern Sweden were at higher risk. Municipal differences were also previously observed and plausible causes for the discrepancy are differences in demographics, work-related factors, health care services, and policy.[34,58,66] Whereas both the 2008 policy and geographical region were important predictors in the analyzed sample, the former is not informative for future patients and the latter could be of limited value depending on its underlying causes. These findings nonetheless highlight the importance of spatio-temporality in sickness absence predictions. In contrast to the aforementioned results, several previously reported risk factors of sickness absence including sex, education, employment status, and multimorbidity did not improve predictions of the final model.[30,35,52,66] Lastly, separating patients with high sick leave and disability pension enabled identification of features specifically associated with disability pension, but the final model's accuracy was not sufficient for individual patient predictions in this class. Instead, an acceptable 80% accuracy was obtained by discriminating only between patients with low or high future sickness absence. To optimize personalized intervention, it could be useful to begin conceptualizing such models as decision support tools into clinical practice. Until then, sickness absence history, age, and confidence in recovery are important factors to consider when allocating rehabilitation modules that target absenteeism.

Our results rest upon a rigorous analysis of high-quality data from a large population-representative sample of chronic pain patients in a specialist treatment setting. The results should generalize to similar patients in Sweden, but predictions could be impaired if the underlying circumstances change, as prediction models are inherently non-causal. Five main limitations should be considered when interpreting the results. Firstly, that non-musculoskeletal diagnoses were pooled under the chronic pain spectrum necessitated the assumption that they were a consequence of the condition, which was reasonable when considering the sample characteristics. Secondly, the non-registered sick leave during the qualifying period introduced some bias, as recurrent short spells were misclassified as no benefits. The consequently slightly underreported sick leave was unlikely to influence the predictions, however, as spells below the employee-qualifying period were omitted for all patients. Thirdly, absence of microdata on migration, death, and retirement resulted in slightly underreported sickness absence due to misclassification as no benefits. The Swedish official statistics support that migration contributed the most bias, corresponding to 1.1 to 2.1% of the general population annually, while the annual death rate for ages 18 to 64 and the proportion retired in the ages 61 to 64 each correspond to 0.1%.[54-56,61] Fourthly, the prediction model is contingent on the validity of the outcome classes. Combining full and partial benefits decreased the clustering solution's statistical quality but was theoretically motivated as the degree of benefits are poorly resolved, owing to their basis on ordinary work hours rather than an absolute amount. This has been done previously and was supported by the inherent class ordering of the prediction model.[66] The visual presentation of the classes further provides an easily apprehensible patient overview, so that the class quality is directly observable (Fig 1D-F). In addition, targeting chronic pain benefits alone resulted in that patients in the low sickness absence class were slightly more likely to collect benefits for other diagnoses, as parallel benefits have a legislated upper limit. Adding this information to the model did not, however, increase its performance. Finally, the predictive analyses were limited to the data available in the registers. This prevented examination of psychosocial occupational stressors and lifestyle factors such as physical activity, body weight, smoking, and alcohol intake, which have previously been identified as important prognostic factors of sickness absence in non-clinical populations.[15,22,65] Similarly, data quality issues provide an alternative explanation for that certain features were not selected in the final model. This included noise owing to missingness between 20 to 30% in some chronic pain experience questionnaires and misclassification in employment status.

Conclusions

Patients evaluated at specialist IDT clinics displayed an overall trend of increased sickness absence from 5 years before to the time of the assessment, that then decreased until the end of follow-up. Eight features were identified that were associated with sickness absence in the 2 years following the IDT evaluation. Sickness absence history was the strongest predictor of future sickness absence, while other predictors included the 2008 policy, age, confidence in recovery, and geographical region. These results could guide personalized intervention in the specialist healthcare.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2021.03.145.

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